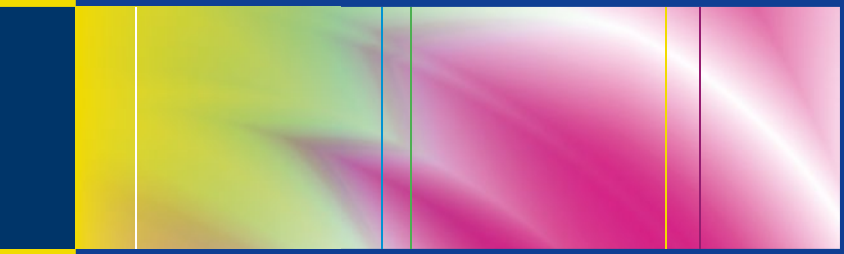
Anthony M. Szema
Editor



Unusual Diseases with Common Symptoms

A Clinical Casebook

Springer

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This book is dedicated to my family: parents Li-Chieh and Alice Szema; sister and colleague allergist/immunologist, Katherine Szema, MD, FAAP; wife, Denise C. Monte, MD, FACS; daughter, Allison, and son, Austin; my late mentors Robert E. Dutton Jr., MD (professor of medicine and physiology, Albany Medical College, and professor of biomedical engineering, Rensselaer Polytechnic Institute), and Sami I. Said, MD (Distinguished SUNY Professor).

Preface: Unusual Diseases with Common Symptoms

By way of introduction and description of what the reader will find in this book, *Unusual Diseases with Common Symptoms* illustrates actual patient cases of unusual diseases, beginning with a clinical vignette, followed by sections on diagnosis and treatment, key bullet points, and multiple-choice questions with references. Included are photos, diagrams, and tables, as well as illustrations to emphasize take-home messages. While the level of detail is that which I teach medical students in the therapeutics course at Stony Brook University School of Medicine, the text is written so that a layperson can be introduced to the subject in an easy-to-read, illustrative manner.

These are my patients with diagnoses such as: geriatric-onset hereditary angioedema, triple diagnoses of stiff person syndrome with hypogammaglobulinemia and orbital myositis, anaphylactic shock to ribeye steak initiated by a lone star tick bite, Iraq-Afghanistan War Lung Injury characterized with titanium in the lung, dyspareunia and Stevens-Johnson syndrome from black hair dye, and shock from implantable contraception.

Volume two of this series will follow with even more cases and others submitted by clinicians from around the world. Our team may be reached at threevillageallergyandasthma@gmail.com. and Sincerely,

Anthony M. Szema, MD

Acknowledgment

I thank Margaret Moore, Editor, Clinical Medicine, Springer, for the opportunity to write *Unusual Disease with Common Symptoms*.

Karthik Periyasamy, Project Coordinator for Books, Springer Nature, also deserves kudos for his patient help.

My students who have contributed chapters, including Niely Mirsaidi, who is our medical illustrator and chapter author, have done a tremendous job!

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Chapter 1
The Many Janus Faces of Angie O'Deemer

Anthony M. Szema

Vignette

Mrs. Banner woke up one morning with lopsided facial swelling that made it look like a water balloon was stuck in her cheek (Figs. 1.1 and 1.2). She freaked out and her husband called 911.

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FIGURE 1.1 Front view of Mrs. Banner suffering from severe angioedema of the right cheek and lip

FIGURE 1.2 Mrs. Banner's angioedema was largely confined to the right side of the face, revealing a left side that was only mildly affected

This had never happened before despite her 82 years of an active life [2]. She was not eating at the time. Mrs. Banner felt as if she could not breathe; her throat felt like it was closing! Paramedics transported her to a big university hospital where she was given intravenous steroids, diphenhydramine, cimetidine, and oxygen. It took a full day for her symptoms to slowly resolve. Fortunately, she was not intubated. Nothing she did made this worse once it occurred—nothing she did attenuated her symptoms in the hospital. Her smart phone photos before and after seem like someone photoshopped her left face and lips in a Kylie Jenner way. On examining her prior medical history, nothing was really remarkable. Mrs. Banner had four healthy adult children delivered via normal spontaneous vaginal delivery. Her grandchildren were all healthy. Her husband was an obese ex-smoker with cardiac disease doctors usually were worried about. She, however, was the picture of health! In the past year, Mrs. Banner's primary care provider prescribed a blood pressure pill for essential hypertension, which was now well-controlled. The name of this medicine is lisinopril—part of a class of drugs called angiotensin-converting enzyme inhibitors, which block the body's conversion of a chemical called angiotensin I to angiotensin II. The reason lisinopril controls high blood pressure is that by blocking creation of angiotensin II, there is no angiotensin II to constrict blood vessels to increase blood pressure. Nevertheless, lisinopril concurrently increases levels of bradykinin, a chemical that makes blood vessels leaky and causes swelling in 15.5%, or about one in five, of patients on the drug. Angiotensin converting enzyme degrades bradykinin. So, an ACE inhibitor increases bradykinin. This often clinically leads to a dry cough—from airway swelling—but in Mrs. Banner's case, a more severe reaction occurred. This was not an allergy per se. This was a severe adverse reaction related to the mechanism of the drug. But was there more to Mrs. Banner?

Why do we care about Mrs. Banner? What makes her so interesting? Why should you be freaking out if you take lisinopril? Well I am sure we all would never want this to happen to us. No one wants to close off their throat and die! But it is quite more common than one would expect. Here's the rub; in the hospital and repeated in my office, we obtained blood work for a special protein in the blood called C4. No, this C4 is not explo-

sives that SEAL Team Six uses. This is what is called a complement protein that you and I have in our blood in high levels. In the rare cases of hereditary angioedema (HAE), C4 levels are severely depleted during attacks of swelling or angioedema. Even in between attacks, when one's face is normal, patients with HAE have decreased levels of C4. Aha! So Mrs. Banner not only had a risk from being on lisinopril to increase bradykinin, but she also was deficient in C4 in her blood! Therefore, she had a super-rare disease hereditary angioedema, a misnomer, because she had no blood relatives with anything like this. What HAE is defined by is not only low C4 but also, specifically, low levels of C1 esterase inhibitor protein, C1INH, a protein that inhibits swelling. Genetically and congenitally, being low in C1INH makes the diagnosis of HAE Type I, affecting only a thousand or so persons out of the 323 million people in the USA—truly a rare, orphan disease! To compound these biological findings, the function of the C1INH, when tested for an assay in the lab, was low, so it did not work! Her function was far less than 20% of normal, with normal being at least 60%, and preferably 100%. This gave her an additional nuanced diagnosis of HAE Type II. An additional consideration, which Ms. Banner did not have, is HAE Type III. Why should you be concerned? HAE Type III entails swelling in previously health young women who take estrogen-containing oral contraceptives. Their joint swelling is not a rheumatologic or orthopedic surgery problem. All they need to do is call the OB/GYN to stop the estrogen-containing oral contraceptive. Use another form of contraception! Another one of our patients had to take cetirizine prior to sex because she swelled so much! (Fig. 1.3)

So voila! Here we had three problems: (1) lisinopril side effect, (2) HAE Type I, and (3) HAE Type II. Mrs. Banner was a rare bird indeed! So who cares? Well, for starters, what makes this even more unusual is that patients with HAE Type I usually have multiple spontaneous attacks of life-threatening angioedema throughout their entire life, and the death rate, or mortality, is sky-high if untreated. Yet, here she was, an otherwise vibrant 82-year-old woman who was otherwise perfectly healthy. Most HAE Type I patients would have exacerbation of angioedema with trauma—like childbirth, of which she had

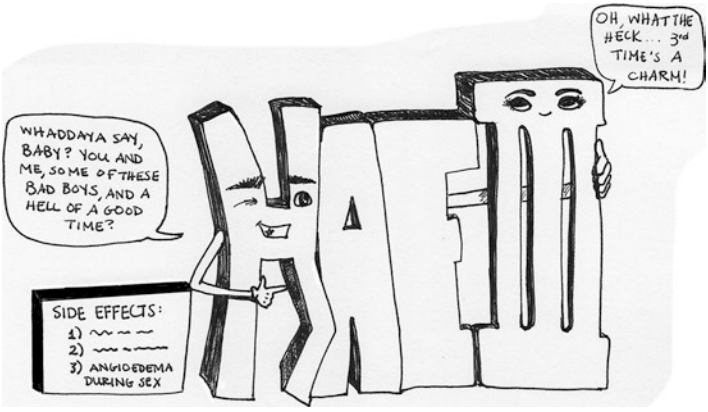

FIGURE 1.3 Oral contraceptives: heroic and empowering or horrifying and evil?

four times—but she did not! Infections can also trigger attacks. Yet, I would surmise that what happened here was that she was the Leaning Tower of Pisa waiting for a brisk wind to topple her over. The wind was the lisinopril, which we stopped. In fact, patients with HAE should never be on these angiotensin-converting enzyme inhibitors or the so-called newer angiotensin receptor blockers (ARBs) like valsartan or losartan. Interestingly, the ARBs do not increase bradykinin but must be interfering with bradykinin signaling or function in some way. There is a lower risk of 4.4% but they are not without risk. The steroids, diphenhydramine, and cimetidine Mrs. Banner received in the emergency room were useless in a setting of a *bona fide* angioedema attack. What makes Mrs. Banner so interesting to myself is that, yes, she can explode like a giant green comic book character, but it is plausible to me that perhaps she has a yet unknown protective chemical that helped her avoid attaches for the first 82 years of her life unlike the typical HAE patient. This will be a future research project to find out what is it about her blood that is different.

Compounding the angioedema issue was the fact that the emergency room (ER) doctors gave her a prescription for an epinephrine auto injector. First, there was a recall on the talking epinephrine devices the month before. These devices, the

size of a pack of playing cards, had an electronic voice—like an automatic defibrillator or cell phone to speak instructions. It was a great innovation, until the manufacturer realized many of these talking devices inadvertently had minimal or no medicine in the device; 26 persons died of anaphylactic shock. Second, we found out she was also taking a beta-blocker (metoprolol) for hypertension, but epinephrine pens are beta-agonists. The epinephrine will not work if you are already blocking the beta-receptors. Besides, I had already mentioned that the swelling, we believe, is from bradykinin. What Mrs. Banner needed was a bradykinin blocker. Fortunately, we had an orange plastic briefcase with a $10,000 syringe containing a bradykinin B2 receptor antagonist called icatibant. Mrs. Banner needed lots of these syringes, which takes weeks to get after filling out paperwork. However, this self-administered syringe could save her life! One drawback is that icatibant is short-acting. It prevents you from getting intubated and a scar from slash tracheostomy by the ear-nose-throat surgeon in the ER, but it does not last. So, we also put in paperwork for the most expensive drug ever: replacement C1INH. This is pooled plasma from blood donors (*e.g.*, medical students who get $50 for donating blood), which is then concentrated for C1INH. It costs a staggering $500,000 per year for the rest of your life! I do not own stock in the company that makes it. For 82-year-old Mrs. Banner, she would be black-and-blue before Saturday, so we elected to only treat this lithe woman two times a week IV prophylactically until we can get her in the subcutaneous C1INH clinical trial while still supplying her with an abundance of the bradykinin B2 receptor blocker syringes.

The title of this chapter is apt, since Janus is the Roman god of beginnings or transitions, being two faced—looking to the future and the past (Fig. 1.4). In an instant, a normal appearance is radically changed unless you wait for the tincture of time or use pharmacologic agents to effect swift recovery from possible death. “Angie O’Deemer” is what you often hear over the phone when patients with diagnoses call for the first time—just like the “disease of sixty-five roses” or cystic fibrosis. As a final note, in the VA system computer, the diagnosis is hereditary angioneurotic edema.

FIGURE 1.4 Take my breath away

However, these patients are not neurotic or crazy. The fact that sometimes they resolve swelling before they get to the emergency department means the ER doctor has to be circumspect and must consider the correct diagnosis and consult with specialists, like myself, who are clinical adult and pediatric allergists/immunologists. These patients are not making this up! The term "angioneurotic edema" was coined decades ago before doctors understood the mechanism of swelling attacks in patients. You would be freaking out 80 years ago if you had recurrent attacks doctors could do nothing about. In fact, another patient with the same disease had apparent brain swelling manifested by abnormal behavior, so they admitted her to the psych ward where she intermittently screamed she had hereditary angioedema approximately every 10 min, until someone finally called the on-call allergist.

Mrs. Banner has not had an attack since she started intravenous C1 esterase inhibitor every 3 days; she now has lots of icatibant (bradykinin B2 receptor blocker) syringes for emergencies (Fig. 1.5).

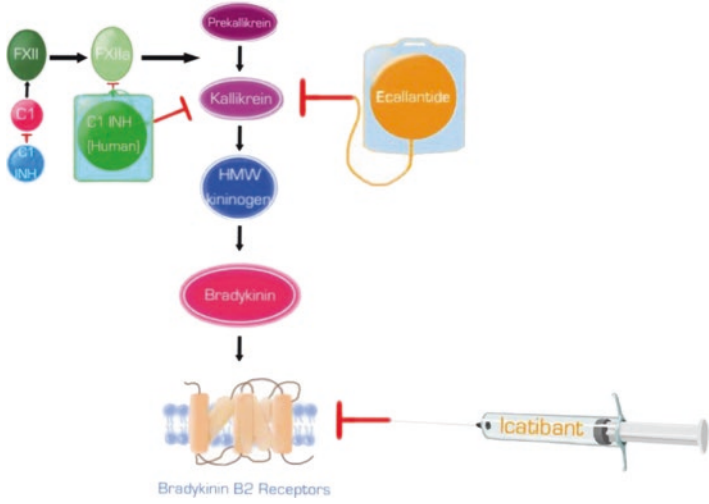

FIGURE 1.5 Pathways of complement with names of drugs blocking

Background/Salient Features of the Case

Hereditary angioedema is a rare disease that causes swelling, affecting hundreds of patients in the USA. Attacks of swelling can occur spontaneously [3]. Type I HAE entails low levels of the C1 esterase inhibitor protein from birth. Type II HAE is characterized by dysfunctional C1 esterase inhibitor protein. Type III HAE involves normal laboratory values but clinical swelling, often occurring in young women taking estrogen-containing oral contraceptives. We treat Types I and II with replacement C1 esterase inhibitor protein prophylactically and during attacks along with kallikrein and bradykinin inhibitors emergently, especially for airway closure.

These patients should not receive angiotensin-converting enzyme inhibitors (ACEI), which predispose even healthy persons to angioedema. In this case, over 82 years accrued before the patient had her first attack, which was concurrently associated with ACEI initiation. Her facial swelling

was associated with undetectable C1 esterase inhibitor levels and reduced function to 20% normal. Even between attacks, C4 levels were low. Lisinopril ACEI was discontinued and her swelling was attenuated with bradykinin B2 receptor blocker, yielding a more rapid recovery and less severity of swelling. C1 esterase inhibitor was subsequently started every 3 days intravenously by home care. We recently started her on subcutaneous C1 esterase inhibitor.

Diagnosis

Low C1 esterase levels and function in a setting of swelling confirm the diagnosis. Anaphylaxis, which is in the differential diagnosis, can be confirmed with a serum tryptase. HAE does not respond to epinephrine, antihistamines, or steroids.

Treatment

For acute attacks, a bradykinin B2 receptor blocker syringe administered abdominally limits swelling. Alternatively a kallikrein inhibitor does the same. In the emergency room, intravenous C1 esterase inhibitor can be used. Prophylactic C1 esterase inhibitor is given every 3 days.

Fast Facts

C1 esterase inhibitor and function levels are low in hereditary angioedema, but Type III HAE has normal values, with swelling often in the setting of using estrogen-containing oral contraceptives.

Bradykinin B2 receptor blocker or kallikrein inhibitor drugs attenuate attacks to buy time to get to the ER, whereas epinephrine, steroids, or antihistamines will not work.

Subcutaneous C1 esterase inhibitor obviates the use of intravenous lines prophylactically.

Test Your Knowledge

1. Which statement is false?

   (A) Brain angioedema with change in mental status and seizures does not occur in HAE patients.
   (B) You should not get pregnant if you take icatibant, and atrial natriuretic peptide levels are low/normal even during attacks [1].
   (C) Life-threatening throat closure is an indication for icatibant and kallikrein inhibitor.
   (D) Abdominal attacks are possible in HAE, leading to clinical nuances, which may be overlooked [4].
   (E) ADGRE2 gene is implicated in vibratory urticarial/angioedema [5].

   ANSWER: (A) Brain angioedema with change in mental status and seizures does not occur in HAE patients.

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Chapter 2
It's Happening Again Dr. Szema, Ahhh!

Anthony M. Szema

Vignette

A 36-year-old woman arrived to my office for the first time and, within minutes, started contorting her body in the waiting room. She screamed, "It's happening again Dr. Szema, ahhh!"

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FIGURE 2.1 Ms. Hummer arrived at the office with stiff muscles, a droopy right eyelid, and a demand for diazepam

Her arms went stiff at her sides and both legs were straight like a mummy or corpse in *rigor mortis*. Her body was horizontal on the armrests of two chairs. Levitation! She had a droopy right eye. Her shouting was loud; this freaked out one of the premedical students; he eventually used this experience to discuss his clinical exposure during an interview with the Stritch School of Medicine at Loyola University in Chicago.

We moved Ms. M.C. Hummer to an examining table and called 911. While we were waiting for the ambulance to arrive, her vital signs were fine—normal temperature, blood pressure, pulse, and oxygen saturation. Her muscles were stiff; her right eyelid was droopy (Fig. 2.1), and she screamed that she needed Val…eee…ummm. "I need Val…eee…ummm! Do you have any Val…eee…ummm? This is how to treat me!"

In the interim, she noted that there was a recent *Staphylococcus aureus* bacterial infection of her right eye in the past month and she had *Clostridium difficile* diarrhea whenever she missed a special medication. Her medical

record indicated a prior history of pneumonia, deep vein thrombosis or blood clot, bronchiectasis, or chronic infection in her airways. She also noted lung nodules were seen on CT scans of her chest in the past. She said she had depression and anemia. There was also an insulin pump on her abdomen.

For a young woman in her 30s, her pharmacopoeia was immense: (1) Warfarin, (2) Venlafaxine, (3) barbiturate + acetaminophen + caffeine, (4) Diazepam at 10 mg a day, (5) Simvastatin (20 mg), (6) baclofen, (7) Hydroxyzine, (8) bupropion, (9) cyclobenzaprine, (10) iron, (11) gabapentin, (12) losartan, and (13) pantoprazole. Ms. Hummer noted rashes with sulfa drugs and wheezing and rash with cats. She slept with a cat. Today she smoked half a pack of cigarettes and had done so daily since age 18. She readily agreed that as an oenophile her consumption was at least several alcoholic beverages a month. The patient was unemployed.

Ms. Hummer was a stocky woman in distress. Her right eyelid did not go up when I had her follow my finger above her head. Arm and leg muscles were stiff but not painful when we squeezed or palpated. She could feel sensation but did not kick her legs on command. Lungs and heart were clear and regular, respectively. My nurse and I agreed the insulin pump looked clean.

Paramedics arrived and did not have Val…eee…ummm or other benzodiazepine muscle relaxants; furthermore, I cautioned that my preference would be to defer in the face of lung disease and possible alteration of her respiratory drive. The drive to breathe is controlled by the brain, and in asthmatics, for example, giving benzodiazepines could knock out this drive and lead to cessation of breathing. Since we hardly knew anything about this patient within the 15 min that elapsed since she walked through the door, the EMS team scooped her up and sped to the emergency room.

So what was the diagnosis? Why did she need Diazepam? Was it appropriate to give a muscle relaxant, or, when the ER called later, they wondered if she was drug-seeking—were they right?

The special medicine Ms. Hummer mentioned earlier was intravenous immunoglobulin, which provides IgG antibodies to fight infection. Her levels were 398 mg/dl, a concentration

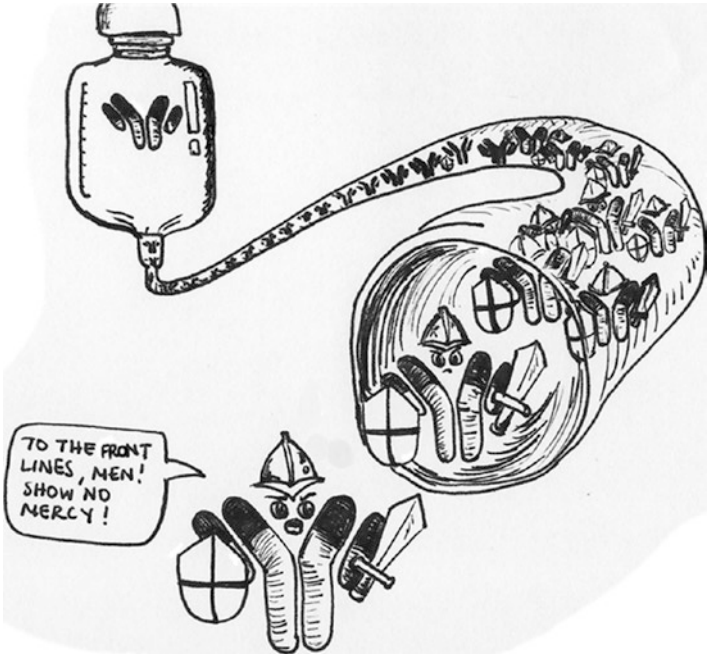

FIGURE 2.2 Crusaders of the lost defense

just below the lower limit of normal between 400 and 1600. Indeed, Ms. Hummer was recently infused, and as expected, the IgG4 subclass (IgG comes in four types: IgG1, IgG2, IgG3, IgG4) was characteristically low at 2.9 since exogenous infusion typically does not correct it. Similarly, her IgA was 37 and IgM 78—both low and expected. While a 398 is near the lower limit of normal after infusion, clinical judgment dictates a high enough dose as necessary to thwart infections. Often this is in the 1000 range (Fig. 2.2).

Ms. Hummer's waiting room problem was related to high levels of an antibody to glutamic acid decarboxylase (GAD). The anti-GAD antibody levels are normally between 0 and 5. Hers were over 250. Ms. Hummer's diagnosis is stiff person syndrome (SPS). This is a neurological disorder characterized by abnormal autoimmune antibod-

ies attacking the muscles. It was not related to being on a HMG-CoA reductase inhibitor, which can cause myopathy. For cholesterol medicines in this class, there are usually painful muscles, which are weak rather than stiff in the event of myopathy. Some of those patients take a supplement coenzyme Q with relief. For SPS, yes, you can treat the stiff muscles with muscle relaxants, so Ms. Hummer was right, though her muscles may have developed tolerance to the diazepam over time. Giving intravenous IgG may block pathogenic antibodies, but her levels were low. Moreover, active smoking not only predisposed her to infection but also likely led to increased catabolism of the protective IgG. So, I strongly urged her to stop smoking because it could literally kill her. The revved up liver she had from drinking alcohol did not help either. The way to eliminate the bad actor antibodies is to use a drug that targets B cells, the source of all antibodies. Rituximab is in order (Fig. 2.3).

The caveat, however, is that the patient's second diagnosis is a lack of IgG antibodies or hypogammaglobulinemia or common variable immunodeficiency. This predisposes to infections and would explain the ocular infection *and* lung diseases such as pneumonia and bronchiectasis [2]. What is warranted is to increase the IgG levels to supranormal (2000) so there is reserve when the B cells get targeted. These B cells not only make bad pathogenic antibodies but also good antibodies used to fight infection. We treat when the IgG is <50% normal (200 mg/dl) with infections, but we increase the levels to clinically rid infection. So the exogenous IgG can block the pathogenic bad actors and fight infection. Sounds easy! Maybe not. The eye myositis is inflammation of the eyelid sans infection. Ophthalmologists treat orbital myositis with steroids, but steroids weaken the immune system to predispose to infections. So in this case, we opted to wait for the IgG to do its job in the hopes of fixing the eyelid droop as well, fulfilling what we call in medicine Occam's razor.

Occam was an English philosopher during the Middle Ages. He said *pluralitas non est ponenda sine necessitate*, which is Latin for "plurality should not be posited without necessity." What this means to you and I is "always use the

Figure 2.3 Anti-GAD antibodies

simpler explanation." In medicine, it suggests to find a unifying single diagnosis for symptoms rather than lots of rare zebras. Here we have three zebras in one patient: (1) stiff person syndrome, (2) common variable immunodeficiency, and (3) orbital myositis. Diagnostic parsimony here suggests a flare of all three diseases due to ineffective immunoglobulin therapy: (1) noncompliance with IV IgG, (2) a low prescribed dose, (3) interference via tobacco and alcohol, and (4) recent infection throwing everything out of whack (Fig. 2.4).

Ms. Hummer received an increased IV IgG dose to boost her levels to 1000, and then months later, we increased it fur-

FIGURE 2.4 M.C.'s three zebras

ther to get her to 2000 in anticipation of going to Johns Hopkins for rituximab [1]. Prior to the Baltimore trip, she went to Aruba. Of course after 1 week in Aruba, what does one want to do? Stay in Aruba! So, after 1 week of eating, drinking, smoking, and scratching her abdomen on coral reefs snorkeling, she decided to stay for an additional week. What happened was that she missed her monthly IV IgG dose, developed pneumonia, and also had an abdominal wound infection at her insulin pump site. She spent her second week at an Aruba Hospital. On return, she spent even more time at a local hospital. When I visited the hospital Friday nights after my office hours, the charge nurses noted Ms. Hummer would sneak out to go to the cafeteria and returned reeking of cigarette smoke. They then prohibited her from leaving the ward floor. Finally, she was discharged from the hospital without infection.

Ms. Hummer has had high levels of IgG since then. She tried a subcutaneous version that is more of a depot form with

less peaks and valleys in her levels so it is not like the stock market. This smoother, sustained formulation does not require an IV so she does not get black-and-blue from ecchymoses of bruised blood vessels. Ms. Hummer did not want subcu because it caused bloating 1 day a month and made her look fat. She went to Hopkins. In their office she had an attack with stiffness and her oxygen saturation went from 100% to 80% (anything under 90% is bad). This suggests her airways got stiff and could not ventilate. They gave her one dose of rituximab without relief even though B cells were completely ablated and wanted to wait until her B cells increased to 0.05% before the next dose, in order to provide some modicum of safety. Then she came home. What happened was that prior to her next dose in Long Island, she went to our infusion center and they gave her an early dose. Miraculously, compared to all the times I saw in the emergency room or inpatient hospital stays on Friday nights after office hours, she showed up to our office with spunk and happiness. She was crying tears of joy and we were equally moved. With this second infusion early, she was *cured* after the infusion. She actually threw her walker across the room and jumped with joy!

Background/Salient Features of the Case

Two pneumonias in a young adult raise the suspicion for immunodeficiency. This clinical history, plus IgG levels at baseline less than 50% the lower limit of normal and after vaccination for bacterial antigens (Pneumococcal vaccine polyvalent, MMR, DPT) with a less than fourfold increase at 4 weeks, clinches the diagnosis. Repletion of IgG should be at a level such that infections do not recur, and often this may mean the upper limit or normal or higher. Peak levels post-doing and trough levels at the end of the month prior to the next dose are utilizing to stabilize dosing regimens, which start at 600 mg/kg q mo given intravenously. Preferably the subcutaneous route allows for smoother and higher levels via a depot reservoir in subcutaneous tissue. Weekly subcutaneous dosing has been supplanted by monthly SubQ Ig Infusion, though it is associated with bloating and

weight gain due to its volume. This is an unacceptable side effect for some women with hypogammaglobulinemia.

SPS requires eradication of pathogenic anti-GAD antibodies, yet rituximab may reduce IgG production due to B-cell elimination. Therefore, exogenous IgG is infused at supratherapeutic levels to provide a cushion [2].

Orbital myositis is often treated with prednisone, but its attendant immune deficiency risk and side effect profile unwanted in a diabetic make this a less likely long-term therapeutic option.

Diagnosis

SPS is a rare neurological disease. Gradually progressive profound muscle stiffness characteristically develops in the spine and lower extremities, with incipient stages often during times of emotional stress. In the case of our patient (*vide supra*), she was in the throes of a divorce and child custody battle. Most patients experience painful episodic muscle spasms triggered by sudden stimuli. Like our patient, Ms. Hummer, often there are other autoimmune disorders. Whereas many cases start in the mid-40s, our patient was in her late 30s with active disease concurrent with other autoimmune disorders. SPS responds to benzodiazepines. Physicians who are unaware of this disease may think that the patient is drug-seeking. EMG (electromyogram) needle will assist the diagnosis, and testing the blood for high levels of anti-GAD (glutamic acid decarboxylase) will confirm the diagnosis [5].

Orbital myositis is an inflammatory process primarily involving the extraocular muscles and typically affects young adults in their 30s, with a female predilection, as in our patient [3]. However, she had unilateral ptosis. This is the most common presentation for being acute and unilateral and responding to systemic corticosteroid therapy. Typical findings in other patients include proptosis, swollen eyelids, orbital and periorbital pain, ocular movement impairment, diplopia, and conjunctival hyperemia. However, chronic and recurrent cases may involve both orbits. Many inflammatory, vascular, neoplastic,

and infectious conditions that affect the extraocular muscles and other orbital tissue can mimic orbital myositis. Differential diagnoses include thyroid-related eye disease, other orbital inflammatory processes (nonspecific idiopathic inflammation, vasculitis, and sarcoidosis), orbital cellulitis, and orbital tumors. With common variable immunodeficiency or during treatment for SPS, recurrent use of steroids should be minimized. In refractory, chronic, or recurrent cases, steroid-sparing agents, immunosuppressants, or radiation therapy may be indicated. We opted to infrequently treat the recurrent ptosis.

Treatment

IV IgG and plasmapheresis—but not both simultaneously—have been used for SPS. The same IgG treats common variable immunodeficiency. For orbital myositis, steroids or immunosuppressants may be helpful.

Three Bullet Points

- Physical therapy and abrupt withdrawal of benzodiazepines may exacerbate SPS, so emergency room physicians should not miss this diagnosis.
- High doses of IgG administered prior to B-cell depletion with rituximab are necessary to provide a robust immune system cushion.
- Emotional stress is often associated with attacks of SPS.

Multiple Choice Question

1. Which statement is false?

   (A) Myositis-specific antibodies may help predict response to treatment in orbital myositis.
   (B) Cigarette smoking does not affect IgG levels.
   (C) Subcutaneous weekly dosing of IgG leads to less bloating vs. monthly administration.
   (D) It is incumbent to administer supratherapeutic doses of IgG prior to rituximab for depletion of pathogenic anti-GAD antibodies in SPS.

   ANSWER: (B) Smoking reduces IgG levels.

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Chapter 3
A Man with Metal Lungs

Anthony M. Szema and Marc Kostrubiak

A.M. Szema (ed.), *Unusual Diseases with Common Symptoms*, https://doi.org/10.1007/978-3-319-58952-7_3

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Vignette

Less than 18 months after saving civilians as a first responder at Ground Zero, Manhattan, on September 11, 2001, Mr. Stark was a senior quartermaster at Camp Anaconda, Balad, Iraq, as part of Operation Iraqi Freedom. In both instances, he was exposed to unusual particles in the air from explosions, fire, as well as sandstorms in Iraq. Mr. Stark occasionally smoked cigars and was exposed to significant amounts of smoke from burn pits. These pits operated daily and used benzene-laden JP-8 jet fuel to burn garbage, including plastic water bottles, polystyrene foam, medical waste, computers,

and unexploded munitions [3]. Burning released toxins and products of incomplete combustion visible as the black smoke given off by the pits; they called it "Iraqi Crud". While he did not seem to have any setbacks after being a 9/11 first responder, after his 15-month tour in Iraq, he found himself consistently coughing, with pain in his chest wall for several years. He underwent spirometry to measure his lung function shortly after returning from Iraq in 2004. When he inflated his lungs to total lung capacity, and then breathed out forcefully, doctors found that his forced expired volume ratio in 1 second divided by his forced vital capacity (FEV-1/FVC) was much lower than expected (86% vs. 103%). These spirometry data suggested that he was suffering from a restrictive ventilatory defect rather than an obstructive ventilatory defect. Despite his difficulties, his DL_{CO}, which measures gas transfer across his alveoli (air sacs), was 86% and was well within the normal of greater than 80%.

Mr. Stark was fed up with his symptoms, which included significant wheezing, and returned to the doctor in 2009 for more testing. A chest X-ray showed hazy infiltrates throughout his lungs, supporting a pathological process (Fig. 3.1). In 2010, he once again returned for more spirometry and still scored 85% on his FEV-1/FVC, when 111% was expected. His wheezing was not alleviated despite a 6-month course 20 mg/day of prednisone, a steroid used to decrease inflammation. Despite the prednisone, his DL_{CO} was only 61%, a large decrease from 2004, suggestive of reduced gas exchange, a possible harbinger of fibrosis. Additionally, as seen by X-ray, he still had significant lesions in his lungs where swelling had not improved. When Mr. Stark was instructed to do jumping jacks, he stopped after only doing 15. In that time his blood oxygen saturation level decreased from 99% to 97%. Despite not having been exposed to any unusual air in the previous 6 years, his lung function had significantly deteriorated since coming home from Iraq. His total lung capacity had dropped a liter from 5.73 L in 2004 to 4.78 L in 2010, a drop of 17%.

In an attempt to find the root of his problem, an open lung biopsy was performed in 2009 after finding persistent ground glass opacities via serial chest CTs. Pathologists at Walter Reed

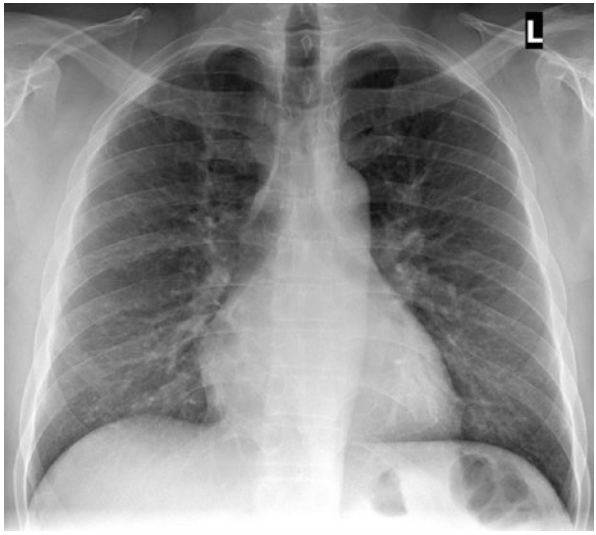

Figure 3.1 CT scan of Mr. Stark

Medical Center first diagnosed him with nonspecific interstitial pneumonitis (NSIP). However, with more circumspect examination, we detected narrowing of his distal airways and thickening on his pulmonary artery on the slide. This is consistent with a diagnosis of constrictive bronchiolitis with vascular remodeling. Due to his unique exposures in both Iraq and his time as a 9/11 first responder, we were concerned that he had inhaled metals. Our suspicion was confirmed when we stained his lung sample for iron. After our shocking discovery, the sample was taken to Brookhaven National Laboratory. His sample was examined using micro-X-ray fluorescence, a technique where a sample is bombarded with X-rays to determine its elemental composition and to determine where exactly the metals were deposited in the lungs. Was it in the airways? Or the blood vessels? Or perhaps in the lymph nodes or even the lung parenchyma itself?

We found titanium in his lungs! The titanium was bound to iron in a fixed 1:7 ratio that our geologist colleagues told us was very rare in nature. The locations of these titanium and iron clusters corresponded to the spots seen via microscope, suggesting that they may be dust particles (Figs. 3.2 and 3.3).

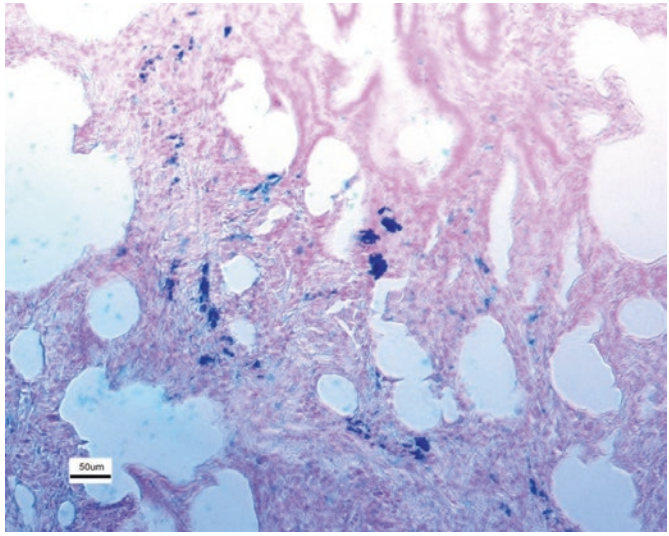

FIGURE 3.2 The blue-stained iron in Mr. Stark's lung is clearly visible

Based on the elemental proportions and his history in Iraq, it is likely that Mr. Stark was suffering the effects of having inhaled anthropogenic metals from exploded Humvees and military equipment. We also found calcium, sulfur, and zinc in a uniform distribution. Interestingly, titanium, iron, copper, chromium, and nickel were found in small discrete clusters. Years after his exposure, these metals continued to assail his lungs and decreased his ability to breathe (Figs. 3.4 and 3.5).

Background/Salient Features of the Case

The increase in respiratory illness among combat soldiers who have been deployed to the Middle East has been thoroughly documented [1–4]. In fact, 13% of all army medic visits in Iraq are for new acute respiratory illness [3]. These symptoms are clearly unique to the location, as spirometry is used ten times more often on personnel who served in the Middle East than for those in other regions [2, 3]. These service members have a distinctly increased chance of developing asthma. Service

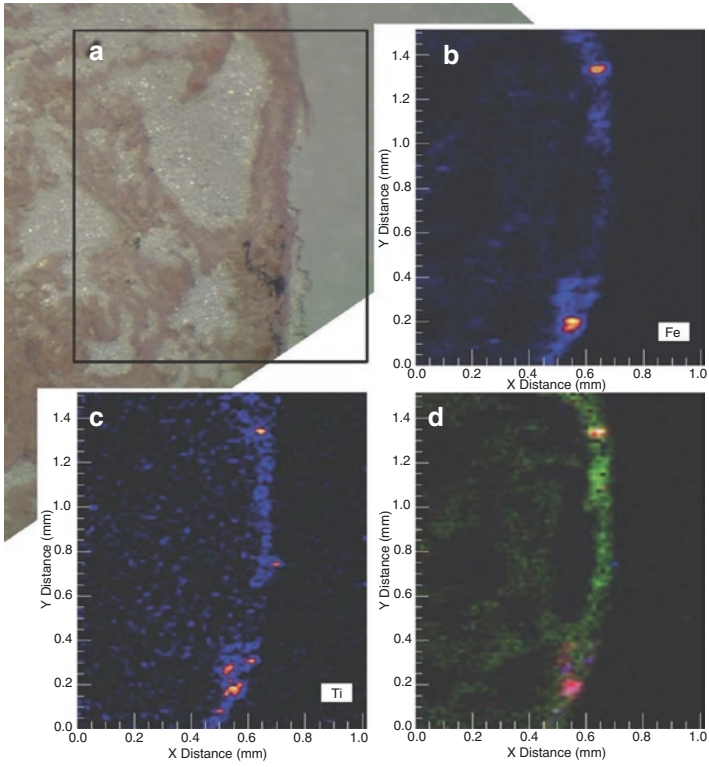

FIGURE 3.3 This four-panel image shows a section of his lungs (**a**) imaged with a light microscope, and X-ray fluorescence of (**b**) iron, (**c**) titanium, and (**d**) all three metals

men and women in the Middle East may experience a number of adverse environmental exposures including burn pits, sandstorms, allergens, and improvised explosive devices (IEDs) and their resultant shockwaves [2]. IEDs alone accounted for just over a third of combat injuries in Operations Iraqi Freedom and Enduring Freedom. IEDs create different airborne particulate than other munitions as they tend to be small but directly impact military vehicles—which often contain the unique ratio of titanium and iron found in Mr. Stark's lungs. In an effort to study the effects of exposure, the passage of the Open Burn Pits Registry Act in 2013 has mandated the

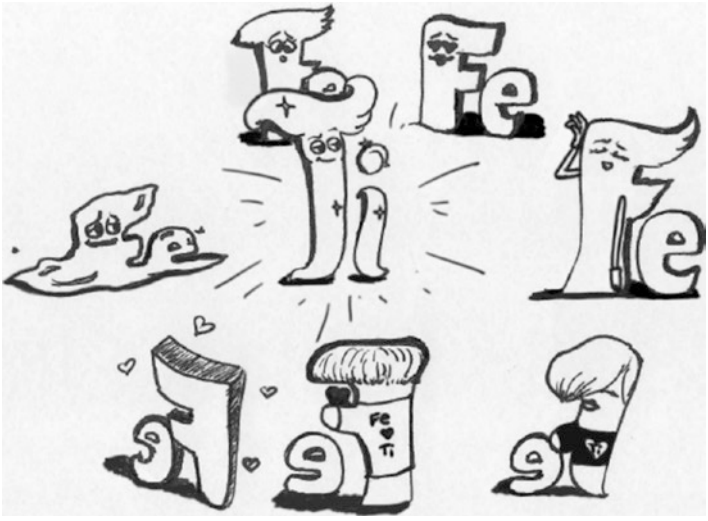

FIGURE 3.4 Like flies to honey: iron drawn to titanium

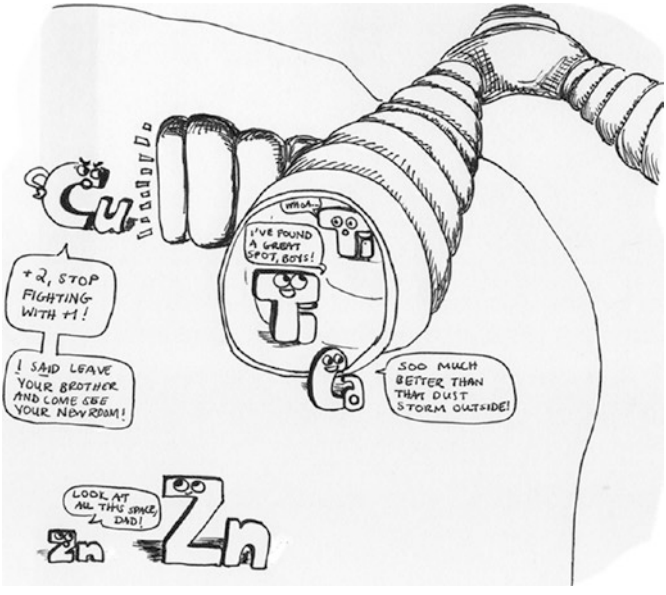

FIGURE 3.5 New tenants

collection health information from veterans and active duty service members [3, 4]. Notably, there does not seem to be a strong link between length of deployment and severity of symptoms suggesting that the hazards of just one deployment may result in severe pulmonary deficits [3, 4].

As previously noted, burn pits routinely contained a variety of materials with toxic combustion products. The exposure to these pits is notably similar to the airborne particulate found near the World Trade Center after 9/11. Firefighters and other rescue personnel with extensive time at ground zero were found to have hyperresponsive airways via methacholine challenge—a test on the airways commonly used to diagnose asthma, using methacholine to induce constriction and measure the resulting response severity. The first responders also tended to lose about 500 mL of lung functioning. Moreover, children with asthma living in the area suffered worse symptoms and had to use more medications.

Finally, sandstorms in the Middle East may be another vector for dust and metals to enter the lungs. The EPA guidelines for exposure to particulate recommends a maximum of three yearly exposures of 150 $\mu g/m^3$ of dust, whereas Iraq averages over 100 days a year of over 200 $\mu g/m^3$ and 5 days per year over 1000 $\mu g/m^3$ of dust exposure. The particulate in these storms has been found to upregulate proinflammatory cytokine IL-2 and directly promote pulmonary fibrosis [2, 4]. Thus, just being present in the region puts people at risk of developing symptoms akin to Mr. Stark's. Overall, Mr. Stark was exposed through a variety of vectors to airborne particles that accumulated in his lungs. While the exact ramifications of his particular exposures remain uncertain, it is clear that they had significant adverse pulmonary effects, including promoting fibrosis and asthma-like reactions.

Diagnosis

Mr. Stark was diagnosed with interstitial pneumonitis and pulmonary fibrosis, caused by his exposure to metals and their accumulation both diffusely and in hot spots throughout

his lungs. Diagnosis can be significantly improved by instituting use of spirometry before and after deployment to monitor for changes. Additionally, echocardiograms before and after exercise can indicate any evidence of pulmonary hypertension that need to be addressed. Finally, impulse oscillometry can provide significant data in assessing pulmonary function, and monitoring changes in patients is of utmost importance. Altogether, these methods can show whether a patient's pulmonary function is continuing to decline after their exposure has long ended and can provide crucial information for further management and care.

Treatment

Unfortunately, there is presently no cure for Mr. Stark's ailment; however treatments are being actively investigated. In the extreme case where pulmonary function continues to decline with progression to full fibrosis, transplants will circumvent the problem. Of course, transplants carry their own list of dangers and complications and thus remain a last resort option [5].

Despite the lack of a universally accepted treatment regime, being diagnosed is important for affected individuals. Because of the unique source of these particular metals, military equipment, diagnosing soldiers and ensuring that they do not redeploy to active war zones is crucial to prevent further accumulation in their lungs. Diagnosis allows for informed monitoring of pulmonary and associated functioning. Echocardiograms before and after exercise are indicated to monitor for pulmonary hypertension. Furthermore, general monitoring can keep the patient and physician aware of progression to decreased serial diffusion and treat this problem accordingly [5]. Due to the decrease in pulmonary function, vaccines for allergic reactions are important, as allergic reactions can be particularly harmful for patients with compromised lungs. Finally, proper specific diagnosis gives patients the opportunity to enroll in clinical trials. Currently two major drugs are being investigated—RuX (largely consisting of alpha-lipoic acid) and a nano-suspension of vasoactive intestinal peptide (VIP). VIP

may be able to provide preventative benefits as well as decreasing any pulmonary hypertension that arises. RuX, while still in mouse trials, appears to completely prevent the formation of fibrosis in the lungs when exposed to these particular metals. While both of these remain investigatory, being diagnosed and potentially joining a clinical trial closer to symptom onset can clearly be of utmost importance for affected veterans.

Fast Facts

Mr. Stark was exposed to unique metals in proportions that suggest anthropogenic sources, likely from both his time in Iraq and as a 9/11 first responder.
Metal accumulation in the lungs can cause asthmatic symptoms, fibrosis, and pulmonary hypertension.
While there are no drugs commonly used to treat these symptoms, diagnosis is important for monitoring and the potential to enroll in a clinical trial using either RuX or VIP.

Test Your Knowledge

1. Which statement is true?

   (A) Burn pit exposure is linked with a high degree of cobalt accumulation in the lungs.
   (B) RuX (alpha-lipoic acid) can prevent pulmonary fibrosis from metal accumulation.
   (C) Unique proportions of iron and titanium in the lungs of veterans suggest exposure to vaporized Humvees and other military equipment.
   (D) DL_{CO} is an accurate method of measuring the rate of CO_2 leaving the alveoli and exhalation and thus indicate pulmonary function.

(E) While sandstorms stir a large amount of particulates into the air, the amounts common in the Middle East have been deemed to be safe by the EPA.

ANSWER: The answer is B. Rux has been shown to completely prevent the formation of lung fibrosis after metal exposure in mouse models.

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Chapter 4
The Man Who Loved Beer, but Malt Did Not Love Him Back

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A.M. Szema (ed.), *Unusual Diseases with Common Symptoms*, https://doi.org/10.1007/978-3-319-58952-7_4

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Vignette

Mr. P.J. had a beer last weekend (alcoholic libation named after a brightly-colored fruit) as per his weekly routine to relax at home on Friday nights. Within minutes, he got itchy, his face turned red, and his head swelled up like a balloon! He felt as if he could not breathe; Mr. P.J. dashed to the kitchen to get a diphenhydramine in the cupboard. Ten minutes after taking his antihistamine, he took a selfie, which still showed a red, puffy face. Then he had diarrhea; his eyes swelled shut.

Mr. P.J. started drinking beer at age 18 and preferred the taste of light ales and pilsners. He denied any prior history of food allergies. His family would drink together every weekend. This reaction to beer repeated itself on subsequent occasions and was sometimes associated with consuming food with beer. None of his family members had

ever experienced anything similar. He did not have other allergies, asthma, or anything that could explain his symptoms. In fact, he did not take any medication whatsoever! There was baseboard heating at home and the house was not dusty. He was otherwise healthy, without a runny nose or coughing. Mr. P.J. slept with dogs yet denied wheezing or rash when exposed. He was a construction worker.

When the doctor examined him, he was normal. Mr. P.J. was not in distress and all of the symptoms had resolved. There was no stridor or high-pitched sounds in the neck when he breathed in. Suspecting a food allergy, we decided to do percutaneous skin prick testing. Mr. P.J. picked 30 foods to test and they all came back negative! In your skin, there are mast cells full of histamine, just like the chips in a chocolate chip cookie. When you have a rash, you are releasing histamine. Even when you have allergic asthma and then wheeze when grass pollen is around, you release histamine. So, for Mr. P.J. the next step was to have him bring in beer to the office. We cleaned off his back and attached bottle caps to a piece of paper to serve as a legend. Then I lined up bottles of beers such as Central Body Libation, Crown Beer Diet Malt Beverage and alcoholic libation named after a brightly-colored fruit. Mr. P.J. brought in the ingredient labels. Only one beer had corn in it. The others all had malt as the unifying common ingredient. I dropped one drop of each beverage in addition to salt water (saline) as a negative control (Fig. 4.1). In addition, I scratched histamine on the back. Instantaneously, there was a rash to each beer (Fig. 4.2)! Fruit beer, sans real fruit, was the worst. Mr. P.J. had anaphylaxis to beer! We gave him a medic alert bracelet and an epinepherine auto-injector. I instructed him to consume alternative beverages (Fig. 4.3).

In German literature, they can detect prolamin proteins in Weissbier, which is a light-colored top 50% malt beer [1]. These proteins are immune-responsive to antigliadin IgA antibodies from patients with celiac sprue. So, now we had to check Mr. P.J. for celiac sprue. While he has not had symptoms, patients with celiac sprue, when they eat gluten—the thick sticky stuff left when you rinse pizza dough under

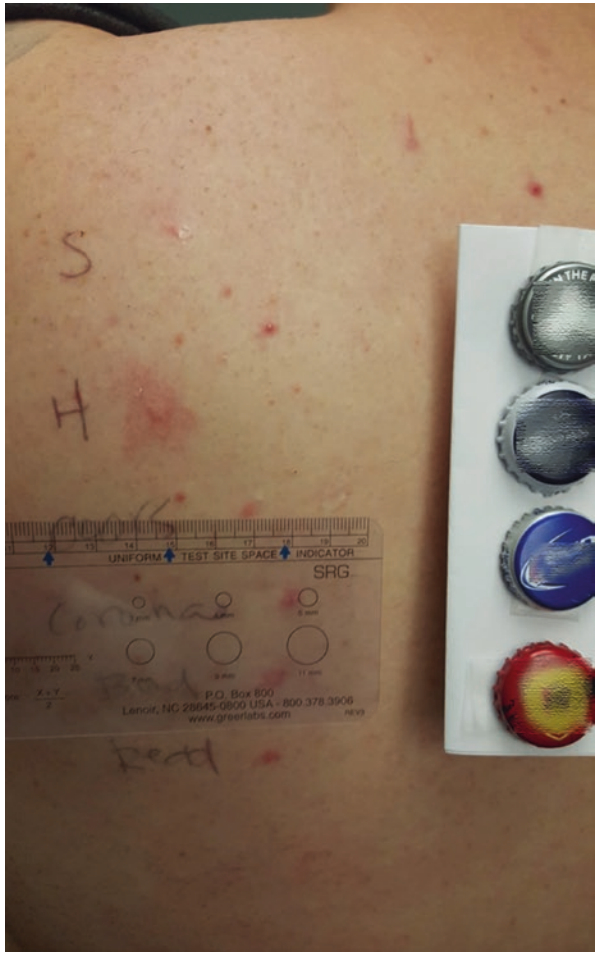

Figure 4.1 Five minutes after skin testing, one beer elicits no reaction but others have positive results

water—get stools that stink and float, leading to loss of fat-soluble vitamins (A, D, E, K), so they cannot see, have brittle bones, lose antioxidants, and cannot clot under the worst circumstances (Fig. 4.4).

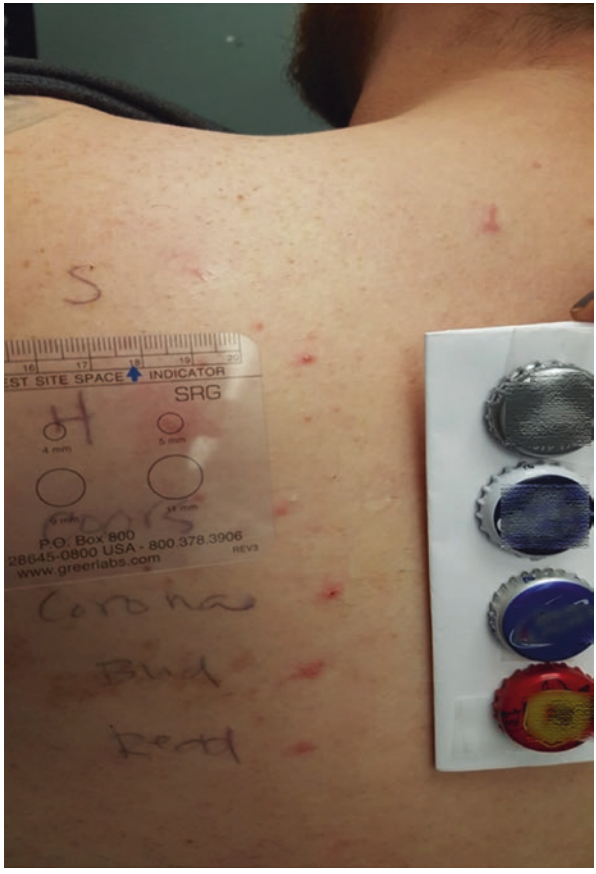

FIGURE 4.2 Fifteen minutes after skin testing, saline remains negative as well as beer 1 but the rest are red, raised

So, having horrible headaches and hangovers after beer may not be simply related to excess consumption in a patient like Mr. P.J.—it could be beer allergy. Another concern is something called rapid acetylation of alcohol dehydrogenase, which typically affects Asians as well as others and means that alcohol is quickly metabolized to toxic by-products and

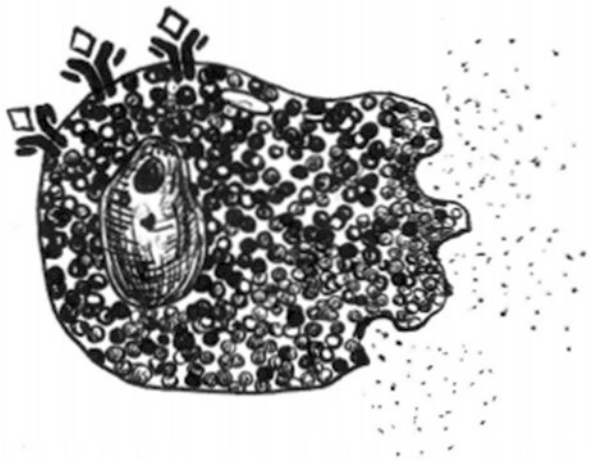

FIGURE 4.3 Mast cell activation

makes people flush with a glass or two of beer [2]. In contrast, those who are slow acetylators—"I can hold my liquor" persons—may simply mean that they are slow acetylators of alcohol dehydrogenase and take longer to accumulate toxic by-products. Still, drinking is bad for your liver, among other organs, *even if* you are a slow acetylator.

The moral of this story is that not all reactions to alcohol may be due to excessive, college-level gallon consumption. You may have allergies to beer!

Background/Salient Features of the Case

Anaphylaxis, severe allergy to beer, is diagnosed on the basis of clinical history of symptoms on ingestion and evidence of allergic antibodies which may be detected by percutaneous skin prick testing to beer and/or IgE to implicated ingredients in serum [4, 5]. Avoidance is the best policy. Western blotting to certain proteins has been described in the literature among affected persons.

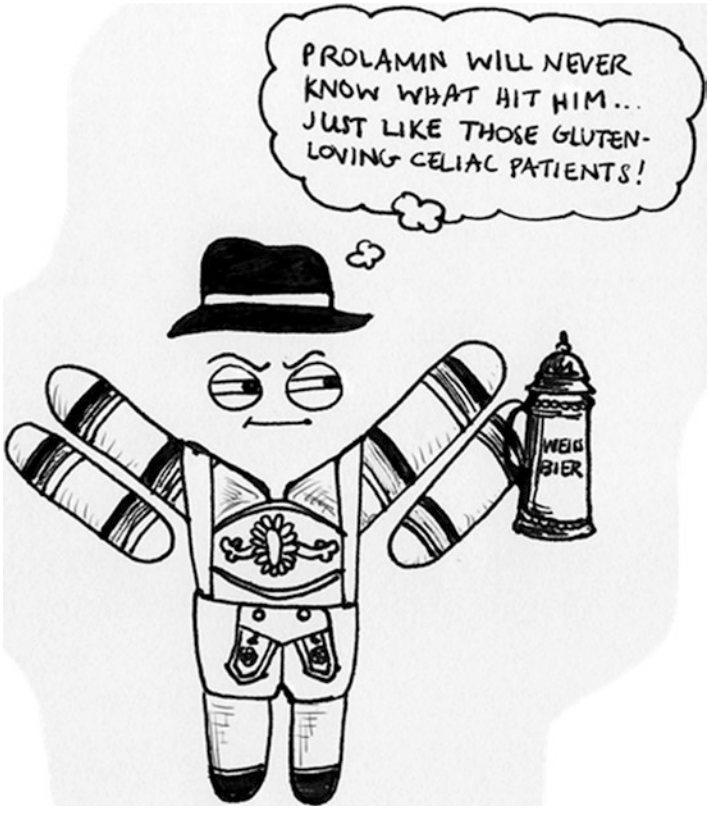

FIGURE 4.4 German spy

Diagnosis

Percutaneous positive skin prick tests with a negative control and a positive control correlated with symptoms on ingestion are critical. Blood IgE may be less sensitive.

Treatment

Avoidance is the best policy. Immunotherapy for food is not available. Antihistamines do not reliably prevent anaphylaxis.

Fast Facts

Beer shock is real in susceptible persons, diagnosed with skin testing.
Certain ingredients such as malt may be implicated and are found in different amounts depending on the brand of beer [3].
It may be possible to tolerate cooked beer, as in beer-battered fish, since heat denatures proteins.

Test Your Knowledge

1. Which statement is true?

   (A) Sulfites are found only in red wine and not beer.
   (B) Cooking beer may potentially reduce risk in those with allergy.
   (C) Beer anaphylactic shock is not real.
   (D) Malt may be a common ingredient, which varies in concentration depending on the type of beer.

   ANSWER: (B) Some patients may tolerate a heat-labile allergen if it is cooked. However, if a patient is allergic to a heat stable allergen, cooking may not help.

   (D) is also true. Malt is a key ingredient in beer and amounts vary. However, if you are allergic to malt, even small amounts can induce anaphylaxis.

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Chapter 5
Anaphylactic Shock to Ribeye

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A.M. Szema (ed.), *Unusual Diseases with Common Symptoms*, https://doi.org/10.1007/978-3-319-58952-7_5

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Vignette

Along the edge of an island by a creek, an 87-year-old man named C.P. dropped a bone-in ribeye on the mesquite-fired grill with salt and pepper. As he ate his first bite of medium-rare seared juiciness, his chest tightened and he was short of breath. Feeling like he was on the brink of death, he collapsed in the forest! Unfortunately the semi-remote place, Shelter Island, he was on did not have a bridge. The only ferry stopped running at 11 p.m. You had to call the ferryman to get out. You had to pay the ferryman to get to the other side. No helicopters can land there safely because it is wooded. The EMS team gave him epinephrine 0.3 mg straight through his pants in his thigh muscle above the kneecaps every 5 min. These interventions did not work. His blood pressure remained low at 80 systolic. The EMTs began sweating, and started an

Anaphylactic Shock to Ribeye

FIGURE 5.1 Collapse in front of the forest

FIGURE 5.2 Epinephrine, stayin' alive, stayin' alive

intravenous line with 0.9% isotonic saline to replenish his fluid status, which was compromised when the inflammatory cytokines were released with anaphylactic shock. After much consternation, Mr. C.P. arrived at a big U hospital. The doctors took away his menu of meat. The next morning, he had cereal and his head swelled up bigger than a balloon! I received a frantic phone call from the hospitalists shortly after he left the intensive care unit. What did he pour in the bowl? Milk, of course! That clinched the diagnosis (Figs. 5.1 and 5.2).

Mr. C.P. was no spring chicken. He was in an iron lung ventilator in 1936 for polio and used a walker since then. He had a stent for coronary artery disease and an ablation for atrial fibrillation related to cardiomyopathy. The cardiologist was planning on using apixaban, a newer blood thinner. He sur-

vived bladder cancer, lung cancer, and a pulmonary embolus or blood clot to the lung. His prostate was enlarged and he had reflux from all that barbecue sauce. He had arthritis.

Surprisingly, Mr. C.P. was on few medications, like aspirin and clopidogrel and a beta-blocker metoprolol, hydrochlorothiazide, and prednisone, a steroid. He smoked two packs of cigarettes per day for 30 years, but then quit for 30 years. Mr. C.P. was a retired teacher. Physical examination revealed nothing. No murmurs, no swelling, no bites. His lungs were clear but his chest showed an old thoracotomy scar.

So, what was the diagnosis? Well, to start with, Shelter Island is a wooded mid-Atlantic area containing a large population of ticks, especially in the summer. During peak barbecue season, ticks come out for their blood meal. One tick, in particular, has a name that is paradoxical. It is called the lone star tick. While this tick may sound like she or he is from Texas, actually, lone star is an East Coast resident, slowly migrating west. The lone star tick, a deer tick, bites and retrieves mammalian carbohydrate antigen from the deer. Indeed, a critical point is that the deer tick has now ingested α-1,3-galactose. For the lone star deer tick, this is no big deal. Nevertheless, for Mr. C.P., this poses a problem. When the tick now bites smoky-smelling Mr. C.P., who cannot run away quickly, the α-1,3 galactose gets transmitted from the deer to the tick to the human. Mr. C.P., despite his infirmity, has a robust immune system and manufactures allergic IgE antibodies against the α-1,3 galactose. The next time Mr. C.P.'s body sees this conserved mammalian carbohydrate—steak, burgers, and meatloaf—the immune system is primed to go and has capacity to rapidly make more IgE to α-1,3-galactose. This leads to anaphylaxis—the most severe, life-threatening reaction. Since milk contains glucose + lactose = galactose, there is cross-reactivity with the mammalian protein α-1,3-galactose. Therefore, Mr. C.P. cannot eat meat, pork, steak, or drink milk. Nevertheless, he can eat eggs, chicken, and turkey (Fig. 5.3).

Mr. C.P. had elevated α-1,3-galactose IgE levels. The next time he snuck in a cheeseburger, he closed up his throat, had

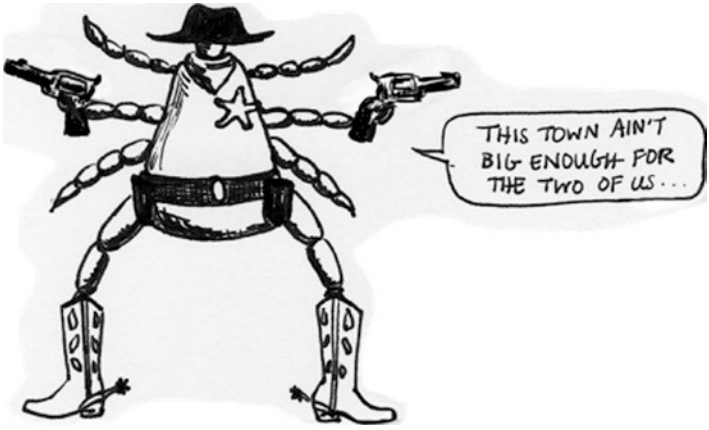

FIGURE 5.3 Lone star tick

facial swelling, and went to ground. The epinephrine did not work again. Fortunately, this time we prepared by special ordering a medicine you cannot get at local pharmacies. Although it is FDA-approved, it is so expensive; the insurance companies require a stack of paperwork for a $10,000 syringe. We required this syringe since epinephrine works by turning on beta-receptors, but Mr. C.P. was on metoprolol—a beta-blocker. The special medicine is a bradykinin B2 receptor blocker. FDA-approved for a rare genetic form of throat closure, it also is given for those with so-called hereditary angioedema type III with normal values and persistent swelling. Mr. C.P. consistently has not benefited with epinephrine but has responded to the bradykinin blocker with significant attenuation of swelling. To complicate matters further, apixaban, requested by the cardiologist, contains lactose. So, we suggested to the cardiologists to give the first few doses in the hospital setting to see how he does. Fortunately, he has not been re-bitten, he has avoided ticks, and, over the course of a year, his antibody levels reverted to near normal. He snuck in one solitary meatball on one occasion and one slice of ice cream cake on another without dire consequences. He is now a happy man (Fig. 5.4).

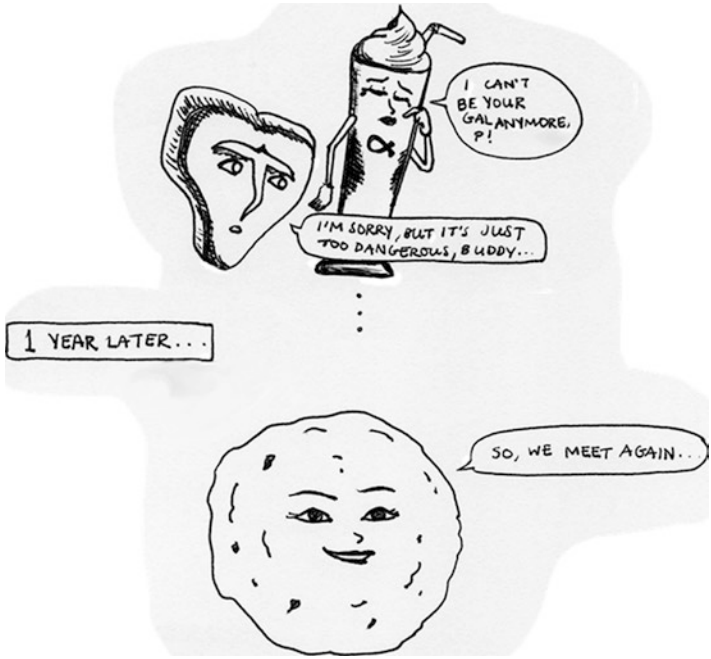

FIGURE 5.4 Old friends

Background/Salient Features of the Case

More likely a disease of endemic areas with deer—Eastern Long Island vs. New York City—and migrating to the rural west, α-1,3-galactose transmitted by the lone star tick may lead to life-threatening IgE-mediated reactions, warranting avoidance of mammalian foods such as meat, milk, cheese, and ice cream [1–3]. Fowl, however, are spared since eggs are nonmammalian. An epinephrine pen (0.3 mg intramuscularly) is critical with activation of the emergency response system—dialing 911. A medical ID bracelet will alert responders to the condition. In some patients, the antibody may wane,

allowing them to tolerate limited amounts of food, *i.e.*, one meatball or a slice of ice cream cake. Caution is advised with lactose-containing tablets. An oral challenge under supervised conditions is recommended.

Diagnosis

An appropriate clinical history relies on a tick bite in an endemic area with deer. There is a subsequent temporal association with intolerance of mammalian foodstuffs such as steak, milk, and ice cream. Diagnosis hinges on a positive IgE to α-1,3-galactose and exclusion of other causes of anaphylaxis such as a cKit mutation in mast cells. Positive skin prick tests to food may be associated but often may require testing with fresh food, such as uncooked meat. Blood component testing to foods such as milk may be positive.

Treatment

Therapy for anaphylaxis includes epinephrine, resuscitation with isotonic fluids, and maintenance of an open airway and respiratory and circulatory systems. In severe cases, patients may not even tolerate cooked meat and must adjust their diet.

Fast Facts

- Lone star deer ticks transmit α-1,3-galactose to humans who may develop IgE-mediated anaphylaxis to mammalian proteins such as meat and milk products.
- Chicken, turkey, and eggs are nonmammalian and are unaffected by α-1,3-galactose allergy.
- Lactose-containing medications possibly may pose a risk and should be test challenged.

Test Your Knowledge

1. Which statement about α-1,3-galactose allergy is false?

   (A) Well-done steak cooked over a grill is safe but hamburger on a flattop is not.
   (B) Pancakes are safe with or without eggs.
   (C) The same tick may transmit Lyme, *Babesia*, and *Ehrlichia*.
   (D) Zika virus is transmitted by *Aedes aegypti* mosquito and is not yet known to be co-transmitted with α-1,3-galactose.

   ANSWER: (A) Both grilled steak and hamburgers on a flattop pose a risk.

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Chapter 6
When Good Grades Go Bad

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Vignette

Mr. Fizz is a boy just like any other: athletic, energetic, and studious. He is his Grandma's pride and joy—always the first to give him rewards for his good work at school. The more he was rewarded, the harder he worked in school. Pretty soon, he began to work longer and longer nights, as his schoolwork became more demanding and his rewards became even sweeter. Grandma began presenting him with liters of a Highly Caffeinated and Carbonated Beverage with Excess Sugar and Citrus Fruit (HCCBESCF) in reward. Pretty soon, this fizzy delight began to act as his driving force. He needed to not only fit in time to do his school work, but he also wanted to have a little fun on the side too—if only he could stay up a little later (Figs. 6.1 and 6.2).

His mother then began to notice her son's increased coughing and wheezing. His plan was sound, and yet his health began to hamper this flawless logic; after all, we are only human, aren't we? I can only imagine the possibilities if we were all able to gain unending, superhuman focus and endurance. The magic of caffeine! But, sadly his invincibility could not last forever. He kept pushing himself night after night to do even better, even though he was also becoming increasingly jittery and began to feel chest pains along with his coughing. His strength had gotten him so far, but his health was getting much worse. His unknowing mother began to increasingly worry, and for fear that he was having an aller-

Amount of caffeine in popular drinks		
Item	Serving size	Caffeine (mg)
Black coffee	12 oz	260
Black tea	8 oz	30–80
Soda	12 oz	30–70
Red bull	8.3 oz	80
Chocolate bar (Dark)	1.45 oz	20
NoDoz caffeine tablets	1 tablet	200
Excedrin migraine	1 tablet	130

FIGURE 6.1 Everyday drinks and snacks may pack more of a caffeine punch than you realize

gic reaction to something, she rushed him off to Dr. Szema (Fig. 6.3).

Upon learning of his symptoms, the case seemed to be a challenging one indeed. Looking for further evidence, we asked about his lifestyle and if there were any recent changes in his diet. Looking under the surface, it was clear that it all boiled down to drinking way too much HCCBESCF. This "HCCBESCF overdose" left his body chalked full of sugar and caffeine and unable to cope with it. He was going through shock, dehydration, and no doubt a horrible imbalance of hormones. He was told to immediately stop his HCCBESCF binges, and as expected, his symptoms soon disappeared. Although this is a strange case for an athletic high school student, large amounts of college students are exposed to the dangers of caffeine overdose everyday (Fig. 6.1). Mr. Fizz is

FIGURE 6.2 Granny's pride and joy

just one of the many students who feel the power of caffeine and yet remains unaware of its detrimental side effects when abused. Mr. Fizz is now able to continue his schoolwork without a problem, but what risk lies just around the corner when Grandma comes to visit? (Fig. 6.4)

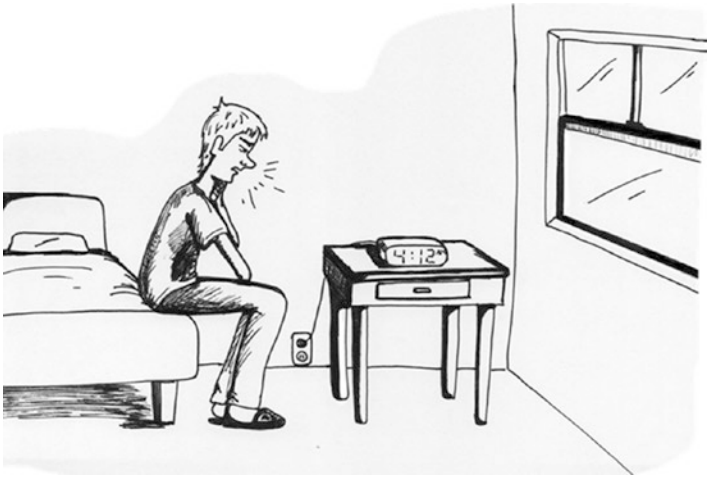

FIGURE 6.3 Midnight disturbance

FIGURE 6.4 "But Granny, what big eyes you have…"

Background/Salient Features of Case

So what is this uniquely named disease—HCCBESCF overdose? Well, HCCBESCF contains a stimulant, caffeine, and like any drug, it should be respected and not abused. Mr. Fizz failed to limit his intake and, as a result, experienced what is called a "caffeine overdose," or intoxication, due to the overconsumption of the recommended 400 mg limit (for adults)—and excess caffeine in the body can be toxic [1]. Although the death tolls of overdose are relatively low per year, a couple thousand people are sent to the hospital each year due to intoxication [2]. The rates of hospitalization, however, are highest among individuals younger than the age of 20 [3].

Caffeine overdose results in the overstimulation of the central nervous system, and symptoms of this condition are similar to overdose of other stimulants: breathing trouble, changes in alertness, confusion, hallucinations, fever, diarrhea, convulsions, irregular heartbeat, muscle twitching, increased thirst, sleeping trouble, and vomiting [4]. These symptoms can vary in intensity, and not all may be present in the individual suffering the overdose.

How does caffeine allow a person to stay awake? Let us look at two situations and some biological processes (in the central nervous system, CNS):

1. Mr. Fizz is awake and alert and has yet to consume any caffeine. He has a small amount of adenosine (a neuromodulator in the central nervous system neurons) → (time) → accumulation of adenosine in the CNS → adenosine binds to its receptor → Mr. Fizz becomes drowsy and cannot continue working, so he wants to sleep → bad grades [5].
2. Mr. Fizz is awake and alert and has yet to consume any caffeine. He has a small amount of adenosine → (time) → accumulation of adenosine in the CNS → adenosine binds to its receptor → Mr. Fizz becomes drowsy, yawns, and then realizes that he needs some HCCBESCF → 1 hour later → caffeine prevents the adenosine from binding to the adenosine receptors by binding to those same receptors (antagonistic relationship) → Mr. Fizz is more awake and continues to study (Fig. 6.5) [5].

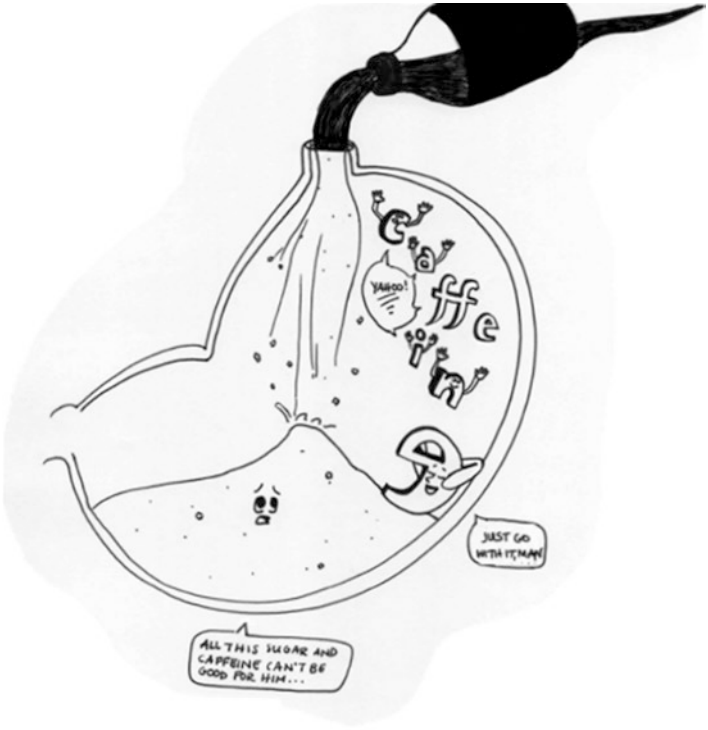

FIGURE 6.5 Caffeine fix

The adenosine receptors and adenosine work like a lock and key. If the adenosine binds to the receptor, the receptor can relay that information to other parts of the body that make you feel tired. Caffeine is similar in structure to adenosine, so it is able to enter the lock (the receptor); but because it is not the same as adenosine, it is unable to activate the receptor in the same way. Caffeine is able to bind to the receptor due to its shape but just sits there so that adenosine is no longer able to bind. It is like having a key fit into a lock but unable to turn to open the lock. No other keys are able to enter the lock until the first lock has been taken off. Caffeine remains on the receptor for some time, allowing you to feel more awake, but as soon as it falls off, the adenosine is able to rebind and successfully make you feel tired.

Diagnosis

To understand caffeine overdose, one should take note of the quantity of caffeinated products consumed, and adults should not consume more than 400 mg of caffeine per day. Symptoms to look out for include breathing trouble, changes in alertness, confusion, hallucinations, fever, diarrhea, convulsions, irregular heartbeat, muscle twitching, increased thirst, sleeping trouble, and vomiting [4]. Breathing rate, heartbeat, and blood pressure (vitals) will be taken at the hospital or doctor's office and factored against caffeine information to determine if the patient is indeed suffering from a caffeine overdose.

Treatment

Mild caffeine/HCCBESCF overdoses are treated by immediate stop of caffeine ingestion and rest.

Severe HCCBESCF intoxication or caffeine overdose can also be treated using:

- Activated charcoal may be used to absorb the excess caffeine. Activated charcoal is commonly used in drug overdose and has small pores to soaks up the excess caffeine.
- Laxatives.
- Gastric lavage—commonly used to clean and wash out the stomach.
- Home remedies (if symptoms are not too severe): stay hydrated by drinking water and eating food high in potassium and magnesium. Caffeine causes you to lose potassium and magnesium; both are beneficial to heart function and movement.

Fast Facts


Caffeine is a drug and should be respected when it is used. Excess of caffeine, as is similar to any drug, is harmful to the body and may cause death.

Adenosine is accumulated in the central nervous system throughout the day, and when it binds to its receptor, it leads to drowsiness and decreased function. Caffeine acts as an antagonist, which delays the drowsiness.

The maximum amount of caffeine that should be ingested per day for an adult is 400 mg. Caffeine overdose can occur in the individual if this amount is exceeded.

Test Your Knowledge

1. Which of the following should you do if you or a loved one is experiencing symptoms of HCCBESCF overdose (caffeine overdose)?

   (A) Have them drink more HCCBESCF because they have to stay hydrated
   (B) Immediately seek out medical attention
   (C) Call poison control
   (D) All of the above

   ANSWER: (B) The severity of the caffeine overdose may not be apparent at first. A doctor will be able to properly assess the situation and provide you with the proper treatment plan. Medical attention should always be sought out in a potential drug overdose situation.

2. What are some symptoms of HCCBESCF overdose (caffeine overdose)? Select all that apply.

   (A) Hallucinations
   (B) Irregular heartbeat
   (C) Muscle twitching
   (D) Hair loss

   ANSWER: (A), (B), and (C) Symptoms in a caffeine overdose are commonly breathing trouble, changes in alertness, confusion, hallucinations, fever, diarrhea, convulsions, irregular heartbeat, muscle twitching, increased thirst, sleeping trouble, and vomiting.

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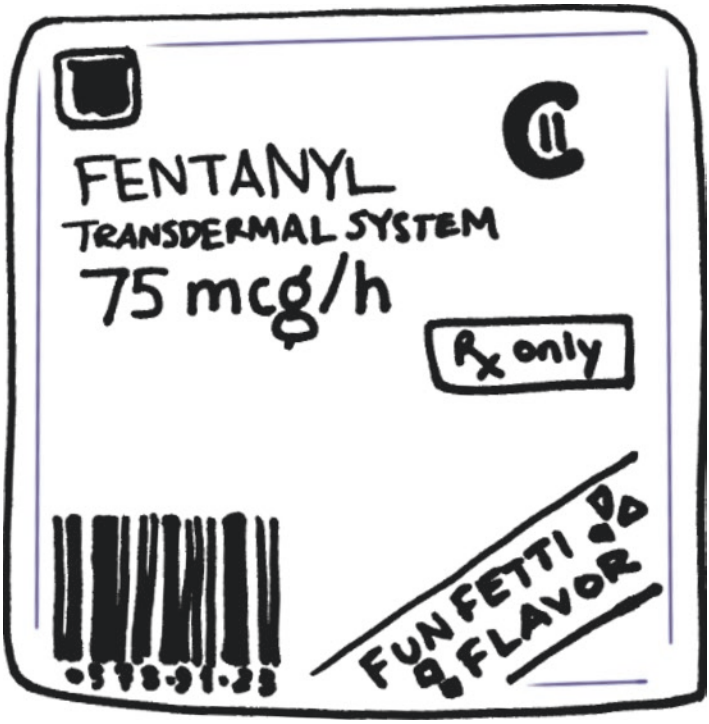
Chapter 7
A Woman in Shock and an Active Subscription to the New England Journal of Medicine

Po Hsuan Huang



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Vignette

When Dr. Szema asked me to talk to a psychiatric patient, I was nervous and shocked. I was afraid of being uncomfortable while staying with her. How do I to talk to her? How do I to start the conversation? What if she stared at me without saying a word? We were asked to see the patient because of recurrent septic shock, and the patient had already been admitted to the hospital three times before we saw her. Although she got a lot of fluid, her blood pressure was still low. As a result, the intensive care unit team was worried that she may be immunocompromised. Nevertheless, based on her medical records, behaviors, and information we gathered from her surrounding people in the hospital, Dr. Szema believed she had Munchausen's syndrome. I researched scientific articles in preparation. I left Dr. Szema's office and anxiously checked my watch for the rest of the day.

I kept asking myself, "Is it going to be okay?" While driving to the hospital, I refreshed my memory about Munchausen's syndrome, a disease that makes patients purposely seek medical attention by feigning diseases. Ms. B was possibly sexually abused; her body was physically healthy until age 21. Suddenly, her world changed. Symptoms and diseases gradually developed. Learning her medical history gave me confidence. I would not be misled by the diseases she claimed to have. I was prepared and eager to see how physicians use medicine to treat her.

We were asked to see 27-year-old Ms. B because of recurrent infections in the setting of Charcot-Marie-Tooth (CMT)—a neurologic disease associated with leg weakness and clubfeet. She was admitted to the intensive care unit for gram-negative sepsis and had allergic shiners. After entering the room, suddenly, I was no longer nervous and anxious.

I was calm. I was reassured by Dr. Szema's presence in the room during the entire half-hour interview. I warmly smiled to her and carefully started the conversation without mentioning sexual abuse to prevent unwanted emotions. I spoke gently and softly to reduce the foreignness between us.

While patiently listening to Ms. B speak about her claimed diseases, I got surprising answers. She told me she had bacterial infections, septic shock, respiratory muscle weakness, hypotension, generalized muscle weakness, and shortness of breath. She even had a note in her purse to list every other disease she claimed to have and could not remember at the time I saw her. "It is like an elephant sitting on my chest," she said. After talking to her for another few minutes, I was astonished to learn that she read medical journals and knew a lot of medical terms which even I, as a senior undergraduate pharmacology major and premed student, did not know (Fig. 7.2). Suddenly, I thought of the symptoms of Munchausen's syndrome. She learned to pretend to be sick! I kept smiling and directed questions toward more medical histories. I hoped that I would be able to solve the true underlying issues.

There were several additional, unverified diagnoses such as hypothyroidism, mixed connective tissue disease, and epilepsy. More surprisingly, Ms. B was not diagnosed with Munchausen's syndrome or treated with a selective serotonin reuptake inhibitor (SSRI), which is used to treat impulsivity related to the syndrome [4]. Instead, she was on *real* medications for the diseases she claimed to have! She was on levetiracetam, lacosamide, and clonazepam for her fake epilepsy problems with no verified histories of seizures or EEG tests from her neurologist. She was taking levothyroxine for her undocumented hypothyroidism and consuming lorazepam and mirtazapine for depression. The only claims we could, in fact, verify were (1) the CMT based on our observation of her lower feet deformity and (2) her mildly low IgA antibody levels in the medical records. Were doctors tired of her factitious symptoms, or did they want to comfort her without verifying those symptoms? I was worried about the potential side effects of polypharmacy and the possibility that she may abuse her medications if she wanted to induce more symptoms.

Dr. Szema said the nurses saw her chew on fentanyl patches, which can induce hypotension (Fig. 7.1). This episode was verified by one-to-one sitters. Ms. B said, "I take fentanyl and a pain killer for growing pain." But Ms. B was 27 years old! In addition, she contaminated her IV line with urine and urethra with feces to try to trick clinicians and even had a history of putting yogurt in her central line. However, one dose of antibiotics eradicated *E. coli* in her urine! I was confused why the physician team did not verify her diseases and

FIGURE 7.1 Patch du jour

wondered whether the team was simply weary of her and needed to concentrate on other patients or not. I thought her doctors might lose her trust.

Starting to doubt the possible sexual abuse history, I thought: was it real? It was clear she needed attention and care from others. However, her doctors seemed to be too busy to spend more time on her. During my 30-min interview with her, Ms. B was very comfortable talking to me and showed no signs of tiredness, muscle pain, or shortness of breath. I tried my best to find a way to understand her feelings and asked about her future plans to make her feel more comfortable. I knew I needed to understand her issues before I could determine ways to help her. I enjoyed interviewing Ms. B, but despite my best efforts, I could not open her mind.

I enjoyed the scientific detective work in determining that Ms. B. was not immunocompromised. Her IgG level was normal but IgA was low—common in CMT. This is typically associated with sinusitis, which she never had. She should not get blood with IgA because of potent IgE to IgA causing anaphylaxis. Unfortunately, we did not have the chance to keep following Ms. B longitudinally for her Munchausen's syndrome problem post-ICU admission. Did she still stay in the hospital and take more medications she should not take? Did she try to go to another hospital to seek new care providers to receive more attention or cares? I would like to know.

Background/Salient Features of Case

Munchausen's syndrome is a disease characterized by patients who pretend to be sick in order to seek attention from others. Munchausen's syndrome is a chronic subtype of factitious diseases whose name was coined by British psychiatrist Richard Asher in 1961 [1, 4]. Patients with Munchausen's syndrome may have frequent hospitalizations with inconsistent symptoms and invalid medical records without supporting test results; the diagnosis of Munchausen's syndrome must satisfy DSM-V requirements [1, 2, 5]. Healthcare providers can be easily frustrated by the intentional deception and manipulation of Munchausen's patients [3], which could

further damage trust between patients and physicians. Unfortunately, there are no cures or standard treatments for Munchausen's syndrome [2].

Patients may harm themselves by taking unnecessary medications when they feign the symptoms and diseases they pretend to have. Ms. B tried to obscure her medical testing results by taking painkillers, eating fentanyl patches, and contaminating her central lines. She learned to be sick by reading medical journals and knew sundry medical terms. Her intentional creation of the symptoms and diseases upset the clinicians in the hospital and obstructed the progress to mitigate her problems (Fig. 7.2).

FIGURE 7.2 Rome wasn't built in a day, but her medical lexicon sure did expand pretty quickly!

Diagnosis

Patient with DSM V suggest factitious disorders with diagnostic criteria:

1. Falsification of physical or psychological signs or symptoms or induction of injury or disease, associated with identified deception.
2. The individual presents himself or herself to others as ill, impaired or injured.
3. The deceptive behaviour is evident even in the absence of obvious external rewards.
4. The behaviour is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

PSN-S specifies the course of illness as either single episode or recurrent episodes. The later diagnosis applies to our patient.

Treatment

The patient was improperly treated with medications that should not have been prescribed. Counseling, psychotherapy, and patient education are recommended. If this is a call for help regarding ongoing abuse, then it behooves investigation [2].

Fast Facts

Munchausen's patients pretend to be sick in order to seek medical attention and care.
There is no cure for Munchausen's syndrome. However, psychotherapies with flexible and gentle approaches are usually used to control patients' conditions.
Healthcare providers should pay attention to the ways Munchausen's patients use to feign their medical conditions. They may hurt themselves.

Test Your Knowledge

1. What was the name of the disease that Ms. B had?

   (A) Munchausen's syndrome
   (B) Negative septic shock
   (C) Rheumatoid arthritis
   (D) Epilepsy
   (E) Mixed connective tissue diseases

   ANSWER: (A) All the other diseases lacked supportive testing results.

2. Charcot-Marie-Tooth was the only disease which can be verified besides Munchausen's syndrome.

   (A) True
   (B) False

   ANSWER: (A) The only disease that can be verified besides Munchausen's syndrome is Charcot-Marie-Tooth based on the supportive testing results in her medical records and the appearance of her feet.

3. Ms. B was on the medications she should be prescribed.

   (A) True
   (B) False

   ANSWER: (B) She was on the medications that should not be prescribed to her, such as Keppra, Vimpat, and Klonopin for her fake epilepsy.

4. Which of the following is false?

   (A) Ms. B chewed on fentanyl patches.
   (B) She told the truth to her healthcare providers and was compliant with clinicians' treatments.
   (C) Ms. B feigned her medical records.
   (D) She contaminated her IV lines.

   ANSWER: (B) She never told the truth to the clinicians but tried to trick them by feigning diseases in order to receive more medical attentions.

5. What can we see on patients with Munchausen's syndrome?

   (A) Irrational medical records
   (B) Frequent hospitalization
   (C) Intentional creations of diseases they don't have
   (D) All of the above

   ANSWER: (D) Patients with Munchausen's syndrome tend to have these characteristics that often frustrate healthcare providers.

Suggested Readings

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Chapter 8
The Unexpected Hazards of Spring Break

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Vignette

Three days after arriving for a ski vacation in Vail, Colorado, 15-year-old Bodie's headache had become so severe that he had to go to the ER. Bodie had come from Long Island, hoping to enjoy a week of skiing with his family during his school break. He had been having a mild cough several weeks prior, but it had not been severe enough to address. His headache started a day after arriving in Vail that steadily worsened, accompanied by nausea and a decreased appetite. Bodie tried taking both acetaminophen and ibuprofen without any effect on his headache. Bodie presented to the ER with a normal heart rate, breathing rate, and blood pressure. However, his blood-oxygen saturation level was only 82%—far below normal. When listening to his lungs, crackles could be heard on the lower right side. While the crackles could suggest pneumonia or pulmonary edema from heart failure, both were unlikely in a generally healthy 15-year-old. The key to understanding Bodie's strange symptoms is to appreciate one particular detail of his trip—Bodie lives essentially at sea level on Long Island but traveled without time for acclimation to the high altitude in the Colorado Rockies (Fig. 8.1). Ideally, the duration of spring break would allow several days at a medium elevation prior to transitioning to the highest elevation [1]. Vail's base elevation is 8120 ft above sea level, and the summit is at 11,570 ft. Bodie was diagnosed with Acute Mountain Sickness (AMS) and High-Altitude Pulmonary Edema (HAPE). As a result of not being accustomed to the thinner air in Colorado, Bodie's lungs were filling with fluid.

Bodie was given oxygen via nasal cannula and was told that he must rest and continue using oxygen canisters for several days, preferably until he was ready to descend to Denver (around 5200 ft above sea level) and take his flight back home. Bodie's family was hoping that he was completely cured the next day when his headache vanished and he was no longer experiencing any shortness of breath. His blood-O_2

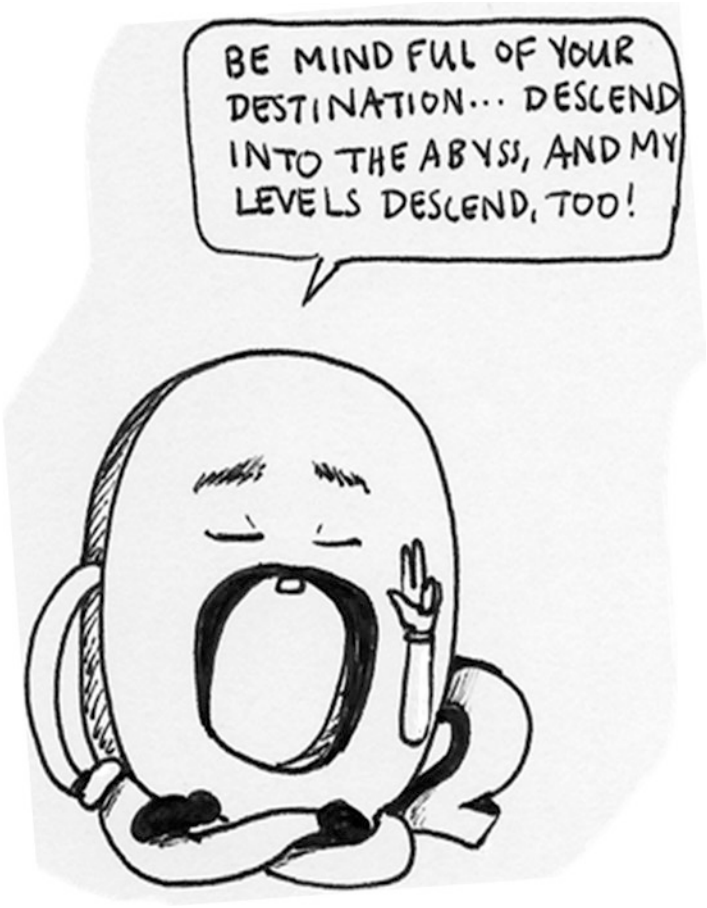

FIGURE 8.1 Guru O_2

level had significantly increased to 92%. Despite feeling better, his lung crackles were still present, and his HAPE had not fully resolved. He was told to continue using oxygen tanks throughout the rest of their stay in Vail and at night even after returning to Long Island until cleared by his primary care physician. Bodie was able to leave Vail having only missed a few days of skiing and suffering from a severe head-

ache but could have easily descended into a potentially life-threatening fight with HAPE.

The following winter, despite the issues in Vail, Bodie and his family went on a trip to Jackson Hole, Wyoming (Fig. 8.2). While the base elevation at Jackson is lower than at Vail (6311 ft compared to 8120 ft, respectively), it is still far higher than Long Island and well above the minimum elevation for altitude sickness—around 5000 ft. They flew straight into Jackson without any preparation for the altitude, despite knowing that the greatest risk factor for high-altitude illness is a previous incidence of AMS [1–4]. It is recommended to ascend to high altitudes in several steps to aid the acclimatization process. Flying directly from approximately sea level to the Rockies greatly increased the potential for Bodie to be stricken with altitude issues again.

Additionally, Bodie could have used drugs to accelerate acclimatization and mitigate or even prevent any altitude issues. Acetazolamide is often used in preparation for and during the first few days at high altitude to alleviate effects from altitude sickness and helps start the acclimatization pro-

Figure 8.2 Skier Marc Kostrubiak

cess [3, 4]. Acetazolamide is a diuretic that causes the kidneys to excrete more bicarbonate than normal and thus acidifies the blood counteracting the blood alkalization that results from faster breathing due to low oxygen levels (Figs. 8.3 and 8.4).

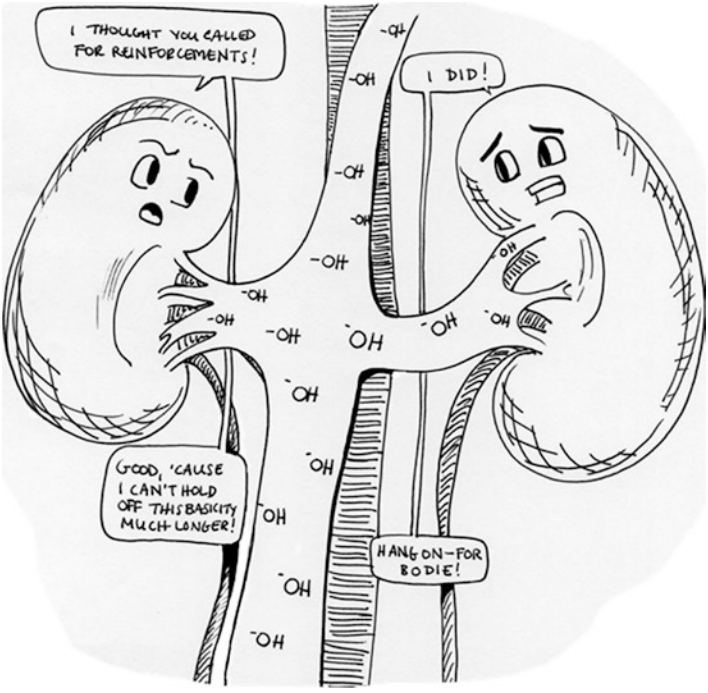

FIGURE 8.3 Not kid-ney'ng about the basicity!

FIGURE 8.4 Diamox to the rescue

It also causes people to take faster, deeper breaths to help get more oxygen and speed up the process of getting used to high altitude. Unfortunately, acetazolamide is a sulfonamide drug and thus may not be able to be used by the large amount of people allergic to sulfa drugs. For these patients, dexamethasone can be used; however it only masks the symptoms and does not provide any assistance in acclimating to high altitudes [5]. Patients who use dexamethasone prophylactically and stop taking the drug could experience a rapid onset of AMS. Finally, there is some evidence that the easily accessible *Ginkgo biloba* may be able to reduce the symptoms, but its efficacy is controversial.

Unsurprisingly, at their hotel at the base of the mountain, Bodie measured his blood-O_2 saturation and found it to be only 91%. However, despite their general lack of preparation, Bodie's family did bring one critical item—portable oxygen concentrator. After using this, he was able to breathe at a higher fraction of inspired oxygen at a rate of 3 L/min, increasing his blood-O_2 saturation level to 99%. But despite the portability of the oxygen purifier, it is not small enough to be used while skiing. Bodie was able to get up to 99% O_2 saturation at the bottom of the ski area—about 4000 ft below the summit. He was able to successfully ski throughout his vacation using the portable oxygen concentrator by saturating his blood with oxygen, as if he was at sea level at the bottom of the mountain. He skied for short bursts, while his oxygen levels steadily dropped, until he refueled with more oxygen.

Luckily, Bodie was recover from his HAPE in Vail and was successful using an unorthodox treatment at Jackson Hole. However, given the severity of his prior reaction, his family's decision to go on another ski trip highlights the importance of recognizing the dangers of altitude as well as the signs and symptoms of AMS before one's ski partner or child rapidly descends into a potentially deadly condition. People generally think about the dangers of skiing fast, hitting a tree, or even avalanches, but they rarely realize that just traveling to their destination might prove deadly.

Background/Salient Features of Case

Most of us rarely think about altitude in our daily lives. We live at whichever elevation we do, and our bodies are adapted to our situation. High-altitude medical issues seem like something from mountaineering movies and disaster stories from far away in the Himalayas. We tend to think that we rarely travel to such extremes but do not realize that just going on a ski trip could end in potentially fatal conditions. AMS commonly occurs at elevations greater than 6500 ft—a very common elevation throughout the Rocky Mountain States and California [1, 2, 4]. AMS is characterized by headaches and nausea resulting from increased breathing and a cascade of events involving blood pH levels. AMS occurs to people of all ages, although it may be less likely in the elderly and is most common in people who have previously had AMS. AMS can progress to HAPE as well as equally deadly High-Altitude Cerebral Edema (HACE). All three occur in people of both genders equally, and there are no clear physiological, anatomic, or genetic factors that increase or decrease their incidences [2]. At greater elevations such as the summit of Mount Rainier in Washington, AMS occurs in up to two in three climbers [4]. HAPE is much less common and occurs in only 0.2–6% of people at these altitudes, but it becomes increasingly common at altitudes experienced by mountaineers in the Himalayas, the Andes, Canada, and Alaska.

In HAPE, fluid accumulates in the lungs from increasing pressure in the pulmonary arteries as part of the physiological response to decreased oxygen availability to the tissues. When it becomes great enough, this pressure causes fluid to leak into the lungs, which inhibits breathing and can eventually cause the lungs' alveoli to hemorrhage as one struggles to breath. While HAPE can rapidly become deadly, it is remarkably quickly reversed with descent and/or oxygen. HACE involves fluid buildup around the brain and can quickly cause critically high pressure on the brain. Luckily HACE is the least common altitude-related illness; however its rarity combined with its early presentation as simply tiredness—a common result of skiing or mountaineering—can result in it being ignored until it becomes severe [5].

Diagnosis

Bodie was diagnosed with Acute Mountain Sickness (AMS) and resulting High-Altitude Pulmonary Edema (HAPE). This was confirmed via with blood-oxygen levels and lung crackles, which indicated edema. His general good health, age, and circumstances ruled out other causes of edema indicating that it was a complication of his AMS.

Treatment

While Bodie was able to repeatedly stave off AMS, his family's treatment choice was certainly unorthodox. Normal treatment for altitude sickness involves oxygen administration, descent to lower elevation (if possible and/or practical), as well as various drugs. NSAIDs like aspirin, acetaminophen, and ibuprofen are most commonly used for the headaches, while acetazolamide also helps treat the causes as well as being a primary method of preparing for traveling to high altitudes [5]. Should altitude sickness worsen into HAPE, like Bodie experienced in Vail, treatment is highly dependent on individual circumstances. Simply providing oxygen and mandating rest may be enough. However, sometimes more aggressive measures are needed to ensure that pulmonary artery pressure is reduced to minimize the pressure that forces liquid into the lungs. Interestingly, warmth is very effective at reducing this pressure and can luckily be found in ski lodges and clinics everywhere. Pharmacological approaches are varied, sometimes controversial, and highly dependent on individual circumstances. Interestingly, PDE5 inhibitors are both commonly used with moderate success [2]. Regardless of the method, HAPE treatment is urgent, as the condition can often quickly become life-threatening. The other potential edema, HACE, requires rapid descent if possible and administration of oxygen and the less commonly used prophylactic, dexamethasone (Fig. 8.5). Finally, for all cases of AMS, hyperbaric chambers can be lifesaving when available, as they are able

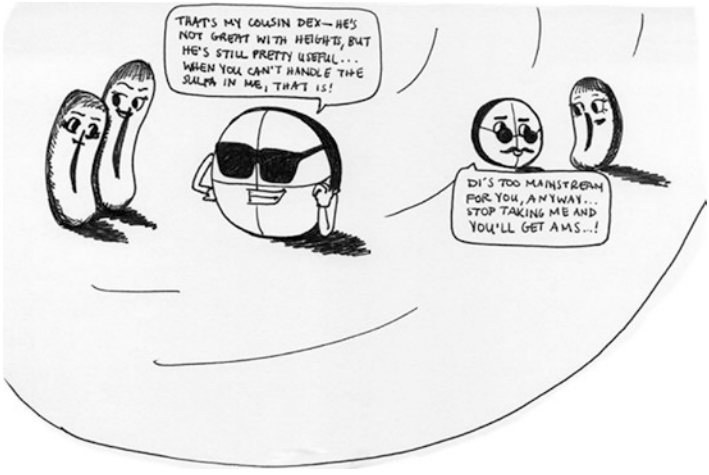

FIGURE 8.5 Dex: an alternative for those allergic to sulfa drugs

to provide high levels of oxygen while simultaneously simulating a descent to lower altitudes.

Fast Facts

AMS can occur at elevations as low as 5000 feet and is common at elevations found throughout the western states. It primarily manifests as headaches and nausea stemming from low blood-oxygen levels and physiologic sequelae.

AMS can result in cerebral and pulmonary edema. All of these conditions are best treated via a combination of oxygen administration and a descent to lower elevations. Pharmacological approaches include (acetazolamide), or PDE5 inhibitors for HAPE and dexamethasone for HACE.

Prevention of AMS can be accomplished most effectively by slowly ascending to high altitudes but can also be achieved via prophylactic administration of acetazolamide or dexamethasone.

Multiple Choice Question

1. Which statement is true?

   (A) AMS only occurs at altitudes greater than those in the Appalachian Mountains, which reach 6683 ft.
   (B) AMS most commonly presents as coughing and GI distress.
   (C) Hyperbaric chambers are effective in treating AMS, HACE, and HAPE.
   (D) Drugs used to treat erectile dysfunction can be used to treat HACE and general AMS.
   (E) Acetazolamide is safe for all patients with sulfa allergies.

   ANSWER: (C) Hyperbaric chambers are effective in treating AMS, HACE, and HAPE. To obtain this answer, we can falsify every other answer choice. Answer choice A is incorrect as AMS can occur at elevations as low as 5000 ft, an elevation reached by several of Appalachian peaks in several East Coast states. While option B seems appealing, AMS presents most commonly as headaches and nauseas rather than coughing and GI distress. Option D suggests Viagra® as a treatment for HACE and AMS in general; however PDE5 inhibitors are only indicated for treating HAPE. Finally, we can rule out option E, as acetazolamide is a sulfa drug and should not be used by patients with sulfa allergies. While there is preliminary evidence that patients with sulfa allergies may tolerate acetazolamide, it is currently contraindicated in these patients. As we have concluded, hyperbaric chambers are effective in treating all forms of altitude-related illnesses as they emulate a descent to lower altitudes.

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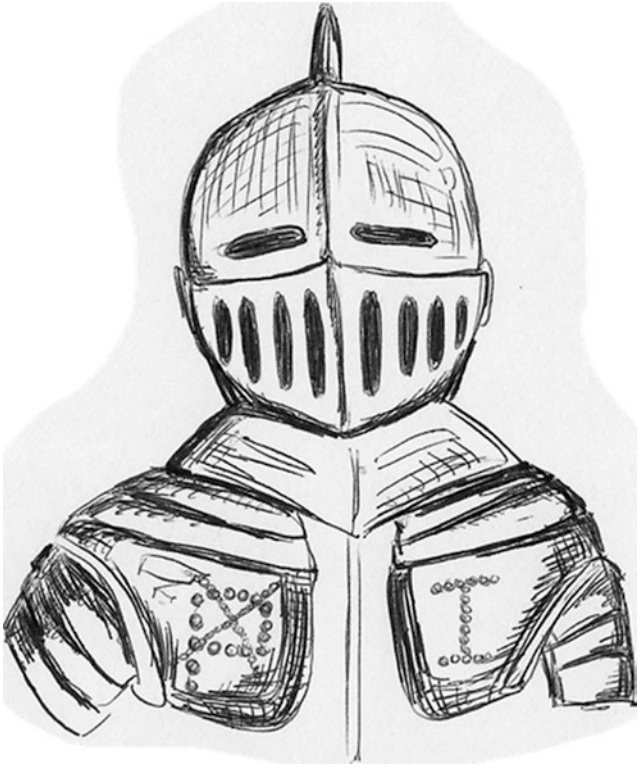
Chapter 9
A Fairytale of a Lurking Evil Fungus, Paecilomyces, and the Knight, Itraconazole

Cyrus Jo



A.M. Szema (ed.), *Unusual Diseases with Common Symptoms*, https://doi.org/10.1007/978-3-319-58952-7_9

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Vignette

Prologue

Once upon a time, Princess Andromeda of the Central Lands was offered a magical pill, acetylsalicylic acid, on her 48th birthday by a roaming wizard, named Dr. Stukup. When she consumed this magical pill, she went into anaphylactic shock. She nearly died! The wizard quickly defended himself and claimed he was not trying to poison the princess, but she was still outraged. She was about to sentence the wizard to a life-long imprisonment, when the wizard offered a solution. He explained that after his procedure, there would be no harmful side effects; he called it desensitization. The princess agreed and was misguided once more. He desensitized her to aspirin, but she was required to take a daily aspirin for the rest of her life. However, for the next 2 years, she was itchy and tired. The royal family's healer, Orion, consistently drew blood for 2 years and always found an abnormally elevated eosinophil count. Orion worried for her health and directed the princess to travel East, where the legendary Dr. Szema resided. Upon arrival, Dr. Szema immediately discontinued her daily aspirin, and she was cured! Her itch and fatigue never recurred. Dr. Szema later treated the princess by re-desensitizing her to aspirin in the ICU, and peace had returned to the Central Lands.

Story

Several years later, peace was broken when an evil fungal army breached the capital walls of the Central Land. The leader of the evil fungal army, *Paecilomyces*, invaded the princess's quarters. The fungus invaded her body and bypassed her immune system. The castle was run over, and the princess

was taken as a hostage. Under the command of Dr. Szema, the brave knight, Itraconazole, pledged to save the princess and retake the Central Lands. The evil fungus and the knight fought for 3 months, and in the end…well, spoiling the ending without the journey is unforgivable, so here's the journey (Fig. 9.1):

A few days after Princess Andromeda traveled from Boston to Long Island, she woke up and noticed swelling around both of her eyes. She also noted an odd sensation in

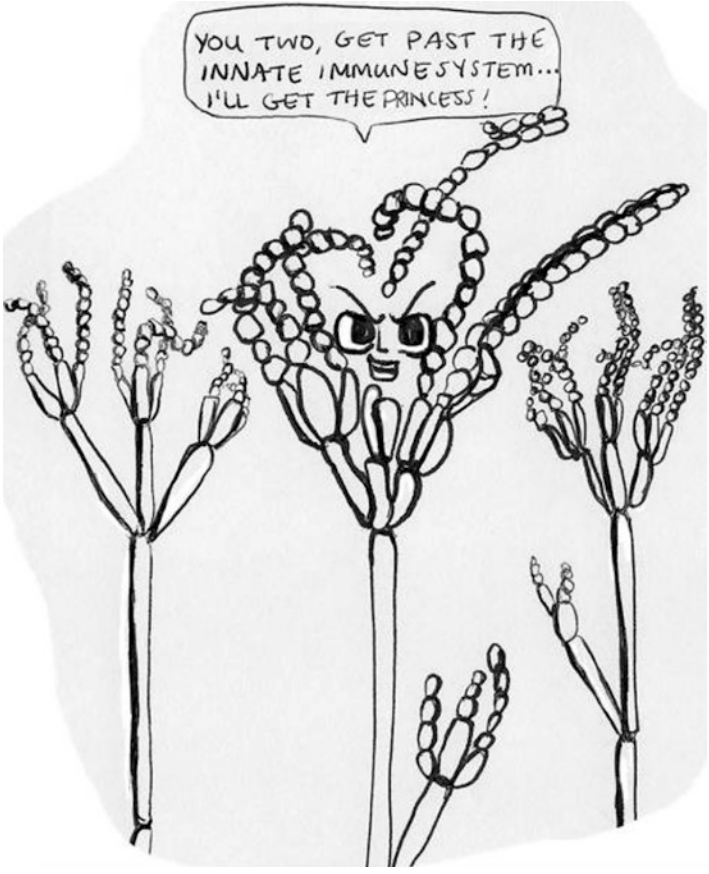

Figure 9.1 Army of invaders

FIGURE 9.2 Brown nasal discharge containing *Paecilomyces*

her sinus. Later that same day, she suddenly blew out a brown curly mass from her nose! The discharge was distinctly abnormal, and the princess immediately took a picture (Fig. 9.2).

After forwarding the photo to Dr. Szema, she received a call back from him instantaneously, and he requested that she save this mass for immediate culture and sensitivities. When the test results came back, the doctor was surprised because the culture tested positive for *Paecilomyces*! *Paecilomyces* is a type of fungus that is isolated from soil and decaying plants. It is surprising for a person with an intact immune system to be infected and grow mold in their sinuses! [2].

On the day of the brown discharge, her vital signs showed no abnormalities. However, her physical exam was quite the opposite—she had giant blue ovals under her eyes! To be specific, she had allergic shiners bilaterally, with a tint of blue blushing her lower eyelids (Fig. 9.3).

The princess was tested via an exhaled breath condensate nitric oxide breathing machine, which measures exhaled breath condensate nitric oxide (NO). A value of 50 parts of NO per one

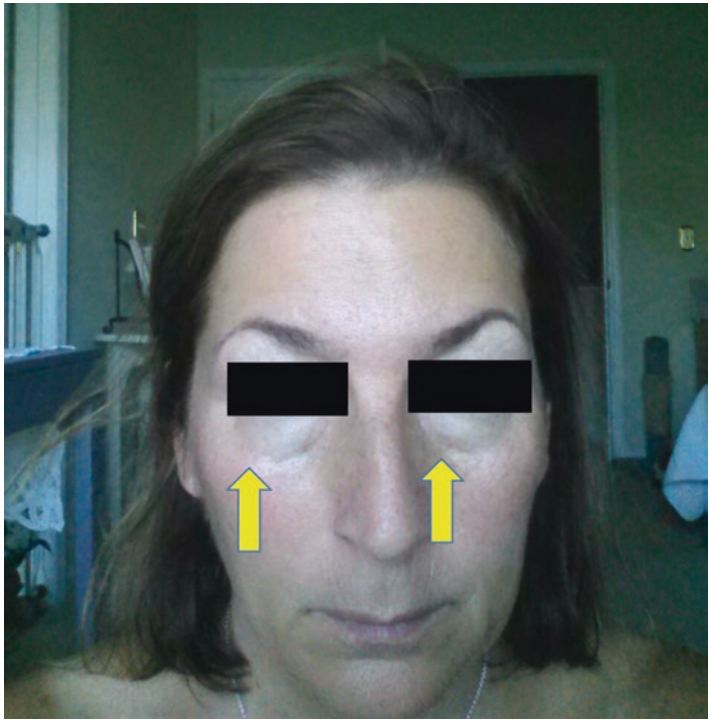

FIGURE 9.3 Allergic shiners—dark discoloration in the eyelid due to fluid accumulation and inflammation in the infraorbital groove (Quantitative assessment of allergic shiners in children with allergic rhinitis—Chen 2009 JICI)

billion particles (ppb) or greater indicates the presence of eosinophilic airway inflammation, since eosinophils produce NO. These patients have allergic asthma and respond well to inhaled steroids. Her results showed 66 ppb. She was treated with 0.5 mg nebulized budesonide (steroid) with 0.083% albuterol (airway dilator). Furthermore, her absolute blood eosinophil count was 22. We conducted another test called impulse oscillometry (IOS), which gave an extremely high value for X5 of 174 L/s. The X5 is a measure of airway hyperresponsiveness or twitchy airways, which is a cardinal feature of asthma. She also was previously diagnosed with chronic sinusitis and aspirin-exacerbated respiratory disease

(Samter's Triad). This triad entails (1) aspirin anaphylaxis, (2) nasal polyposis, and (3) asthma [1]. Her testing also determined she was allergic to cyclic peptides produced by organisms of the licheniformis group used as an antibiotic, trimethoprim/sulfamethoxazole, ciprofloxacin, levofloxacin, and tetracycline. A skin test for multiple allergens was conducted, and results showed allergies to cats, dogs, and various trees, weeds, molds, dust, and grasses. The princess began immunotherapy, a treatment designed to adjust the body to not react to specific allergens. In addition to these tests, she was treated for allergic rhinitis and allergic fungal sinusitis, her total IgE level and IgE aspergillus, which were 45 and 0.19, respectively (both quite high).

Don't forget anatomy! Due to multiple sinus surgeries in an attempt to alleviate the pressure buildup and symptoms of her chronic sinusitis, her sinus was obliterated, not in terms of "being wiped off the map," but rather, the anatomy of her sinus became abnormal due to the tissue removal and scarring from the multiple sinus surgeries (Fig. 9.4). No matter how many attempts via surgery, the symptoms kept coming back like a boomerang. Therefore, her surgeons inserted plane screw fixations as a last resort "in order to hold back the river."

Due to the metallic properties of titanium, the dark and moist environment, and exposure to the external world, a home for *Paecilomyces* was created. Finding out that she had

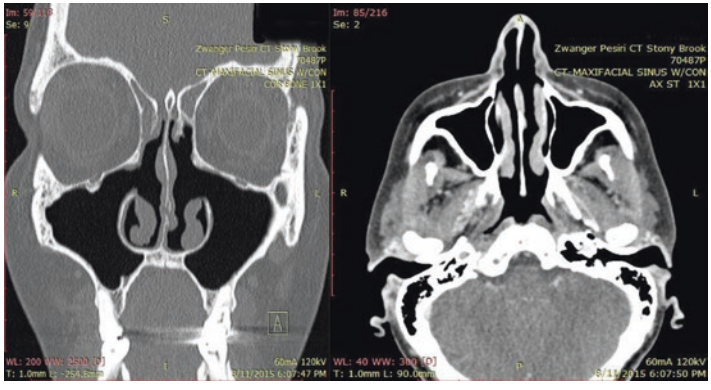

Figure 9.4 CT scan showing opacification of the ethmoids

been living in a moldy basement apartment with a leaky roof in Boston suggested her consistent exposure to mold in the basement contributed to the buildup of mold in her blood.

However, there were more medical issues related to the *Paecilomyces* infection. Concurrent with her sinusitis, she could not swallow. The severity of this issue was not clear; therefore, an esophagogastroduodenoscopy and esophageal motility study was performed. The results were astonishing! The esophageal motility report was the worst the gastroenterologist had ever seen. The former showed up to 100 eosinophils per high-powered field, and the latter showed extremely poor esophageal motility (Fig. 9.5) [5].

In summary, the patient had developed an extremely high eosinophil count due to the failure of aspirin desensitization. The patient became infected with mold from living in a

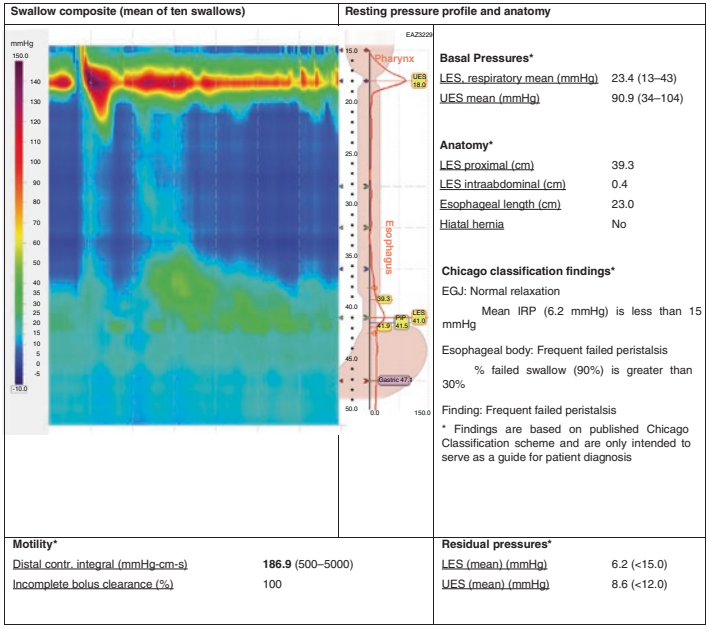

FIGURE 9.5 Esophageal motility study showing extremely poor motility

moldy and dank environment. She had recurrent sinusitis causing nasal polyps, swelling, and a mucus buildup. The patient had an obliterated frontal sinus from multiple sinus surgeries with a reinforced titanium plate, which caused the nasal passage to become more susceptible to sinusitis due to the inserted titanium plate exposed to the outer world. These factors led to the development and discharge of *Paecilomyces* from her sinus. Furthermore, the patient was both infected with *Paecilomyces* as well as having an allergic immune reaction to the mold itself, manifested by eosinophilia in the esophagus and in the peripheral blood.

So what did we do to the rare fungus that had infected her blood? The only thing to do: eradicate it! A treatment plan of Itraconazole 200 mg per day for 6 months was administered to eradicate the antigenic load and the burden of the *Paecilomyces* infection [3]. However, the plan didn't go as intended. After 3 months into the treatment, the patient drank red wine (Fig. 9.6). Her liver function test showed that the AST and ALT values increased, so itraconazole was discontinued. You might ask why was itraconazole discontinued when the liver functions test increased? Well, once the liver begins to metabolize again, enzymes will be created that will render itraconazole ineffective. There is also the danger of hepatotoxicity (liver damage).

So even though the treatment was discontinued after 3 months, significant progress had been made. The treatment lasted long enough to cause the patient to become asymptomatic. The knight, Itraconazole, defeated the evil fungus, *Paecilomyces*, and the princess was saved. Happily ever after!

FIGURE 9.6 The red devil

Background/Salient Features of Case

Paecilomyces lilacinus is a fungal species that is found in a great array of habitats. This fungus is known to cause subcutaneous swelling in infected individuals. Most other cases of an infection with *Paecilomyces* are in conjunction with another set of symptoms but rarely with an immunocompetent host [4]. Patients infected with *Paecilomyces* are most often prescribed Itraconazole for 6 months, but few have undergone surgery for the removal of the fungus.

Infected patients should have their AST and ALT levels checked before consuming itraconazole; high levels of these enzymes will inhibit itraconazole. The patient's liver function test showed low AST and ALT values, which allowed the patient to consume itraconazole and experience its full effects. But due to complications, her AST and ALT values increased, and itraconazole was discontinued after 3 months.

Diagnosis

Fungal nasal sinusitis due to *Paecilomyces lilacinus*. The patient showed cyanosis and bilateral swelling of the eyes, along with acute onset nasal symptoms. CT scans of the sinus showed complete opacification of the ethmoids. The brown nasal discharge tested positive for *Paecilomyces lilacinus*.

Treatment

A prescription of itraconazole for 6 months is recommended to remove the fungus, *Paecilomyces lilacinus,* from her peripheral blood [6].

Fast Facts

The patient had an irregular sinus anatomy with a titanium plate and a serious case of poor esophageal motility, which caused a series of sinusitis infections and fostered the growth of *Paecilomyces lilacinus* in her sinus.
The patient's allergy to mold and moldy living conditions caused an allergic reaction and caused a sharp increase in her IgG levels (this effect was constant for a long duration).
The patient had an infection to *Paecilomyces lilacinus* and an allergic reaction to the mold itself, which was revealed by eosinophilia in the peripheral blood.

Test Your Knowledge

1. What is the name of the fungus that invaded the patient?

   (A) *Amanita arocheae*
   (B) *Pleurocybella porrigens*
   (C) *Lepiota subincarnata*
   (D) *Paecilomyces lilacinus*

2. An allergic reaction will cause an increase in:

   (A) IgG count
   (B) IgM count
   (C) IgE count
   (D) IgA count

3. How many months was the treatment plan planned for?

   (A) 1
   (B) 6
   (C) 9
   (D) 3

4. The patient was having both an infection with *Paecilomyces*, as well as:

   (A) A case of chronic asthma attacks
   (B) An allergic reaction to zyrtec
   (C) An allergic immune reaction to mold itself
   (D) A case of stiff-arm syndrome

5. The patient's abnormal sinus anatomy and the lodged titanium plate played a part in the infecting the patient with *Paecilomyces lilacinus*.

   (A) True
   (B) False

   ANSWERS: 1. (D), 2. (C), 3. (B), 4. (C), 5. (A).

Suggested Reading

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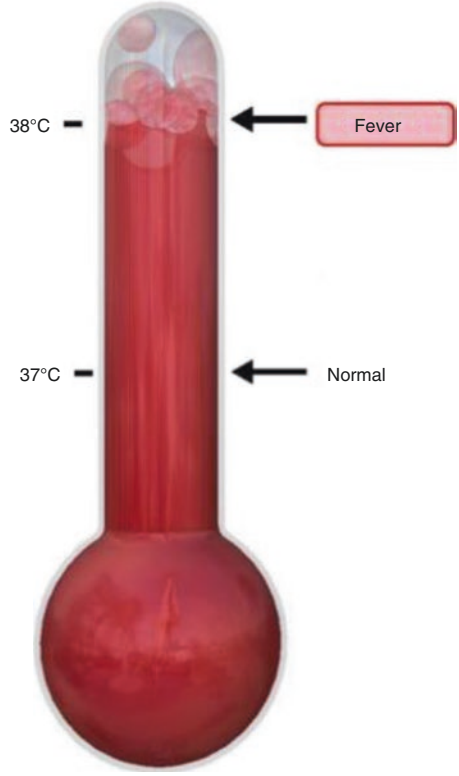
Chapter 10
"The Breast Cancer Is Cured, but I Still Have This Fever…"

Roxane Javadi



A.M. Szema (ed.), *Unusual Diseases with Common Symptoms*, https://doi.org/10.1007/978-3-319-58952-7_10

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Vignette

In early September 2015, Mrs. Lesbos (yes, as in the infamous Greek island) came into our office complaining primarily of hives. She was a resilient woman in her early 70s and was often accompanied to our office by several family members: her gentle husband, thoughtful son, and attentive daughter-in-law.

The first time we saw Mrs. Lesbos, her son suggested that she might be reacting to the metal chest expanders that remained in her breasts after her mastectomy in 2014 to treat breast cancer. Based on this, we first asked ourselves whether she could be having a severe case of contact dermatitis to the metal. However, this would not have explained why she started having symptoms now—a full year after her mastectomy. Another possibility was that Mrs. Lesbos was suffering from an irritating, but unremarkable, food allergy. We patch tested her for contact dermatitis reactions and she reacted to nickel and several chemicals. However, she had not been exposed to any of the substances that made her skin react. The food skin prick allergy testing was also normal.

Dr. Szema then turned his focus elsewhere. He had been intrigued by a very curious symptom: her "hives" were always accompanied by noninfectious fevers. At the very least, the fevers were annoying. They muddled her mind and caused sleepless nights. At their worst, the fevers could last for several weeks and put her entire life on hold. Without any explanations for her condition, she was forced to medicate with acetaminophen and risked possible liver damage.

About 4 months before her first visit with Dr. Szema, she was admitted to Big University Hospital for a relentless fever. She remained in the critical care unit of the large academic hospital under surveillance for days. The doctors could not offer any explanation and were left to treat her

dehydration and any signs of impending shock. She was hallucinating, shifting in and out of consciousness, and losing fluids rapidly. Fortunately, doctors managed to relieve her symptoms, and after two and a half weeks, she was sent home.

Still, the fevers would come and go as they pleased. I for one get very irritable with a simple case of hiccups. I can only imagine the frustration and fear that Mrs. Lesbos and her family felt when dealing with these uncontrollable fevers.

After hearing about her hospital trip, the fevers caught Dr. Szema's full attention, as did a seemingly simple detail that Mrs. Lesbos had casually mentioned during her history. She had emigrated here from Greece with her husband long ago before her son was born. With that key detail, Dr. Szema began faintly suspecting that this could be a rare case of familial Mediterranean fever (FMF).

Furthermore, several blood tests showed that her levels of C-reactive protein (CRP) were persistently elevated over the span of many years. CRP is produced in the liver during an inflammatory response to infection. Mrs. Lesbos had high levels of CRP even when she was not infected or not febrile. During a later visit, Mrs. Lesbos presented with a rash localized on her shins that only heightened Dr. Szema's suspicions. It seemed as though the hot Greek climate had managed to follow Mrs. Lesbos to the US East Coast (Fig. 10.1).

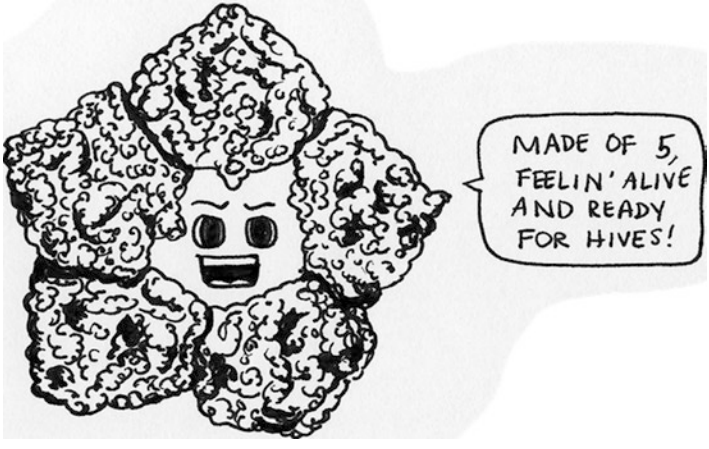

Figure 10.1 C-reactive protein (CRP)

Background

Unbeknownst to most Americans, FMF is a condition most commonly characterized by spontaneously occurring episodic fevers, inflammation, pain, and a characteristic rash that appears along the shins [1]. Episodes vary in severity and usually last from half-a-day to 3 days. They can be triggered by stress, hormonal changes, or unknown causes. In between flares, patients are asymptomatic, with these periods lasting between days to months. While FMF is relatively rare in Long Island, it is more common among populations that originated in the Mediterranean region, such as individuals of Armenian, Greek, Turkish, Jewish (Sephardic), and Arab ancestry [3].

FMF is typically an autosomal recessive disorder, meaning that both parents need to have a malfunctioning gene for an individual to have the disease [4]. Therefore, reviewing the family tree is critical. Most pathogenic mutations occur in the MEFV gene, which directs the production of pyrin in white blood cells [2]. An essential protein in the inflammation pathway, pyrin, is thought to control the migration and modulation of white blood cells. Though its exact mechanism is still unknown, pyrin is thought to be critical in winding down the inflammatory response when it is no longer needed. Malfunctions in the MEFV gene reduce pyrin production and lead to an extended inflammatory response. Clinical manifestations entail fever, pain, joint swelling, and rashes. During symptomatic episodes, patients may also have inflammation of the abdominal lining (peritonitis) and lining of the lungs (pleurisy).

The bulk of disease occurs in youth, with most individuals presenting in later childhood and their early teens. By their twenties, about 80–90% of patients with FMF will have experienced their first episode. Although these episodes can be exacerbated or brought on by emotional or physical stress, no such source was evident in Mrs. Lesbos' case. It is possible that others like her can also develop

episodes much later in life, but Mrs. Lesbos is a very rare exception. Perhaps this may explain why she had not gotten a diagnosis of FMF until seeing Dr. Szema, especially since she had relatively classic symptoms of the disease.

Diagnosis

After her initial visit, it became necessary to rule out common conditions that are covered in the differential diagnosis. In fact, in the early visits of Mrs. Lesbos, FMF felt like a more far-fetched diagnosis, like something you would see on House M.D. or Scrubs.

As with most suspected cases of contact dermatitis, the first thing Dr. Szema did was to perform a patch test for various metals and chemical compounds such as epoxy resin, nickel, parabens, and other possible allergens. Mrs. Lesbos was determined to be allergic to 7 of the 27 tested compounds, including nickel.

Dr. Szema quickly got in touch with her surgeon, Dr. B., but was told there was no nickel in the expander. Despite her diagnosis of urticaria and contact dermatitis, Mrs. Lesbos still had no explanation for her fevers. Regardless, Dr. Szema advised that Dr. B. should remove the metal and see if her fever and pain symptoms could resolve themselves.

In November, the breast expanders were removed. Her last febrile episode had been in October, so, for several months, everything seemed to be going okay. However, Mrs. Lesbos could not catch a break. On February 3, she came down with a fever of 104 °F. Dr. Szema wanted to see her immediately. During the visit, he noticed the skin blanching and a rash along her shins, a key sign of FMF (Fig. 10.2).

In February, after several family meetings in our office and discussions with the National Institutes of Health (NIH), Mrs. Lesbos decided to get a blood test done to detect genetic markers of periodic fever syndromes. The MEFV gene sequence analysis is the most accurate marker of diagnosis we have to date. Approximately 70–80% of patients

FIGURE 10.2 Save the date

with an FMF diagnosis have identifiable variations in the MEFV gene. Mrs. Lesbos was found to be heterozygous for a mutation in the MEFV gene, meaning she inherited a malfunctioning copy of the gene from one of her parents. That might explain her late-in-life symptoms and diagnosis, which is rare among FMF patients. According to some studies, the chance of a heterozygous patient having clear, clinical manifestations of FMF is relatively rare. Still, being heterozygous may predispose individuals to developing FMF later in life, perhaps after some environmental or epigenetic stressors. It is uncertain exactly how symptoms of FMF manifested in Mrs. Lesbos so late in life. Perhaps her breast cancer treatment acted as a late-in-life stressor to trigger FMF. In general, it is contested within the literature what the exact relationship between the heterozygous MEFV mutation is

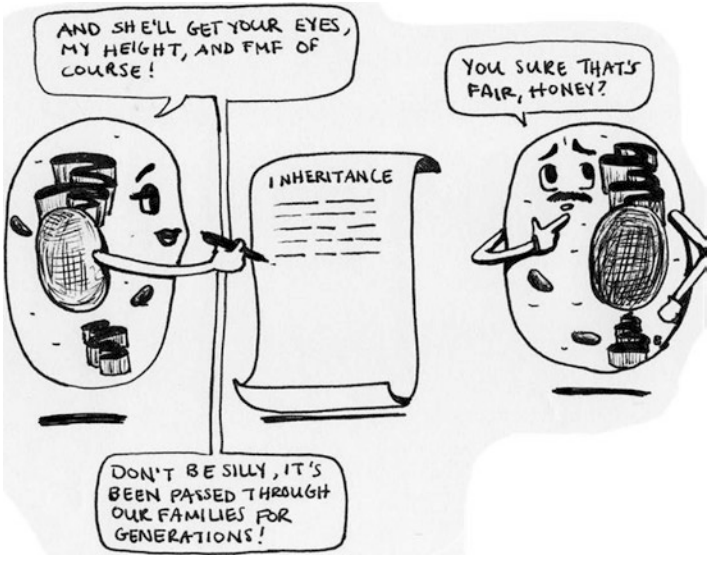

Figure 10.3 It runs in the family

and FMF manifestations. Regardless, we now had genetic evidence for our strong symptomatic diagnosis (Fig. 10.3).

She came in for an appointment the day we received her genetic testing results. For so long she had suffered from an unknown disease, which heavily impacted her daily life. She could not see her grandchildren whenever she had a fever and was even wary of being near them during her asymptomatic periods. Now, she was sure her fevers were not contagious, which meant she could see her grandchildren more often. Upon receiving her diagnosis, she and her husband quickly locked eyes and let out an excited giggle. They were just happy to have an answer that did not prevent them from seeing family.

After getting a definitive diagnosis, we also asked Mrs. Lesbos about any other symptoms she may have had. In addition to fevers, Mrs. Lesbos also told us that she had joint inflammation, especially in her wrists and fingers.

Treatment

Even with a heterozygous mutation, clear clinical symptoms of FMF warrant enough evidence for starting Mrs. Lesbos on colchicine therapy, which is the first line of defense against FMF. Though there is known cure for FMF, colchicine treats symptoms of the disease by mitigating the overactive inflammatory response and buildup of proteins that occur during attacks. It has stopped all attacks in 75% of patients who take colchicine and reduced symptoms of approximately 90% of affected patients. However, extreme compliance is essential when taking colchicine as it is expected that patients take it every day. If a patient stops treatment, he or she is likely to have an attack within the next several days [5].

The presence of high CRP, clinical symptoms, and genetic tests seem to suggest that Mrs. Lesbos should respond positively to colchicine, but she has not yet started treatment.

Fast Facts

Being heterozygous for FMF is not a certain sign that a patient will have FMF; however with sufficient clinical evidence—as in the case of Mrs. Lesbos—a diagnosis can be established. Common symptoms of FMF, paired with a heterozygous MEFV gene, are enough to start a patient on colchicine trials.

FMF is common among populations of Mediterranean origin and causes an inflammatory response as if the body is fighting off infection.

FMF usually presents itself early in life but can also present later in life as is in the rare case of Mrs. Lesbos.

Test Your Knowledge

1. Which of the following statements is false?

   (A) Pyrin stops and slows the inflammation response.
   (B) A single variation in the MEFV gene leads to a definite diagnosis of FMF.
   (C) FMF is relatively common in Mediterranean populations.
   (D) Colchicine treats symptoms of—but does not cure—FMF.
   (E) Pyrin is located within the cytoskeleton of white blood cells and directs their movement.

   ANSWER: (B) The single variation of the MEFV gene must be accompanied by sufficient clinical evidence before a diagnosis can be established.

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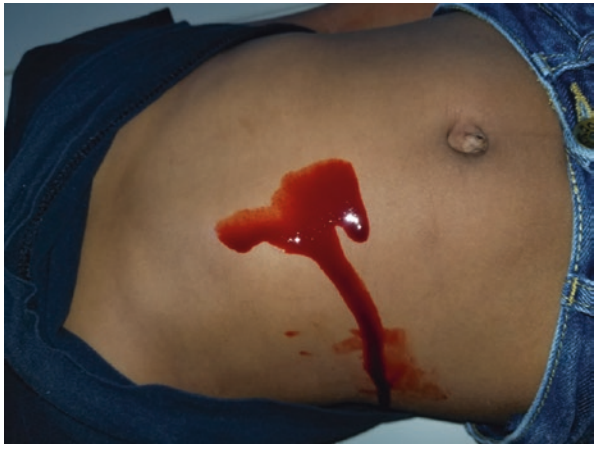
Chapter 11
"As a Matter of Fact, I Do Not Want This Blood"

Jheison Giraldo



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Vignette

How many times can one person get pneumonia in a lifetime? This is the question Mr. Enfiktid had after *40 episodes of pneumonia*, requiring antibiotics and frequent hospitalizations! Sick and tired of always being on antibiotics, Mr. Enfiktid sought help from our team. At Big University Hospital, Mr. Enfiktid complained of multiple recurring bacterial infections. He spoke to us about his quest to create his own business. Every time he set up a shop, he would be hospitalized for pneumonia, and his businesses would fail. His immune system was certainly compromised! We obtained an IgG level to verify low immunoglobulin levels. High levels are necessary to fight bacterial infections. The concentration of IgG was less than 50% of lower limit of normal. His symptoms and his test results led us to diagnose Mr. Enfiktid with CVID (common variable immunodeficiency disease)—also known as hypogammaglobulinemia—a rare and lifelong disease where B cells do not produce enough antibodies (such as IgAs, IgEs, and IgGs) [5] to fight off infection (Fig. 11.1) He was put on a regimen of intravenous or IV IgG to increase his levels and prevent further infection. While on these doses, Mr. Enfiktid was saved, until we received a hair-raising call from his mother years later (Figs. 11.2, 11.3, 11.4 and 11.5).

Let us backtrack a couple of years before the call. Mr. Enfiktid was treated with IV IgG monthly. He responded very well and had no infections for the longest period of time since his childhood. Years went by before he had another pneumonia. Then calamity struck when Mr. Enfiktid was unable to take his medication due to financial problems. Bacterial infections started coming back, and he began to smoke to relieve some of the stress. Then, things took a turn for the worse. Mr. Enfiktid felt helpless; he searched across the whole county until he found someone who provided pro bono infusion. They started him on IV IgG as fast as they could and redid his IgG levels. His IgG levels were back up

to the lowest limit of normal and were kept there. He was finally relieved and was ready for his health to improve.

After months of being on the treatment, Mr. Enfiktid saw no change. He was not getting any better even though his new physicians reassured him that he was immunologically treated. Being back at square one, he looked for help where he could. Doctors looked at his X-rays and saw that his lungs had some scarring, specifically the left lower lobe. They said that this area could be a petri dish for bacteria by letting it grow unchecked by the body's immune responses. They wanted to take it out. They would do a risky procedure to remove the lower portion of his left lung and possibly rid him of his frequent hospitalizations. Mr. Enfiktid knew he was already somewhat immunocompromised and would do anything to get his life back. After much thought, he finally said yes and headed for the operating room. This was almost the last decision he made.

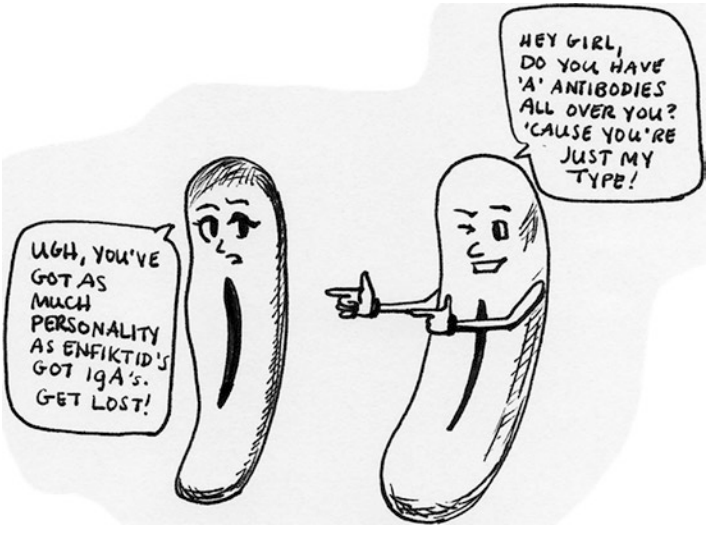

FIGURE 11.1 Smooth operator

FIGURE 11.2 Call for help

During his procedure, something went wrong, and he started losing blood. His body was bleeding from the inside. Bright red blood (frank blood) was pumping out of his chest tube into the boxy container on the floor! His blood pressure

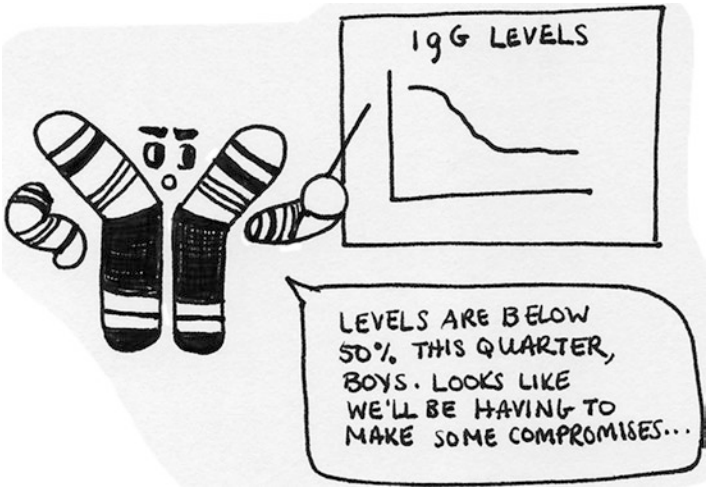

FIGURE 11.3 Low IgG levels prompt changes

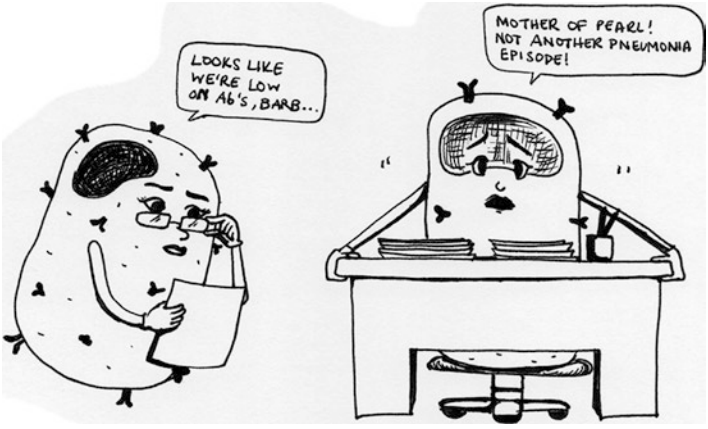

FIGURE 11.4 Panic of the lymphocytes

and hematocrit started sinking. He felt weak. He was quickly in need of a blood transfusion. The surgeons rushed to his mother to ask for consent, and she quickly remembered something our team had told her—Mr. Enfiktid could not

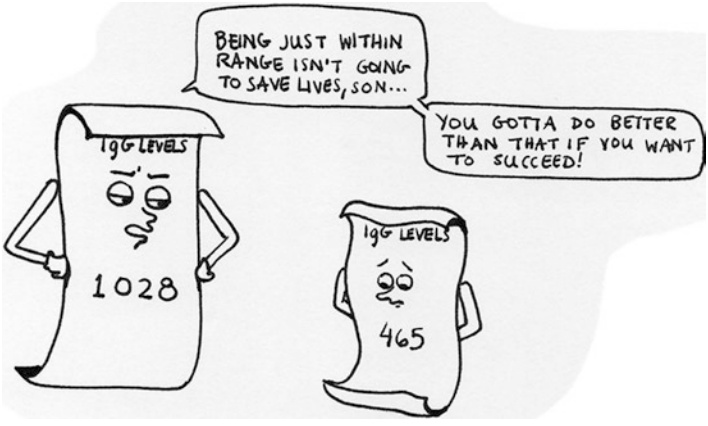

FIGURE 11.5 Not going to cut it

receive normal blood because his body could have an allergic reaction because of his CVID—the lack of IgAs in his system. Since his immune system could recognize IgAs as foreign invaders, it could trigger a systemic and potentially life-threatening IgE allergic response. This was the point when his mother, Mrs. Enfiktid, gave us a call.

Worried half to death, she told us all of the details and got us in contact with the ICU, where Mr. Enfiktid was admitted. We quickly visited him and looked for blood that had no IgAs (IgA-depleted blood), so that we could save this dying man. Unfortunately, we could not find any rapidly from the Greatest State Ever Blood Bank. The bleeding needed to be stopped. A stopgap measure was to use wash platelets and keep our fingers crossed. The surgeon was able to take Mr. Enfiktid to the operating room to sew up a lacerated thoracic artery to stop the bleeding from going further, but Mr. Enfiktid had already lost a lot of blood. Even with a cell saver device, a device that can recycle blood that is being lost by patients back into their bodies, Mr. Enfiktid was in a bad shape.

When Mr. Enfiktid resumed care with our team, during his visit we found some of the reasons why his disease became

symptomatic, even though he was being treated. Mr. Enfiktid was being undermedicated, and though his IgG levels were at the lower limit of normal, in the 400 range, they should have been toward the upper limit; the clinical response at which point he does not have bacterial infections is key. His body, which normally does not have a very good immune system to begin with, should not have been kept at such a low level of IgG. Secondly, more testing should have been done before the invasive removal of his lung's left lower lobe. A tagged white blood cell scan or gallium scan—along with a blood erythrocyte sedimentation rate—may have provided a clue that the region was not actively inflamed.

The surgical removal of Enfiktid's left lower lung led to a histological diagnosis of scar. The persistent haziness on his CT scans prior to surgery was a fixed, permanent scar. In retrospect, surgery may have been avoided, and, despite the success with washed platelets, planning may have provided enough time to obtain IgA-depleted blood. Mr. Enfiktid is now back on a higher dose of IgG, and his infections have resolved. Mrs. Enfiktid sent me a very lovely card thanking me profusely. It was one of the most gratifying cards this year, since she actually remembered something I told her—anaphylaxis risk from IgA-containing blood in hypogammaglobulinemia—over 10 years ago!

Background/Salient Features of the Case

CVID is a primary immune disease that affects about 1 in 50,000 persons [1]. Also known as hypogammaglobulinemia, it is usually diagnosed at an adult age, after several persistent or recurring infections. It can present with benign lymphoid proliferation, lymphadenopathy and splenomegaly, and autoimmune diseases such as rheumatoid arthritis, lupus, vitiligo, thrombocytopenia, neutropenia, and idiopathic thrombocytopenic purpura (ITP). This disease is caused by a malfunction in the B cells of the immune system, causing low levels in all of the immunoglobulin classes.

Diagnosis

Clinical diagnosis entails recognition of multiple infections affecting various organ systems:

- Pneumonia with fever
- Sinusitis documented by X-ray or CT scan
- Otitis media (although this can be common in children)
- Meningitis or sepsis
- Gastrointestinal infections
- Cutaneous infections

Other autoimmune disorders that can appear with CVID are rheumatoid arthritis, lupus, vitiligo, thrombocytopenia, neutropenia, and ITP [4].

Enlarged lymph nodes and splenomegaly are also useful physical findings in diagnosing CVID.

The most useful tests that can be done to confirm a diagnosis for CVID are quantitative serum immunoglobulin levels. Once a low level of immunoglobulin is confirmed, a measurement to specific vaccines can be taken. If these are low, a vaccine can be administered, and after 4 weeks, the levels are rechecked to see if they increased fourfold [3].

Treatment

CVID can be treated with IgG replacement therapy. The antibodies for replacement are from pooled plasma. Administration is subcutaneously or intravenously. For IV IgG, the loading and maintenance doses can be 400–600 mg/kg every 4 weeks [2].

Fast Facts

Recurring bacterial infections with other autoimmune diseases can be a sign of CVID.

A patient diagnosed with CVID will have very low levels of IgG created in their body and should be kept much higher than the lower limit of normal (639–1349) if still symptomatic, especially if they are smokers since this can cause increased metabolism of the IgG.

Before doing invasive surgery on patients with recurring respiratory infections, multiple diagnostic tools are available to look for current infection before hastily going through with the procedure.

Test Your Knowledge

1. If a patient with CVID is currently being treated with IV IgG at 400 mg/kg once a month and continues to have recurring bacterial infections, what can you do to help?

   (A) Refer them to a surgeon since there is obvious scarring in the lungs that might need to get removed.
   (B) Increase their IV IgG dose to see if infections will decrease over time.
   (C) Give the patient on antibiotics and send them home.
   (D) Stop the IV IgG treatment since it is clearly not working.

   ANSWER: (B) Increasing the dose or the frequency as interventions to consider. Dosage is titrated to elimination of infections rather than a set concentration of IgG in blood.

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Chapter 12
The Man Who Got an Unwanted Taste of the Rocky Mountains

JacqueLyn Kinney

Vignette

Mr. Balboa is a crossing guard in Suffolk County, Long Island. He spends the majority of his workday outside with all of the nature Long Island can provide him. It is not uncom-

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mon for him to be bothered by sundry insects from the nearby foliage. One hot summer day, he noticed that a tick had latched onto him, and, as Mr. Balboa removed it, he thought that he had put an end to this trouble. Soon after, a fever erupted. A few days later, a rash appeared, and his toes began to turn purple. Mr. Balboa had not yet realized that the fever seemed to be linked to something more serious, so taking into account his rashes and pigmentation of his toes, he rushed to see his local dermatologist. Upon examination, his dermatologist realized that this could have been an allergic reaction, so he was referred to Dr. Szema (Fig. 12.1).

After seeing Mr. Balboa, it was clear that he had been infected with life-threatening Rocky Mountain spotted fever (RMSF), brought on by the unsuspecting tick. When he took off his shoes and socks for us, Mark, a premed student in our office, had his second freak-out episode—they do not have patients with purple feet in Taiwan! RMSF, despite the name, is very common in much of the United States, particularly the Southeast coast, although it is not overly abundant in Long Island [1]. The fever is brought on by a species of bacteria, *Rickettsia rickettsii*, and it is not actually by an allergic reaction, as the rash would suggest. Although it can be deadly to live with RMSF, there are effective antibiotics that can stop the disease in its tracks (Fig. 12.2).

This is exactly the approach we used. Mr. Balboa's symptoms soon cleared up, but residual purple remained in his toes. As his symptoms were greatly improving, there seemed to be no further concern for him, and he went on his way. He soon returned to our office, complaining of more rashes, even after he had been treated. He had bought some cheap sunscreen from Bullseye Rash Supermarket without a second thought, but when he applied it, the rashes reappeared. No matter where he put the screen, a rash would soon follow—sparing his covered T-shirt area. He was photosensitive with sunscreen! We performed a patch test to the 85 allergens in household products called the North American Series. The result was negative or normal. Clearly there was something different about Bullseye Rash Supermarket sunscreen in Mr. Balboa. He had never had a reaction to sunscreen prior to his tick bite,

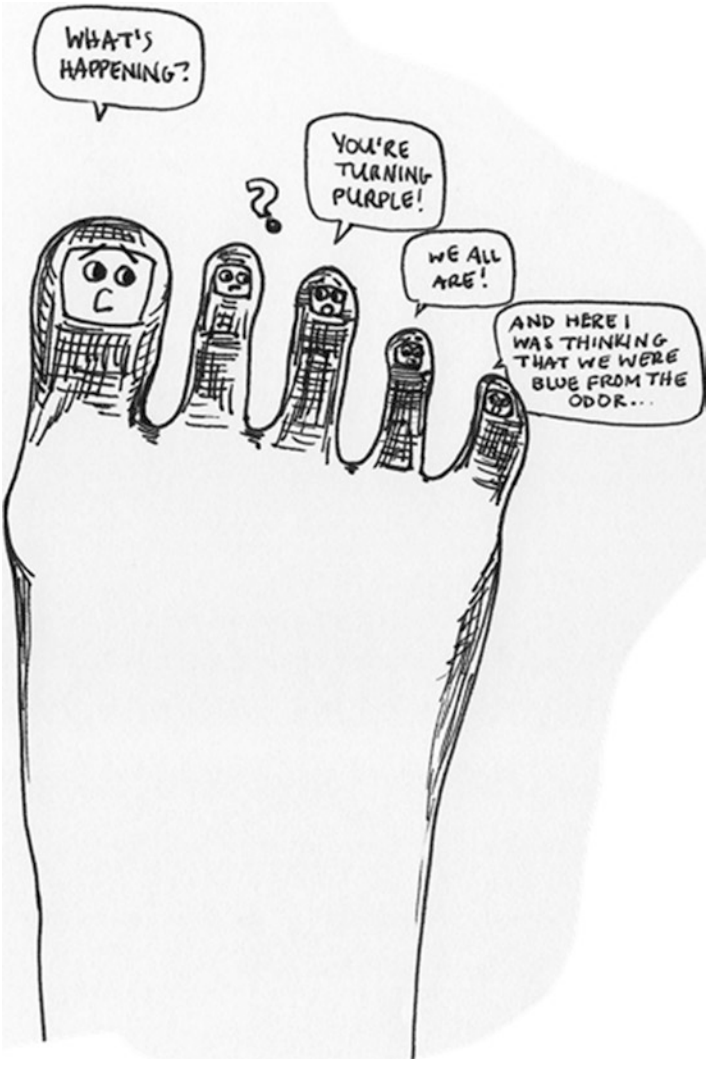

FIGURE 12.1 Something foul afoot

Figure 12.2 Ticked off

but whether this effect was a result of his RMSF is not certain; however, he was then advised to stay away from this sunscreen and other similar brands. There have been similar effects in patients, where the tick had previously bitten a deer, or similar mammal, that contained the bacteria for RMSF. When the tick then bites a person, the immune system recognizes the disease and the animal meat from the first bite as two parts of one invader. So if the body were to be "reinfected" with either one, an immune response, such as a rash or swelling, would result. Unfortunately for those people, the meat of the animal, and similar animals, would then be rejected by the body's immune response, likely to cause great swelling. Unfortunately for Mr. Balboa, his tick bite created this response as well. He is now only able to eat small portions of animal products, such as dairy or red meat, before he starts to have an allergic response. There are individuals who are still able to eat such foods and others who are no longer to ingest ANY animal products for the rest of their lives due to a severe allergic response! Being that Mr. Balboa does not have to completely stop eating meat, he got off lucky. He will be sure to wear bug spray the next time he is out on the job though! (Fig. 12.3).

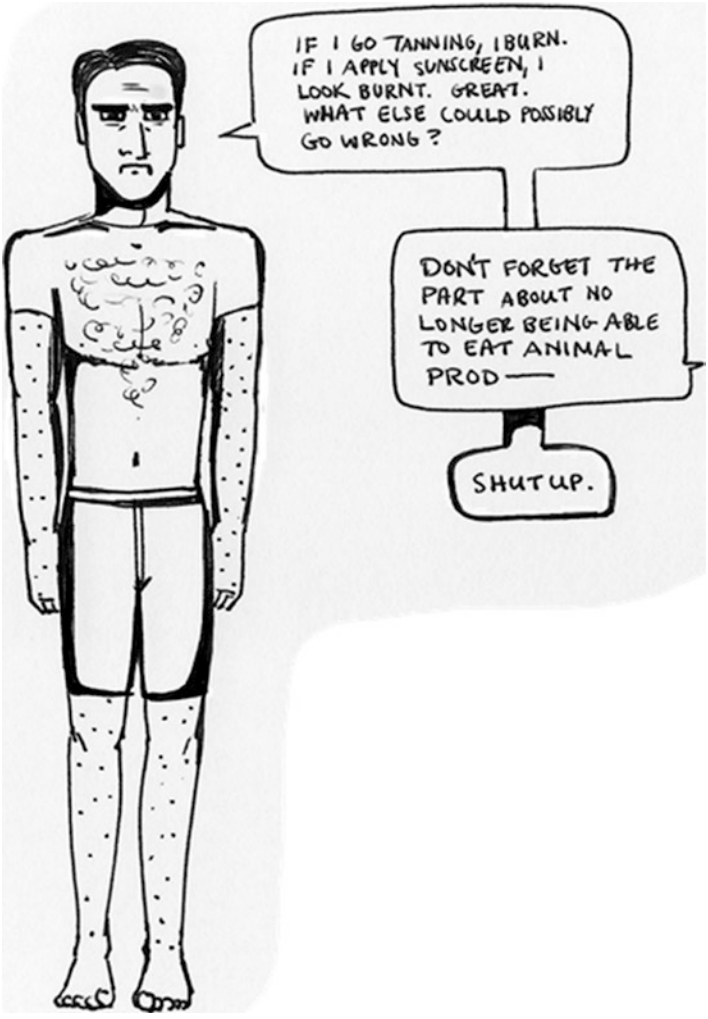

FIGURE 12.3 Groucho spots

Background/Salient Features of the Case

RMSF is caused by an infection of *R. rickettsii* in a human host [2]. Even in young healthy individuals, this infection can be life threatening and quite common. RMSF is the most common tick-borne disease in the United States and is not limited to the Rocky Mountain region but is most common in North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri. RMSF is one of the most virulent infections in our nation today.

The first published medical record of the illness was described in the late 1800s in Idaho, and by 1910, Howard T. Ricketts had isolated the bacteria. *R. rickettsii* can only survive when supplied with living host cell cultures and lives in the nucleases of those cells. It can be inherited through tick generations and thus remains in "natural reservoir." It can also be found in household pets and animals in nature, but those "natural reservoirs" are less understood. Many different types of ticks carry *R. rickettsii*, including, but not limited to, the American dog tick, the Rocky Mountain wood tick, and the brown dog tick, depending on the area you live in and the types of ticks that live there as well.

When an infected tick bites a human, *R. rickettsii* is able to enter the body. Not only does the bacterium enter the body but the tick also continues to supply new pathogens to the body, acting as a sort of reservoir. However, the bacterium is not exactly "activated" in the tick. It lies dormant until it is able to enter a host animal's cells [3]. This process takes a minimum of 4–6 h to reactivate the bacterium. Once infected, one should seek medical attention immediately. It will take 2–14 days for symptoms to manifest, but treatment is most effective earlier in the infection. Symptoms include fever, rash, headache, nausea, and abdominal pain. The rash may begin small but quickly spread over the span of a few days—although no rash could appear—which is when RMSF can be misdiagnosed and become fatal [4]. Many of these symptoms are seen in other common illnesses, so misdiagnoses are frequent. Thus, it is very important to always check for ticks when enjoying the outdoors.

To avoid such tick bites in the wild, the CDC recommends to treat your clothes with permethrin and to apply DEET as a bug repellent. In addition, the best way to prevent your lawn from harboring ticks infected with *R. rickettsii* is to treat it with pesticides monthly. This might not be feasible for all households, but to reduce your risk: remove leaf litter, mow your lawn frequently, place a 3-ft wide buffer zone of wood chips between your yard and wooded areas to restrict tick migration, construct fences to restrict wildlife migration, and keep playground equipment away from foliage. If you have a pet, such as a dog, tick collars are recommended and need to be replaced every 3 months. Infections in humans are most common in late spring and summer.

Diagnosis

When your immune system begins to identify foreign invaders and create antibodies formulated to identify the said invaders, those antibodies can be identified with immunohistochemical staining of a skin biopsy for rickettsiae if the diagnosis is not visually clear. If those antibodies are present in the skin biopsy, such as in the rash, then the test will be able to stain those specific antibodies. Unfortunately, this test is nonspecific to RMSF but instead to all rickettsiae bacteria. Therefore, RMSF is often diagnosed based upon visual symptoms, such as fever or chills, rash, headache, nausea, purple toes/fingers, cough, sensitivity to light, muscle pain, and abdominal pain [5]. In addition, treatment is often more effective sooner rather than later, so treatment generally begins before lab tests can be completed.

Treatment

Rocky Mountain spotted fever is often treated with 100 mg doxycycline twice daily for adults and 2 mg/kg bodyweight per dose given twice daily for children weighing less than

45 kg. Treatment lasts from 5 to 7 days and at least 2–3 days after the fever has gone. To prevent gray baby syndrome in pregnant women, 50–75 gm/kg dose of chloramphenicol per day, divided into four doses for 7 days [5]. Treatment is most effective at preventing fatalities when administered within 5 days after the symptoms manifest; therefore, antibiotics should be administered before lab tests confirm the diagnosis. No vaccines have been developed to date.

Fast Facts

RMSF is caused by an infection of bacteria with *R. rickettsii*, spread to humans via a tick bite from an infected tick.
RMSF is common throughout the United States, and thus proper precautions should be made to avoid tick bites.
There are treatment plans for RMSF, largely using doxycycline, that are most effective when administered early.

Test Your Knowledge

1. Which of the following are symptoms of RMSF?

   (A) Vomiting
   (B) Rash
   (C) Shortness of breath
   (D) Fever

   ANSWER: (A), (B), and (D) Symptoms include vomiting, rash, and a fever. Shortness of breath is not a common symptom in infected individuals. Other symptoms include chills, headache, nausea, purple toes/fingers, cough, sensitivity to light, muscle pain, and abdominal pain.

2. Who should be concerned about contracting RMSF? Select all that apply.

   (A) Those working near/in foliage
   (B) Those living in suburban environments

(C) Those visiting/living in the countryside
(D) Those working in office buildings

ANSWER: (A), (B), and (C) Those that are near to any form of foliage should be cautious of a tick bite. Although those working in office building are not near foliage, if they leave the office building and do yard work, they are then at risk. The best way to avoid a tick bite is to always wear bug spray, especially when you are in areas such as a field or the woods.

3. How long does it take for symptoms to manifest themselves in someone infected with *R. rickettsii*?

(A) 24 h
(B) 2–14 days
(C) <24 h
(D) >14 days

ANSWER: (B) Symptom manifestation varies depending upon the person and the exact bite but normally manifests itself in 2–14 days. This gives the body enough time to recognize the foreign invaders and begin to have an immune response. This immune response is visually seen via your symptoms, such as a rash or swelling.

4. RMSF can have lifelong side effects.

(A) True
(B) False

ANSWER: (A) Long-term effects, such as the inability to consume meat or other animal products, are a possibility in previously infected individuals. The long-term side effects are caused by your immune system reacting to the animal products in the same way it reacts to the bacteria. If the tick had previously bitten an animal, traces of the animal's blood is likely still within the system. So when the tick trades fluids with you when it bites you, both the bacteria and the animal are "infecting" you. Although this trace

amount would not harm you, your immune system is able to recognize it, with the bacteria, but is unable to distinguish which is the harmful entity. Therefore, to take precautions for the future, the body "remembers" the identity of these invaders by keeping a few of the antibodies for that specific antigen. These antibodies then recognize and latch onto the bacteria or meat whenever they enter the body and cause an immune response. This immune response is normally manifested in swelling and/or rash.

5. How long after the bite does *R. rickettsii* reactivate in the animal host?

   (A) 1–2 h
   (B) 10–12 h
   (C) 24 h
   (D) 4–6 h

   ANSWER: (D) The bacterium reactivates in the animal host 4–6 h after infection. *R. rickettsii* lives inactivated in the tick without impairing the tick, which can lead to increased rates of animal infection—as opposed to a sickly tick that is unable to find or latch onto a prey so easily. Once the bacteria enter the animal blood stream, it senses that it is time to reactivate and causes illness in the host.

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Chapter 13
An Imitation Game

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Vignette

In early April of 2015, a man in his late sixties, Señor Roncha, came into my office complaining of rashes and itchy skin. He had throbbing inflammation in his hands, which pointed to a bad allergy, and he was convinced he had developed a reaction from some of the plants around his house. He came in during the peak of allergy season, and everything appeared to be routine until I discovered he had been experiencing these symptoms since January—nearly 4 months ago!

Upon further inspection, I found that he also had purple feet! Sr. Roncha had severe purpura, a condition of bleeding under the skin that is characterized by the presence of large, purple spots. It usually appears in patients with bleeding disorders or vascular problems—and occasionally with the use of cocaine. The extent of Sr. Roncha's drug use was smoking cigarettes, which he had quit decades ago. He was also not taking any medication when the purpura seemingly appeared out of nowhere, so I contacted his dermatologist to find out more about his medical history.

The situation became clearer when I learned he had recently developed inflamed blood vessels or vasculitis. Among a variety of other symptoms such as high blood pressure and weight loss, vasculitis can cause pronounced purpura, and this helped to explain the sudden purpling of Sr. Roncha's feet. He reported not having any notable change in weight recently, and his blood pressure was normal by all standards. His cardiovascular activity was otherwise normal, so the questions remained:

1. How did he get vasculitis?
2. Why did it not emerge any time earlier in his life?

Sr. Roncha works as a crossing guard and spends a large amount of time outdoors. On duty one day, he unknowingly came across a tick and received a painful bite, something that is common around the wooded areas of Long Island. Now one might say, "Dr. Szema, I've been bitten by ticks plenty, and my feet have never shown even the slightest inclination of turning purple!" and they could absolutely be telling the truth.

There was something very special about the tick that bit Sr. Roncha: it happened to be carrying a species of bacteria known as *Rickettsia rickettsii*, the sole causative agent of Rocky Mountain spotted fever (RMSF). Despite its name, RMSF is actually much more prevalent on the east coast of the United States, and Sr. Roncha had indeed contracted the disease, unfortunately.

By the time I saw him, he was undergoing the standard treatment for RMSF, consisting of doxycycline and steroids. The rashes on his extremities appeared to be residual effects of the disease, and they had been steadily improving since their onset in January. I suspected they would go away completely once the underlying cause was cured, so I advised Sr. Roncha to continue on his current treatment plan.

I was quite surprised to see him return to my office only 5 months later.

When he returned, Sr. Roncha had already been cured of his purple feet. The symptoms of RMSF were all but gone. Yet, a new set of rashes had developed, and this time they were presented in a suspicious pattern: the V-neck of his collar, his hands and arms, and also his ears. He had been out boating, but these rashes were not burns. Instead, they pointed to a clinical diagnosis of contact dermatitis. The isolated locations on the body all had something in common: they were not covered by summertime clothing. In fact, these parts of the skin are exposed directly to sunlight and should be protected with sunscreen of adequate SPF—Sr. Roncha had experienced an allergic reaction to his sunscreen!

The brand of sunscreen he had used was Hampton's Friendly Kid's Lotion—SPF 50—purchased from a local Bullseye Rash Supermarket. I ran a patch test of the 85 most common chemicals in consumer products, but the results all came back negative. The exact component causing the reaction still remains unknown. It is also a possibility that the ingredient is not alone enough to cause the reaction and may require exposure to direct sunlight, as were the conditions when Sr. Roncha first developed the rashes. Doxycycline can also cause

photosensitivity, so taking the antibiotic combined with applying the sunscreen may have compounded the effect. According to Sr. Roncha, the rashes developed slowly over the course of the day and had lasted at least a few days. Interestingly, he is able to use other brands of sunscreen without a problem.

Was he sensitized to the sunscreen because of his doxycycline treatment plan—or perhaps it was the Rocky Mountain spotted fever itself that sensitized him? What may come as a surprise is that sunscreen is actually the number one cause of photocontact dermatitis in the United States. It is likely that Sr. Roncha had always been allergic to a specific compound all along and had just never encountered it before in all of his 60 some-odd-years of life.

If you are walking along the beach or swimming in the pool and suddenly feel a burning, itching sensation, it could be something in the water or that food you ate earlier—but it might also be a good idea to check your sunscreen!

Background/Salient Features of the Case

RMSF

RMSF is an incredibly rare disease, with an incidence of under 2000 cases per year in the United States [2]. Prior to the antibiotic era in the middle of the twentieth century, the mortality rate of the illness was incredibly high at around 30%, but it has since steadily declined down to less than 0.5% as of 2010 [4]. Described as "the great imitator" due to how diverse the initial symptoms can possibly be (fever, nausea, muscle pain, headache, etc.), one of the biggest challenges for physicians is being able to make a timely diagnosis.

RMSF is a multisystem disease and can cause damage to the central nervous, gastrointestinal, pulmonary, microcirculatory, renal, and respiratory systems or any combination of the above. Neurological symptoms may present as lethargy and confusion but can be severe as to include seizures, ataxia, and coma. One in ten patients may also develop jaundice; advanced RMSF requires hospitalization [4].

Red/purple spots, or petechiae, are not usually seen until after the first week of the patient contracting RMSF, and these rashes actually indicate progression to severe disease. In the case of Sr. Roncha, his RMSF had developed enough to cover both of his legs in purpura. At the same time, it is important to note that in 10–15% of RMSF cases, the rashes may not develop at all [4].

Contact Dermatitis

Modern sunscreens contain numerous different active chemicals that can either absorb or block UV radiation. The vast majority of products also contain various fragrances and preservatives, and any of these compounds can elicit an allergic reaction. These differences between brands explain why Sr. Roncha was able to use sunscreen brands in the past without any problems and only reacted to the Hampton's Friendly formula.

There is also a special condition known as *photo*contact dermatitis, where the allergy is actually triggered by the interaction of UV radiation and one of the chemical compounds rather than either individually [3]. I suspect that Sr. Roncha had this latter condition due to the rashes developing slowly over the course of the day rather than within minutes of the sunscreen being applied.

Diagnosis

RMSF

The initial symptoms of RMSF are unexceptional and include fever, nausea, headache, and a variety of other general symptoms that vary from patient to patient and are difficult to use for diagnosis [2]. Roughly 90% of people with RMSF develop red or purple rashes, the hallmark of the disease [4]. The classic triad for diagnosis is the presence of fever, rashes, and a history of tick bite [2].

Currently, no tests are available that can provide conclusive results within a clinically practical time frame, so healthcare providers are required to use clinical judgment for diagnosis and treatment on a case-by-case basis [2]. Most diagnoses should be made on the grounds of history, epidemiology, and a clinical exam. Diagnoses can be confirmed later by laboratory tests, but treatment should never be delayed, since survival rate decreases after 5 days of the patient becoming symptomatic. Currently, the gold standard for laboratory confirmation relies on an immunofluorescence assay (IFA) on paired samples and requires a fourfold change in IgG-specific antibody titer [4].

Contact Dermatitis

Contact dermatitis can result from either a physical irritation (nonimmune modulated) or an allergic reaction. It is an inflammatory skin condition that presents with erythema and can also include lesions and/or bullae [5]. Contact dermatitis is common, and patients often experience itchiness and discomfort [1]. Diagnoses can often be made through a patch test (if the causes of rashes are not immediately apparent). Additionally, medical history and a physical examination can be used by a doctor to help identify allergen(s) that may be causing a reaction.

Treatment

RMSF

For both adults and children, the current first-line treatment is doxycycline (2.2 mg/kg body weight up to 100 mg administered every 12 h) [2]. Treatment is most effective at preventing death if initiated within 5 days of the patient becoming symptomatic. If patients have life-threatening

allergies to doxycycline, treatment with chloramphenicol can be used instead.

Contact Dermatitis

Topical steroids, such as triamcinolone 0.1% or clobetasol 0.05%, can be used to treat localized, acute contact dermatitis [1]. If the symptoms are extensive and cover more than 20% of the skin, systemic steroid therapy should be used instead. Prednisone can be administered orally or IV/IM at 1–2 mg/kg each day, for 3–7 days with a taper over 1–2 weeks [1].

Fast Facts

The interaction between UV radiation and various compounds in sunscreen formulas can elicit a photoallergic reaction in certain individuals.
RMSF is a multisystem disease which can present initially with generic symptoms before developing into severe, system-specific ailments.
Treatment for RMSF should not be delayed and should be administered immediately once there is reasonable suspicion for the disease.

Test Your Knowledge

Which of the following diagnostic tests is typically unrelated to contact dermatitis?

(A) Repeat open application test
(B) Patch testing
(C) Skin biopsy
(D) DNA microarray

Explanation

The answer to the multiple choice question is (D) DNA microarray. DNA microarray is useful in genetic testing for determining congenital or hereditary anomalies rather than for specific antigens.

Repeat open application test (ROAT) is a commonly used test to determine contact dermatitis through repeated exposure of the skin to potential allergens.

Patch testing is commonly used to test multiple allergens at a time under an airtight dressing.

Skin biopsy is typically not used as a tool for diagnosis but may be useful in cases of severe and repeated contact dermatitis. It is useful for determining the cause of a skin rash and also for ruling out skin cancer as a possibility.

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Chapter 14
Clozapine Gone Wild

Tram Nguyen

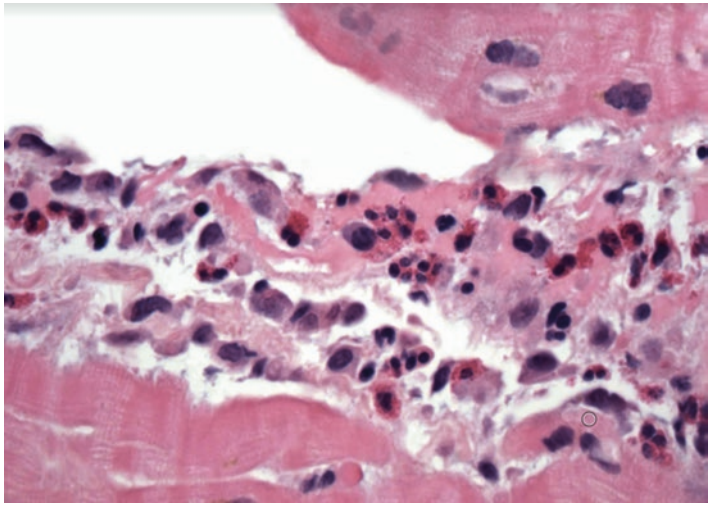

Photo courtesy of Charles Marboe, MD, Columbia University Medical Center

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Vignette

In March 2010, Kountdookyu was admitted to the Suburban Private Hospital emergency room due to a severe episode of paranoia. He appeared terrified, insisting that he was getting "messages from the Pope"! His helpless mother explained that his current antipsychotic medications (olanzapine, aripiprazole, and fluphenazine) had stopped working, so she had no choice but to bring him to the hospital in the middle of the night. After examination, the attending psychiatrist, Dr. Fritz, administered clozapine to manage Char-lie's symptoms. Within 2 weeks, Kountdookyu's paranoia subsided, and he was transferred to the inpatient medical ward. Unfortunately, a gastroenteritis outbreak at the hospital did not spare Kountdookyu. He quickly developed a high fever, explosive diarrhea, and pneumonia. His blood pressure fell and his heart became inflamed. This inopportune conglomeration of acute conditions shocked the medical staff! Clozapine was thought to be responsible, and thus it was immediately discontinued. An air ambulance helicopter transferred Kountdookyu to Ivy League University Hospital to receive appropriate treatment, but the doctors could not save him. Char-lie passed away at the age of 22 (Figs. 14.1 and 14.2).

Just a week following the tragic case of 41-year-old Faux Dud was admitted to Suburban Private Hospital as Faux insisted he could crash into cars on the highway without injuring himself. Dr. Fritz quickly learned about Faux's bipolar disorder from his family. Since other antipsychotics Faux was taking at home were not responding well to this particular manic episode, Dr. Fritz decided to put Faux on clozapine—the most effective antipsychotic. Faux's grandiose delusions faded away. Unfortunately, the gastroenteritis outbreak at the hospital had not yet been contained. Like Kountdookyu, Faux started having high fever and diarrhea. Faux eventually developed cardiomyopathy, a

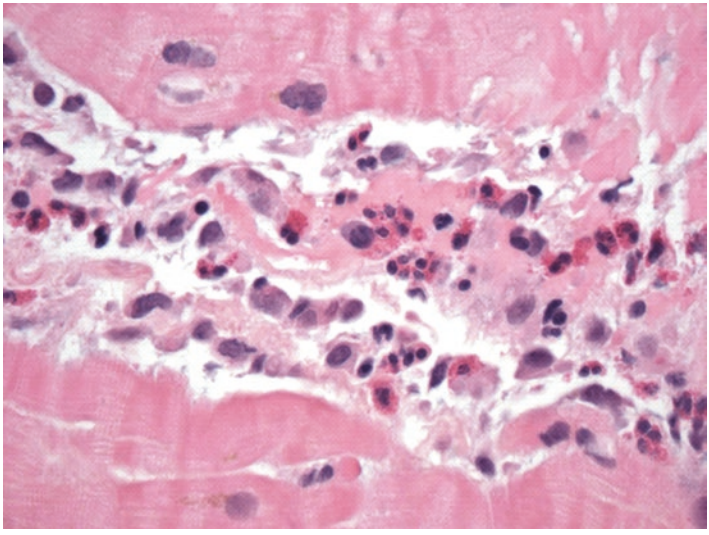

FIGURE 14.1 Cardiac muscle biopsy from Faux Dud, a 41-year-old patient, with blood eosinophilia and elevation in creatine kinase in a setting of a new-onset fever and clozapine usage. Eosinophils, shown as eccentric red cytoplasm with bilobed nuclei in this illustration, are present in cardiac tissue (© Anthony Szema)

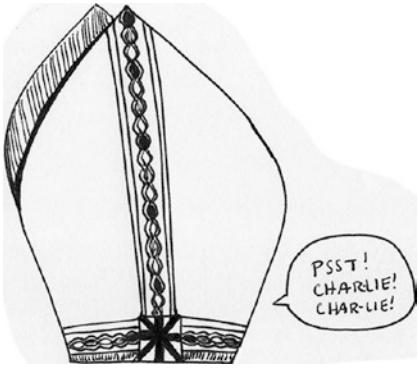

FIGURE 14.2 Messages from above. Photo courtesy of Charles Marboe, MD, Columbia University Medical Center

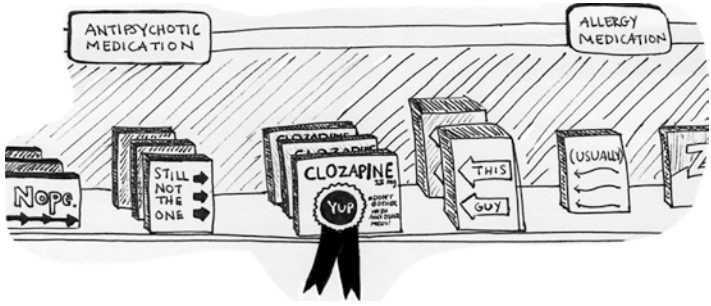

Figure 14.3 Winner takes all

heart muscle disease that prevented his heart from pumping blood to the rest of his body. If you guessed that Dr. Fritz stopped giving Faux clozapine immediately, you would be correct! Faux was luckily rescued by the critical care team, and his health gradually stabilized over the next month (Fig. 14.3).

After Kountdookyu and Faux, two other patients with adverse reactions to clozapine were also reported at Suburban Private Hospital. These patients suffered from infectious gastroenteritis, and one of them eventually developed myocarditis. Unlike Kountdookyu, Faux and the other two patients managed to survive, yet their similar complications following clozapine initiation beg the question: What impact does clozapine really have?

Background/Salient Features of Case

Schizophrenia is a devastating psychiatric disorder; it slowly decreases normal mental functions and manifests itself as paranoia, hallucinations, and delusions. While no cure exists, atypical antipsychotics are commonly used to control the symptoms and improve quality of life. Among these drugs, clozapine is the most effective in regard to managing treatment-resistant schizophrenia. Compared to typical antipsychotics, clozapine has been reported to pose similar dose-related risks of sudden cardiac death [1].

Within merely 3 months during the spring of 2010, three patients treated with clozapine at Suburban Private Hospital developed high fevers as well as cardiac and gastrointestinal problems. In 2011, another psychiatric patient admitted to Suburban Private Hospital suffered a similar reaction 2 weeks after clozapine initiation. These patients all administered the standard dosage of clozapine ranging from 50 to 300 mg per day, ruling out the possibility of an overdose. It is important to note that clozapine-induced cardiac adverse reactions are rare, occurring at the rate of 0.7–1.2% among treated patients [2]. In other words, among a *thousand* psychiatric patients taking clozapine, only 7–12 patients will start having heart problems! Inasmuch as Suburban Private's Inpatient Adult Psychiatric Unit could only accommodate 27 psychiatric patients, clozapine-induced myocarditis was observed at a much higher rate at this hospital than reported in the literature.

One common comorbid factor among these four patients was the presence of high fever and fulminant, explosive diarrhea following infectious gastroenteritis. Although gastroenteritis caused by Coxsackievirus can lead to myocarditis, lab tests showed the absence of viral nucleic acids, confirming that this outbreak was not caused by this viral agent.

Diagnosis

Kountdookyu and Faux Dud were both given clozapine because other psychopharmacologic interventions were no longer responsive to their psychotic symptoms. While Dr. Fritz was aware of clozapine's possible side effects, he considered it a viable treatment for Char-lie's persistent paranoia and Faux's severe delusions, as they had both no known history of structural heart failure or hematological abnormalities.

During their hospital stay, both Char-lie and Faux developed high fever (103 °F) and diarrhea like the other patients affected by infectious gastroenteritis, yet their health continued to deteriorate. Char-lie's respiratory system also became infected. Approximately 2 weeks after the clozapine initiation, Char-lie's cardiac ejection fraction (EF) eventually

dropped to 10% (a normal heart's EF is 85%), resulting in a myocardial infarction (heart attack).

Char-lie and Faux's cardiac biopsies revealed abnormal results. Leukopenia (low white blood cell count) is a possible side effect of clozapine use and is often observed following viral gastroenteritis, yet both Char-lie and Faux's white blood cell counts remained elevated. Char-lie and Faux were also presented with eosinophilia, an increase of a particular type of white blood cell, which is another notable and uncommon side effect of clozapine use. These complications led the providers at Suburban Private Hospital to doubt the safeness of clozapine.

You might think it was no surprise that Char-lie and Faux shared similar clinical outcomes. You might even question Dr. Fritz's decision of choosing clozapine as a treatment for Faux when Char-lie just had adverse reactions to it merely a week ago. However, keep in mind that Char-lie was deemed an outlier, because clozapine-induced myocarditis is rare. Thus, Dr. Fritz was reasonable when he put Faux on clozapine.

Treatment

Clozapine was promptly stopped after it was deemed the underlying cause of the patients' acute reactions. Char-lie was referred to Ivy League University Hospital for left ventricular assist device management and endomyocardial biopsies. On the other hand, Faux received treatment at the Medical Intensive Care Unit (MICU) of Suburban Private Hospital. Although ventricular assist devices could not save Char-lie's heart, they were successfully used to manage the other patients' cardiac conditions. Following clozapine discontinuation, the additional patient who did not develop myocarditis was able to recover as well.

The interaction between gastroenteritis and clozapine initiation has not been formally examined as a possible cause of myocarditis. Moreover, the observation of adverse reactions to

clozapine in four patients within 1 year challenges previous statistical findings. It is therefore possible that clozapine-induced myocarditis occurs at a higher rate than that previously reported. Based on these four unusual cases, we urge providers to stay alert to the link between clozapine, gastroenteritis, and myocarditis.

Fast Facts

Clozapine-induced myocarditis is rare, but it was observed at a much higher rate in the same hospital within 1 year [2].
While clozapine has been previously reported to induce gastrohypomotility (constipation), these four patients had explosive diarrhea [3]. Explosive diarrhea might occur when a patient takes clozapine [4]. However, the outbreak at Suburban Private Hospital suggests that diarrhea was induced by infectious gastroenteritis.
Prior to this observation, no formal investigation had been conducted on myocarditis as a result of the possible coupling of gastroenteritis and clozapine use in drug-naïve patients. The outcome for these patients suggests that clozapine-induced myocarditis might occur more frequently than previously reported.

Test Your Knowledge

1. Which of the following statements is false?

   (A) Clozapine is an atypical antipsychotic drug effective in managing symptoms in patients with schizophrenia.
   (B) Myocarditis, gastroenteritis, and clozapine use might be related to each other.
   (C) Cardiac adverse reactions to clozapine are very common.
   (D) Eosinophilia is a rare side effect of clozapine.

   ANSWER: (C) Like many pharmacological agents, clozapine has side effects, most of which are not life

threatening. It is very uncommon for clozapine to cause adverse reactions. However, the unusual incident observed at Suburban Private Hospital suggests clozapine-induced myocarditis might occur at a higher rate than previously reported, especially with concurrent gastroenteritis. More extensive research still needs to be conducted to make a significant conclusion.

A, B, and D are true. Clozapine is by far the most effective drug to relieve psychotic symptoms in patients with drug-resistant schizophrenia and/or bipolar disorder. Thus, clozapine is only used when other antipsychotic drugs no longer work. As suggested by literature and the incident reported in this chapter, there is a possible relationship between myocarditis and gastroenteritis and clozapine use. In addition, eosinophilia rarely occurs following clozapine initiation [5].

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Chapter 15
Mrs. Merda: An Avid Consumer of Third-Generation Antibiotics and Morphine

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Vignette

Mrs. Merda has chronic back pain; her physician prescribed morphine and hydromorphone, but they were unable to provide relief for her pain. In desperation, she hoarded syringes and needles, along with multiple bottles of the aforementioned medications. In conjunction with her diabetes mellitus type 2, her medications made her *very* constipated. She had not had a bowel movement for days. Then suddenly one morning, she had fever as high as 101.3 °F, nausea, vomiting, diarrhea, and altered mental status. Was this simply common viral gastroenteritis? (Fig. 15.1).

Rather than see her primary care physician, Mrs. Merda went to Big University Hospital for treatment. In the emergency department, doctors cultured her blood, stool, and urine and initiated antibiotics. Because of her history of 14 hospital admissions for *Clostridium difficile* infections in the past year, and therefore the possibility of a prolonged course of antibiotics, the hospitalist team had the interventional radiologist install a semipermanent catheter called a peripherally inserted central catheter (PICC) line—rather than use an IV—and started antibiotics. Five days later her

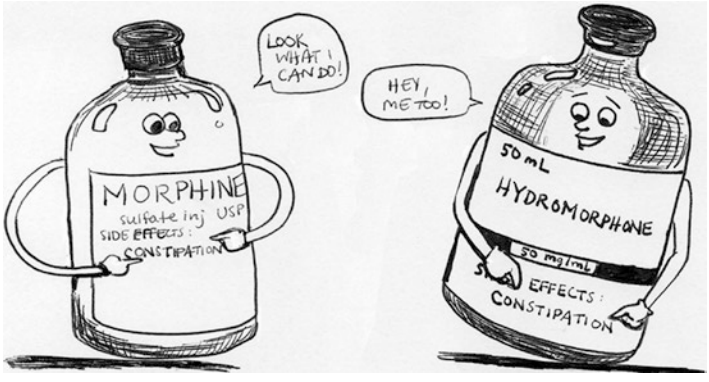

Figure 15.1 Constipationople

blood cultures were negative! Nevertheless, antibiotics were not discontinued. Unfortunately, the PICC line malfunctioned, could not flush its contents, and it was removed. A new culture of the PICC line grew gram-negative rod-shaped bacteria in her blood along with a potpourri of other bacteria. Mrs. Merda was diagnosed with systemic inflammatory response syndrome (SIRS) associated with gram-negative sepsis, a diagnosis that hinged on the results of the cultures.

It is important to understand that a PICC line is inserted in a sterile fashion, and it would be unexpected to find any bacteria on it, particularly since antibiotics had already been started. Was she seeding bacteria from her gut to her blood? We think probably not. It turns out that Mrs. Merda's son brought special deliveries of her morphine and syringes to the hospital. She avidly used these gifts. Now, why is this important? She could have injected herself through a large muscle, like the buttocks, or through the PICC line.

Even with Mrs. Merda's history of *C. difficile* infections, it is likely she arrived at the ER with a simple case of gastroenteritis. This is supported by the fact that her initial blood culture showed no growth after 5 days. However, by injecting herself with morphine using unwashed hands into her PICC line, she developed sepsis-requiring treatment with antibiotics. Mrs. Merda was switched from ceftriaxone to meropenem to daptomycin to vancomycin to cefepime and finally to ciprofloxacin and linezolid. There are a few problems with using multiple antibiotics. First, these drugs exert a type of selective pressure on bacteria to transmit genetic material in the form of plasmids to one another thereby fostering resistance. Secondly, *C. difficile* infections commonly follow antibiotic use that has disrupted regular intestinal microbiota [1]. If the initial gram-negative bacteria were sensitive to penicillin, this should have been the first choice of antibiotic. Even if she had a history of severe allergy to penicillin with anaphylactic shock, she could have been desensitized to it in a few hours in the Intensive Care

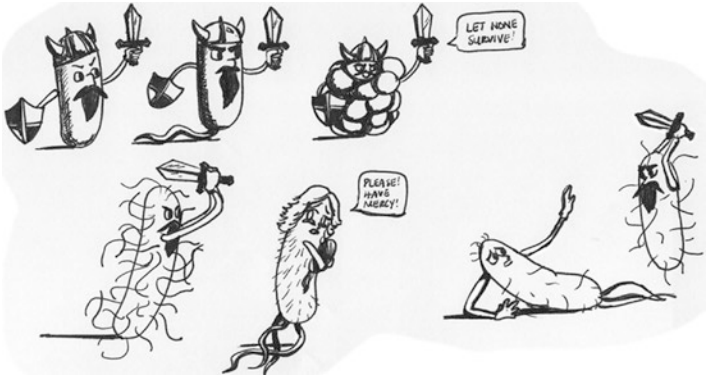

Figure 15.2 Microbial invasion

Unit (ICU). Instead, Mrs. Merda was placed on a quickly changing regimen of antibiotics, depleting the trillions of healthy bacteria in her gut, while also promoting resistance and proliferation of harmful bacteria (Fig. 15.2).

As a result of her therapeutic misadventures, Mrs. Merda had been admitted 14 times to Big University Hospital prior to this visit. From the emergency room, she was transferred to the ICU, but her problems didn't end there. Even after 2 weeks, Mrs. Merda was still abusing her catheters with her son's special deliveries. She was caught; a psychiatric consultation was requested. Unhappy with the prospect of being babysat, Mrs. Merda stated her desire to leave against medical advice (with her infection still not under control), but decided to stay. After the medical team recovered multiple bottles of opiates, syringes, and Mrs. Merda's oral confession of supplementing morphine, she was determined to be a danger to herself. Visitors were barred. It was at this juncture that she was switched to oral ciprofloxacin and linezolid—almost a month after admittance. She was finally discharged a week later. Along with her discharge note was a request for a consult by an immunologist for a low white blood cell count (Fig. 15.3).

Just a month prior to this hospitalization, she had received a fecal transplant and her *C. difficile* had been under control. Following the barrage of antibiotics, it is of little surprise that

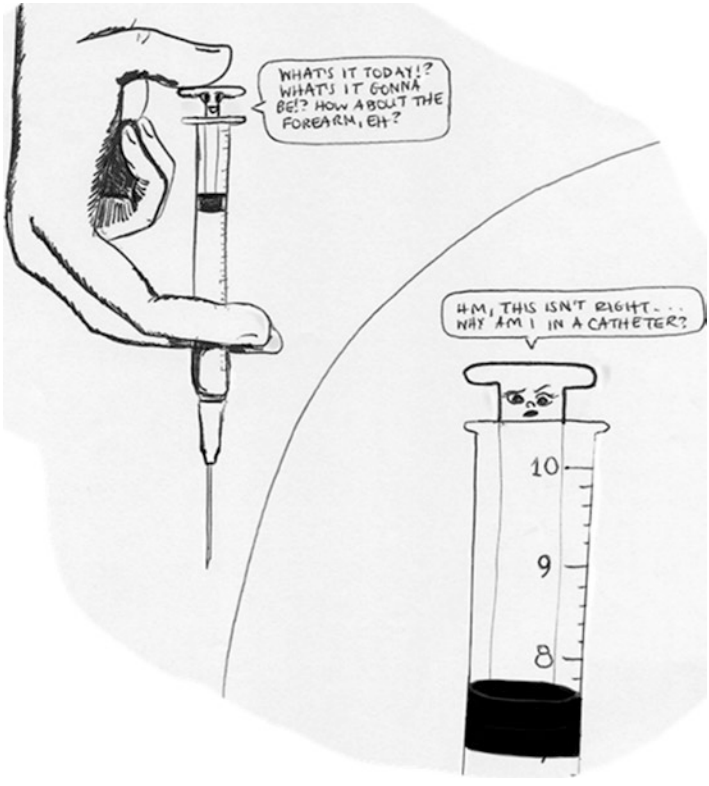

Figure 15.3 Cath you later

she had another *C. difficile* infection just waiting to flare up. After yet another round of antibiotics wiped out everything in her gut, probiotics were unable to restart her gut flora. What option was there for treatment? If you were thinking "another fecal transplant," you would be right (Fig. 15.4).

One month after the hospital admission detailed above, Mrs. Merda headed back to Big University Hospital for a second fecal transplant to help restore her intestinal flora and prevent further *C. difficile* infections. The procedure was a success! Mrs. Merda spent her recovery period in the Gastroenterology Department. However, she found herself with one devastating hiccup: Mrs. Merda's suitemate in recovery, and the person she

FIGURE 15.4 How many antibiotics does she need?

shared a bathroom with, had a *C. difficile* infection, and the bacteria was reintroduced into her system. A month after her fecal transplant, Mrs. Merda was back for her third fecal transplant that year!

Background/Salient Features of Case

C. difficile is a gram-positive anaerobic bacillus that can cause infection after antibiotic use, hospital stays, or exposure to the bacteria or spores, such as when a patient shares a bathroom with another patient with *C. difficile* infection. The *C. difficile* bacteria initial colonization is dependent on a disruption of the normal intestinal flora, and patients may have a range of presentations from asymptomatic carriers to pseudomembranous colitis to fulminant colitis with toxic megacolon. Two exotoxins, termed Toxin A and Toxin B, are released by *C. difficile* and cause much of the damage. Toxin A is an enterotoxin capable of binding to the luminal aspect of the intestinal epithelium, and Toxin B is a cytotoxin with less activity in humans. Toxin A is involved in the monoglucosylation of threonine 37/35 on GTP-binding proteins in the Rho family. Cdc42, Rac, and Rho are all inactivated leading to depolymerization of actin filaments, cell rounding, disruption of the cytoskeleton, disruption of tight junctions, and cell death by activation of caspases [2].

Most of the cases described in this book present with common symptoms diagnosed with unusual causes. The case of

Mrs. Merda is somewhat different as a common diagnosis with an unusual result. Many variables confounded Mrs. Merda's diagnosis and treatment, first the hospital's assumption that they were dealing with something exotic from the get-go as opposed to the mundane gastroenteritis she most likely came in with. Secondly, Mrs. Merda's continued use of opiates via her catheters only muddled proper treatment. These two factors combined resulted in Mrs. Merda's *C. difficile* flare-up after her release and the necessity of a unique treatment.

Fecal microbiota transplants are not a new concept. They have been used in one form or another for thousands of years in traditional Chinese medicine practices for gastrointestinal distress, but it wasn't until the mid-twentieth century that it became used in Western medicine as a treatment for chronic diarrhea. Although it may lack in aesthetic, in recent years it has become a common and effective treatment for patients with recurrent *C. difficile*-related diarrhea, like Mrs. Merda, when traditional antibiotic therapies no longer work [3].

Exact methods for fecal transplant vary, but common routes include colonoscopy, nasogastric tube, esophagogastroduodenoscopy, and retention enema [4]. Donors are screened for a variety of factors including transmittable diseases and pathogens such as hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus, *Giardia*, *Salmonella*, and *Shigella.* Medication usage and recent history are also considered [5]. On the day of the transplant, fecal samples are collected and filtered before the procedure. A small study in Canada found fecal transplant by low volume enema could be accomplished relatively easily at home by a friend or even by the patients themselves. The patients in this study remained infection free even after use of antibiotics [6].

As our understanding of the role of the intestinal microbiome develops, we may find new uses for fecal transplantation. A 2011 study published in *Nature* discovered a connection between autoimmune-mediated demyelination, similar to that in multiple sclerosis, and intestinal bacteria [7]. In fact, several studies have found patients with chronic fatigue syndrome or multiple sclerosis treated with fecal transplants exhibited a decrease in disease-state related symptoms lasting for years after treatment. Other diseases with demonstrated improvement post-fecal transplant include insulin-resistant diabetes

mellitus, ulcerative colitis, and Crohn's disease, and even more are being investigated as treatment targets [8].

Diagnosis

The diagnosis for Mrs. Merda was initially viral gastroenteritis, but after the contamination of her PICC line and multiple antibiotics, the final diagnosis was recurrent *C. difficile* infection. In the hospital, there were no diagnostic tests run specifically for *C. difficile*. A cytotoxin assay is considered the "gold standard" for *C. difficile* diagnosis with results available 24–48 h after and high specificity (sensitive to 10 pg of Toxin B). Enzyme immunoassays are less sensitive, but the results are available within hours and can test for both Toxins A and B [9]. Because of the opiate abuse and continued issues with catheters throughout her admittance, it is unlikely the cascade of events could have been avoided.

Treatment

There is a difference in treatment between primary and recurrent *C. difficile* infection. Recurrent *C. difficile* infection can be very difficult to treat definitively, as was the case with Mrs. Merda. Two main antibiotics are used, vancomycin and metronidazole, and more recent studies have shown effectiveness with fidaxomicin [10]. There has been success with a longer course of pulsed dosage vancomycin [9]. The theory behind the pulsed dosage is to accommodate the life cycle of *C. difficile*. Spores may become stuck in diverticuli and growth postponed. Pulsing allows for lingering bacteria to be wiped out while beneficial bacteria is able to grow.

Many studies have demonstrated advantages for combination therapy of antibiotics with probiotics, specifically *Saccharomyces boulardii* and *Lactobacillus GG* [11].

The treatment used in this case was fecal microbiota transplant, which is an effective method to clear *C. difficile* infection. Fecal transplants introduce bacteria able to recolonize

the intestinal microbiota, thereby keeping *C. difficile* at bay, preventing further infection.

Fast Facts

Recurrent *C. difficile* infection is an increasingly common bacterial infection that may take years to clear.
Mrs. Merda came into the emergency room with a real, albeit common, concern which was misinterpreted due to her history, then exacerbated by nonsterile injection drug use resulting in sepsis. The antibiotics required for sepsis then created an environment for *C. difficile* infection to occur.
Fecal microbiota transplant has been proven by multiple studies to be an effective treatment against recurrent *C. difficile* infection, when traditional therapies prove ineffective.

Test Your Knowledge

1. As one of the leading causes of nosocomial infection, which of the following does not help healthcare providers prevent the spread of *C. difficile* infection?

   (A) Consistent usage of alcohol-based hand rubs
   (B) Limited use of antibiotics, trying to use narrow spectrum antibiotics when possible
   (C) Use of hypochlorite-based disinfectants
   (D) Isolation of infected patients for several days beyond symptom resolution

   ANSWER: (A) Alcohol does not kill *C. difficile* spores. Soap and water are more effective at removing spores.

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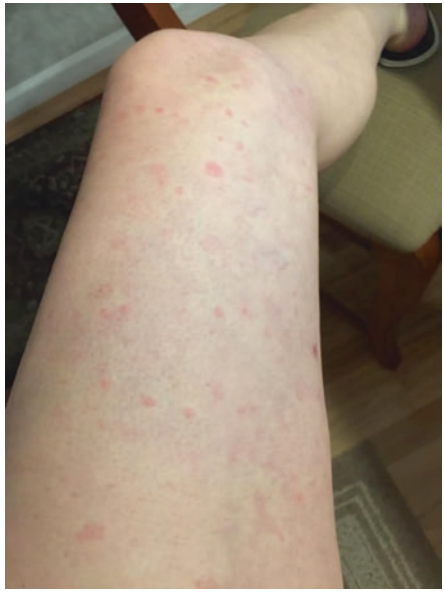
Chapter 16
Chronic Urticaria Leads to an Unexpected Diagnosis

Lindsay Stemke



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Vignette

When 22-year-old B came into Three Village Allergy and Asthma on a sunny spring afternoon, she appeared to be having an allergic reaction. Localized areas of her skin had become swollen and had broken out in hives, causing uncomfortable and unceasing itchiness and turning the affected areas a dark, angry shade of red. Rashes from allergies are not unusual, especially in the spring, when flowers and other plants burst into bloom and expose people to a variety of pollens and other airborne allergens. Therefore, the case at first seemed routine. However, when Dr. Szema asked B to describe her symptoms, he noticed that two hallmarks of an airborne allergic reaction—sneezing and a runny nose—were conspicuously absent. In fact, other than the swelling and rash, B appeared to be in perfect health and had no known allergies. Intrigued, Dr. Szema probed for possible non-airborne allergy triggers but found none. B owned a dog, worked in a local store, and had previously been prescribed Lexapro, Adderall, and a multivitamins, but none were new developments in her life, and the hives didn't appear to have been caused by any of these factors. It also didn't seem likely that the rash had been caused by accidental contact with an unknown allergen, as B had been suffering from this rash for 3 months, an improbably long time for an allergic reaction to persist without repeated exposure to the allergen. This detail proved to be crucial to discovering the underlying cause of B's symptoms (Fig. 16.1).

Background/Salient Features of Case

Hives, or urticaria, is a type of rash that occurs when mast cells, a crucial component of the human immune system, release histamine and other chemical signals into the bloodstream, causing blood vessels to widen. This widening of the blood vessels, or vasodilation, brings excess blood and signaling chemicals to the affected area, causing the surface of the

Figure 16.1 Dermatographism ("writing" on one's skin)

skin to become red, inflamed, and extremely itchy. B suffered from a type of urticaria called dermatographism, in which the skin becomes reddened and raised in response to pressure, making it possible to "write" on the patient's skin with one's fingertip. Although hives can result from a number of factors, including stress, infection, and overexposure to sunlight, the most common cause is an allergic reaction, in which the immune system overreacts to a harmless substance that it mistakes for a threat. Hives are frequently short-lived, often resolving themselves without intervention in a few minutes, hours, or days, but when hives last for 6 weeks or more, they are considered to be chronic. Like the acute version, chronic urticaria may be caused by allergies, mild illness, and other factors, but this condition may also be correlated with autoimmune diseases, in which the body's immune system perceives its own tissues as foreign invaders and accordingly attacks (Fig. 16.2).

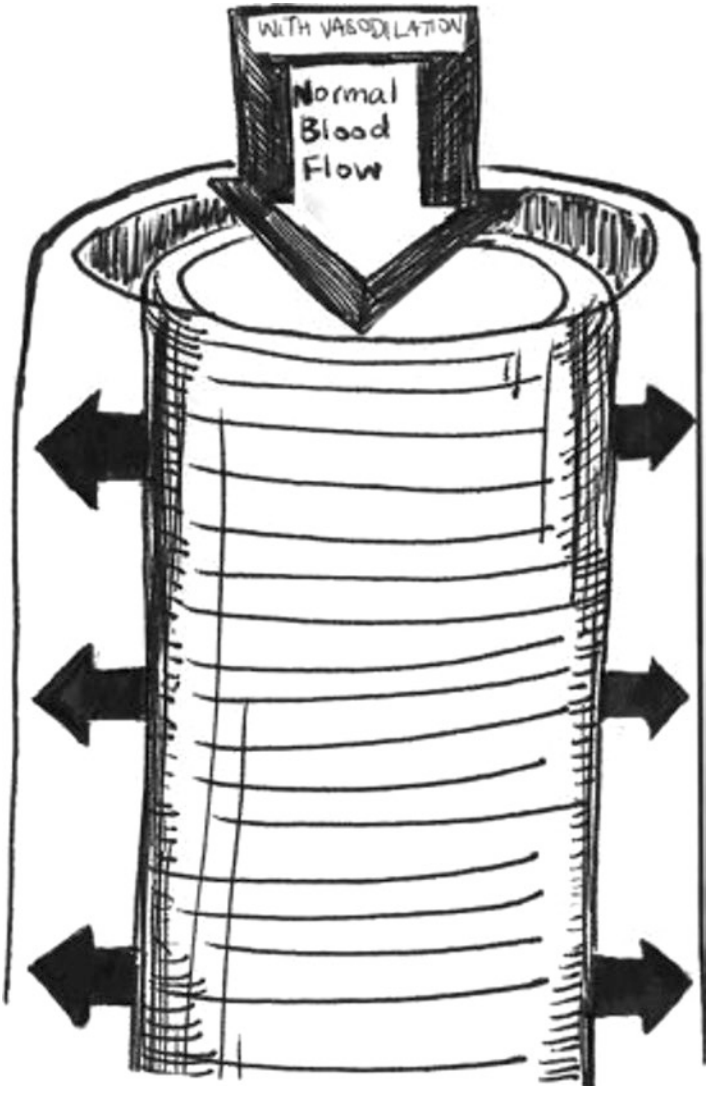

Figure 16.2 Vasodilation

Diagnosis

Following B's initial description of her symptoms, Dr. Szema inquired about B's family history and from this discussion learned that B's mother had suffered from a thyroid storm, a rare condition in which chronic hyperthyroidism leads to an overproduction of thyroid hormones, which can be fatal if left untreated [2]. Making a connection between this family history of thyroid disease and the abovementioned possibility of an autoimmune condition, Dr. Szema surmised that B might in fact be suffering from Hashimoto's thyroiditis. In this disease, the immune system attacks the thyroid, causing inflammation and eventually suppressing thyroid function [3]. This illness is often accompanied by palpable thyroid swelling, which B did not have, but the chronic urticaria and maternal history of thyroid illness were nevertheless strong indicators in favor of the diagnosis [1].

To ensure that a potential allergy had not been overlooked, Dr. Szema conducted a percutaneous skin test on B, introducing common allergens into small scratches in her skin in order to determine if any would trigger the histamine response. B was found to be allergic to dust mites, but as this finding did not rule out the possibility of Hashimoto's thyroiditis or other conditions, B was sent for blood tests. In normal immune function, specialized white blood cells known as B-lymphocytes produce antibodies, which are proteins that identify and remove particular invaders, with each type of antibody being specific to one type of invader [4]. Therefore, when a patient has an autoimmune disease, their body produces antibodies that are specific to one of their own particular tissues, and blood testing can determine the presence of such antibodies. B was tested for two anti-thyroid antibodies, thyroglobulin and thyroid peroxidase, and was positive for both, confirming that she did indeed have Hashimoto's thyroiditis [5]. B was also found to have elevated levels of class of antibodies known as IgE, which are produced during allergic reactions (Fig. 16.3).

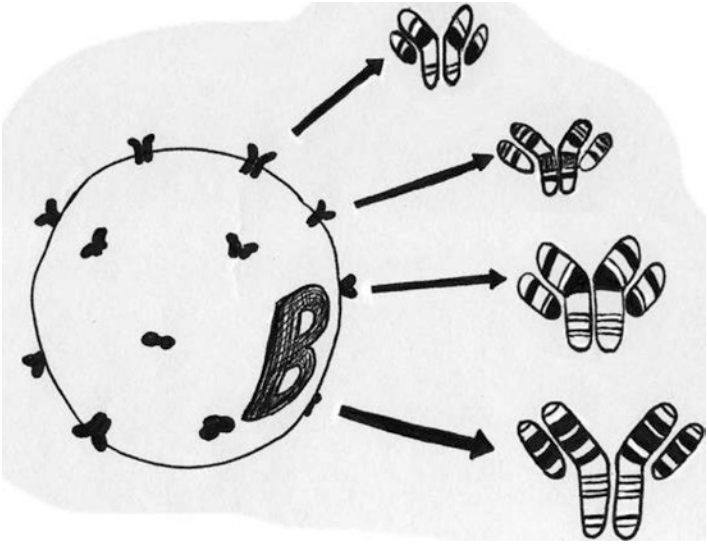

FIGURE 16.3 B-lymphocyte antibody proliferation

Treatment

To treat her urticaria, B was prescribed Omalizumab, an antibody used to treat asthma and chronic hives, and was also given epinephrine for emergency allergic reactions. She sought treatment for Hashimoto's thyroiditis with a qualified endocrinologist.

Fast Facts

- A seemingly simple complaint, such as persistent hives, can be a symptom of a much more serious condition.
- Family history can play a crucial role in arriving at the correct diagnosis, especially if all of the "standard symptoms" (in this case, an enlarged thyroid) are not present.
- The presence of one condition doesn't rule out the possibility of a second, even if the former seems to explain the patient's symptoms. In this case, the patient did have an allergy to dust

mites, a relatively ubiquitous allergen, and this may have seemed to explain her persistent rash. However, with the family history and known correlation between chronic urticaria and autoimmune disease, it was imperative for Dr. Szema to follow through with the complete testing protocol.

Test Your Knowledge

1. Which statement is false?

   (A) Hives are only caused by stress, infection, overexposure to sunlight, and allergens.
   (B) Hives and urticaria are the same thing.
   (C) Hives occur when histamine and other chemical signals are released into the bloodstream, causing swelling and itching in the affected areas.
   (D) During allergic reactions, the body produces a type of antibody called IgE.

   ANSWER: (A) Another cause of hives is Hashimoto's thyroiditis.

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Chapter 17
Blastocystis from the Past

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Vignette

Mark entered his apartment, rubbing the back of his neck. It had been a long day seeing patients, but he was glad it was finally over. He and his wife, Beth, had been looking forward to the weekend to catch up on some long overdue outdoor adventures. As he put his keys down on the table by the door, he called out to his wife.

"Beth! I'm home!" he said loudly. As the words left his mouth, he winced, grabbing his throat; it had been bothering him for some time, but he had not had the time to see a doctor about it. Despite being surrounded by physicians at the hospital, where he was training to be a physician assistant, it had been almost a year since he went to see one for himself. The last time he went, he had visited a gastroenterologist at Big University Hospital, where he was finishing his studies. He'd been experiencing dysphagia (difficulty swallowing) for which the GI could not surmise the cause; he had Mark undergo both an endoscopy and colonoscopy to find out what was causing his symptoms. His results came back positive for eosinophilic esophagitis (EE), an immune reaction in which eosinophils, a type of white blood cell, line the esophagus and cause inflammation (Fig. 17.1). Although this was certainly a pain in the neck for Mark, his bad medical luck went back 10 years to a mountain climbing trip in Utah, when he experienced vague and diffuse upper and lower gastroenterological symptoms. He had episodes of dysphasia that coincided with symptoms of irritable bowel syndrome and saw a physician assistant (PA) for his symptoms. He was then prescribed an ova & parasite (O&P) screening, which revealed *Blastocystis hominis* in his stool. *B. hominis*—a parasite known to cause gastrointestinal problems, predominantly in developing countries—was most certainly not the world's worst diagnosis, but it was also not something an American male of his living conditions should have. In fact, its onset remained a mystery. The PA who saw him deduced it was from contaminated water consumed during a previous mountain climbing trip. But which trip? Mark had been an avid mountain climber since childhood and could have been colonized as early as age 12! Whatever the answer,

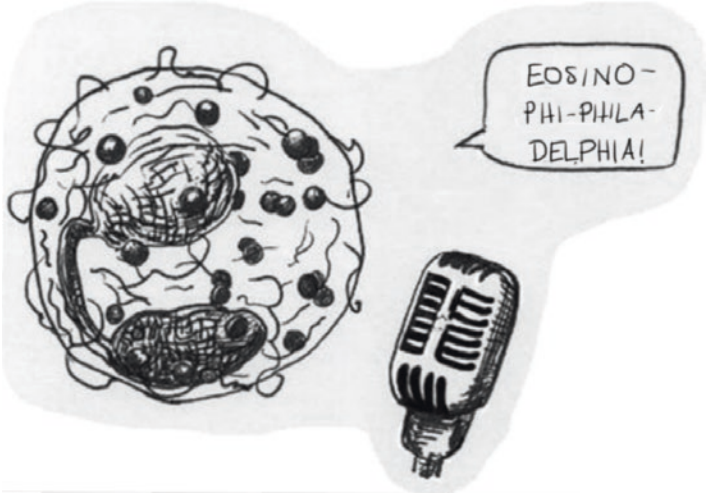

Figure 17.1 Eosino-Phil Cullen

the PA prescribed antibiotic known as metronidazole, but the treatment was unsuccessful in ridding Mark of the parasite.

As Mark heard Beth's footsteps approaching, he turned to face her.

"There you are!" she greeted him cheerily as she entered the living room. In each hand she carried a camping backpack, which she then placed in the corner of the room. "How was your day?"

"Pretty good," he replied, suppressing a cough. "Everything packed and ready for tomorrow?" he said, nodding to the nylon camping gear.

"Almost," Beth said enthusiastically. "I couldn't find the carabineers anywhere this morning, but it turned out they were just…" Her voice seemed to trail off into the distance as Mark became more distracted by the contractions in his throat. Each spasm felt like his throat was being squeezed shut. He considered reaching for his inhaler, but recalled its ineffectiveness, and shook off the idea. He then thought about taking the omeprazole, a stomach acid-reducing drug that his doctor prescribed for his EE, but wondered if it would really help him out—recently, nothing seemed to be working.

Finally, as if someone had raised the volume in the room, Beth's voice boomed in Mark's ears. "Isn't that crazy?!"

Mark, startled, looked dumbfounded at his wife.

Beth, annoyed from his lack of attention, put one hand on her hip and raised an eyebrow. "Okay, what is it?"

"It's nothing," Mark replied, trying to play it off.

"Is it your throat again?" Beth insisted. Mark, ever impressed by his wife's astuteness, and ashamed he did not listen to her story, nodded.

"You know how many times I've told you to go see Dr. Szema about that!" she exclaimed. "He's a great doctor, you know. Why don't you just make an appointment?"

Mark knew the time had come for him to take the initiative to do something about his throat. Despite his previous hesitations, Mark found Dr. Szema's number in Beth's address book and picked up the phone. In 5 minutes time, he was booked for an appointment for the following week.

* * *

Dr. Szema examined Mark, noting his history of both EE and *B. hominis*. Mark told the doctor his history of outdoor adventures and how in a moment of distress, from the hot Utah sun beating down on him during a previous mountain-climbing trip, he had become inpatient and drank mountain water without waiting for it to be completely filtered (Fig. 17.2). He mentioned that in the aftermath he developed *B. hominis* infection and had been treated with metronidazole unsuccessfully.

Mark also told Dr. Szema that he was hesitant to take inhaled steroids, since none seemed to alleviate his symptoms. After completing his examination, Dr. Szema administered a skin prick test to check for food and environmental allergies. Aside from the 5 millimeter wheal (raised skin due to an allergic response) that appeared where one of his arms had been pricked with histamine (a positive control that will always flare up as a reference point), the rest of his arms looked as if they had never been pricked. Upon seeing the results, Dr. Szema leaned back in his chair, crossed his arms, and looked at Mark reassuringly.

FIGURE 17.2 "I'll drink to that"

"I think your EE is related to your *Blastocystis hominis* infection," he said with a hint of confidence. Mark was momentarily taken aback, trying to make a connection.

"What do you mean?"

"I mean," Dr. Szema responded, "that you've had a history of EE and blood eosinophilia. Your skin tests were negative, which means it's unlikely that your EE is due to an aeroallergen or some food you're eating. There have been a few

cases of *Blastocystis hominis* reported linked to EE." Mark raised his eyebrows in surprise, not imagining Dr. Szema to so quickly deduce the cause of his throat pain.

Before he could ask what the next step would be, Dr. Szema continued. "You should get tested for *Blastocystis* again. I'm going to send you for parasite and ova testing." Mark gladly agreed to get the testing done—perhaps his throat troubles would then come to an end!

Fortunately for him, it turned out Dr. Szema's hunch had been correct—Mark's stool contained amounts of *B. hominis* that should not have been present after medicating with metronidazole. However, in an attempt to rid Mark of his infection forever, Dr. Szema prescribed the strongest dose of metronidazole—7.5 mg/kg every six hours—for Mark to take over a period of 1 week. After taking the prescribed dosage, Mark was instructed to get another stool sample to see if there was any change in the *Blastocystis* culture.

* * *

Two months had passed. Mark scheduled a visit with the doctor during his only break between rotations, but it was enough time between visits to see if there was any change in symptoms and overall health. Dr. Szema's staff prepared Mark's lab work for him and laid out the papers on the examination room desk. Dr. Szema took a look at the tiny print under the *Big Laboratories* logo indicating his results. It did not look good.

Unfortunately, even after taking the full dose of metronidazole, *B. hominis* was still found in his stool. Yet despite this, there was a sign of hope: he was asymptomatic.

"What does this mean?" Mark questioned. Dr. Szema shrugged—not because he did not know the answer, but because the answer simply surprised him.

"It means that this parasite no longer poses a threat!" he said with astonishment. "Seems it's become part of your normal flora!"

What this meant was that his throat problems were no more! Intriguingly, this showed that such an infection—particularly in an American male with access to clean water and good sanitation—was not necessarily harmful. It appeared to

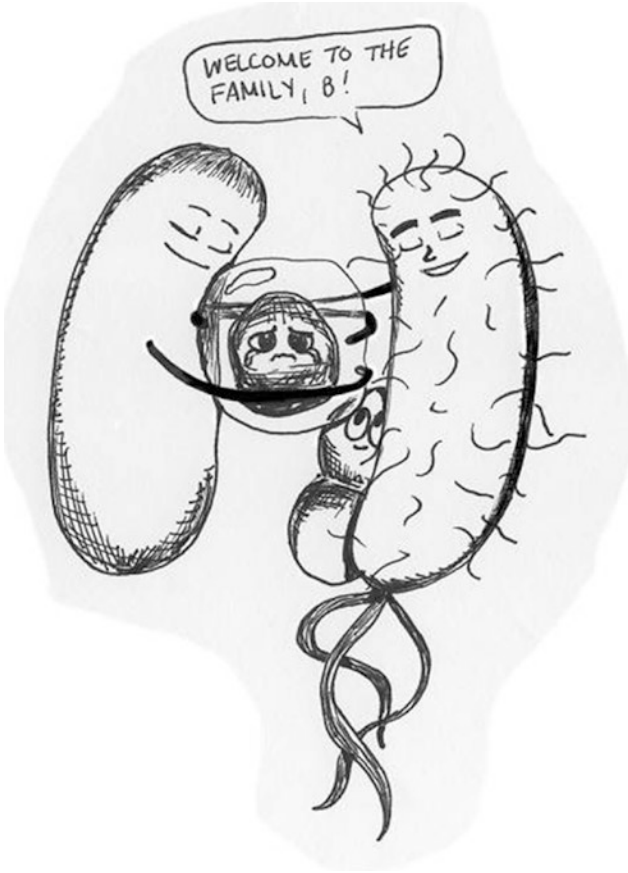

Figure 17.3 New addition to the family

have become part of his normal flora, taking permanent residence in his gastrointestinal tract (Fig. 17.3).

* * *

Since his visits to Dr. Szema, Mark and Beth moved to Utah, where Mark is working as an Internal Medicine PA hospitalist. He has been asymptomatic since his departure from New York.

Background/Salient Features

Eosinophilic esophagitis (EE) occurs as an immune response to food, environmental allergens, or acid reflux, and predominantly in Caucasian males and in atopic patients (those with a family history of allergies or asthma with symptoms). In patients with EE, eosinophils (allergic white blood cells) line the esophagus. Patients may be diagnosed with EE only after endoscopy or biopsy of the esophagus [1].

B. hominis, on the other hand, is a protozoan found in areas of the world where there is poor water quality or inadequate sanitation. Waterborne transmission is not uncommon [2]. When infected, *B. hominis* causes gastroenterological problems in patients, including diarrhea, nausea, and flatulence. Other symptoms associated with *B. hominis* infection are fatigue and hives. It can be diagnosed by fecal exam (parasite and ova testing), endoscopy, or, less commonly, blood tests [3]. In rare instances, such as in Mark's case, *B. hominis* can lead to EE.

Diagnosis

Mark's case was special in that two of his previous diagnoses, which were thought to be unrelated, were in fact a cause-and-effect event. Mark had both a *B. hominis* infection and EE, with the former leading to the latter. He had been diagnosed for *B. hominis* by a physician assistant in Utah in 2014 and later by his allergist/immunologist for EE in 2015.

Treatment

Currently, there is no proven treatment for infection, although several medications, including antibiotics like metronidazole and combination medications like sulfamethoxazole/trimethoprim [3], have potential to work. However, studies have

found resistance of *B. hominis* to treatment by metronidazole [4, 5]—much like in Mark's case.

Fast Facts

EE is an inflammatory reaction of the esophagus with numerous causes, including allergies, acid reflux, and, as discovered more recently, *Blastocystis* hominis infection.
B. hominis is a protozoan found in stools of people who typically live in areas with poor sanitation or poor water quality; however, travelers may also become infected by consuming unclean water.
B. hominis has shown to be resistant to treatment by metronidazole, despite it being considered the drug of choice for treatment.

Test Your Knowledge

1. Which of the following statements is false?

   (A) EE has multiple possible causes, including acid reflux and allergies.
   (B) Infection by *B. hominis* can lead to inflammation and spasms of the throat.
   (C) *B. hominis* infection is most common among Caucasian females.
   (D) *B. hominis* infection can be treated with use of antibiotics, antiprotozoal medications, or combination medications.

   ANSWER: The correct answer is (C). *B. hominis* is a protozoan found predominantly in Caucasion males. It is typically found in people living in areas of poor water quality and sanitation.

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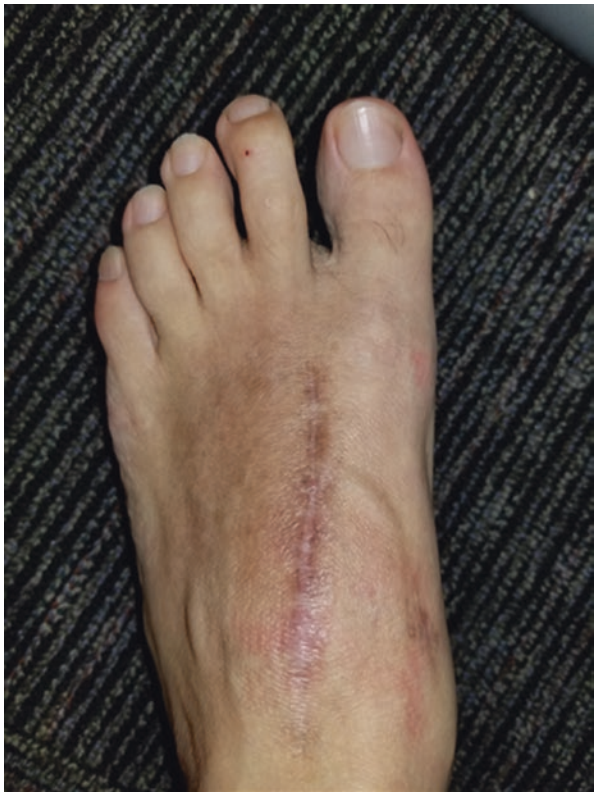
Chapter 18
Frankenstein Foot

Brittany Dukes and Lorenzo Gamez



A.M. Szema (ed.), *Unusual Diseases with Common Symptoms*, https://doi.org/10.1007/978-3-319-58952-7_18

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Vignette

"One more round," the taekwondo master insisted. This particular Saturday, throughout the match, Dr. Szema was leading against his opponent, who was half his age but double his size. He followed the all rules "to a T" and fought hard. Dr. Szema thought for sure that the last round was the final round and this slighted match would expire. To Dr. Szema's dismay, the match continued.

"Whap!" While attempting a fake left front kick, Dr. Szema's foot was met by the force of the massive teenager's right foot flying through the air. "Crunch!" Dr. Szema came down hard on the squishy mat with underlying concrete. Just like that, the match officially ended, with Dr. Szema no longer victorious (Fig. 18.1).

"That's definitely broken!" exclaimed a parent of one of Dr. Szema's classmates, who happened to be a physician. Post-collision, the master instructed Dr. Szema to clean up the chairs in the dojang. Dr. Szema proceeded to walk and even drive home on his injured foot.

Despite conservative efforts to combat his symptoms, Dr. Szema's foot was erythematic (red) and riddled with pain still swelled to about 20 times its original size. The next morning, it did not take long for Dr. Szema and his wife to make their way to St. Charles Hospital's Emergency Room

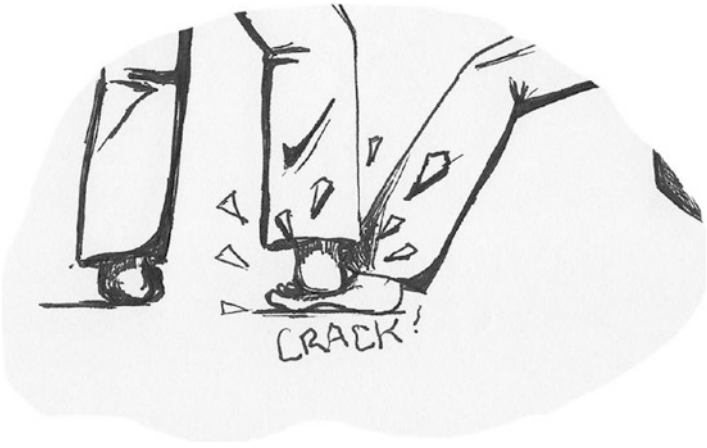

Figure 18.1 That crunch!

(ER). Initially, the injured foot was examined and X-rayed. Despite Dr. Szema's excruciating pain, the radiologist and ER physician reported that the film was unremarkable. Dr. Szema was told that it was a sprain injury and he would recover in a few weeks. Dr. Szema was displeased with the diagnosis, so the ER physician offered to perform computed tomography (CT scan) on the injured foot. At the expense of a small dose of radiation exposure, Dr. Szema agreed. While waiting in the ER, Dr. Szema's wife suggested they contact an orthopedic surgeon who specialized in foot and ankle injuries to interpret the CT scan. Worried by the physical exam and the location of the erythema and swelling, the orthopedic surgeon knew this was much more than a minor sprain. The CT provided a quality picture of the injury, finally revealing the true extent of the injury. Not only was it the single worst break the orthopedic surgeon had ever seen, but also it was so notorious that it had its own name: the Lisfranc injury.

Background/Salient Features of Case

The term "Lisfranc" refers to the tarsometatarsal (TMT) articulation. The term was coined from the name of the French field surgeon Jacques Lisfranc, who first discovered an amputation technique through this joint [2]. Lisfranc injuries are extremely rare (0.2% of all fractures) and commonly missed [5]. Approximately 20% of all Lisfranc injuries remain undiagnosed, largely due to the fact that they occur in an area where it is difficult to visualize the bony anatomy [4]. These injuries may include sprains, fractures, and/or dislocations. Although incidence and prevalence are low, overlooked Lisfranc injury is noted as one of the most common causes for malpractice lawsuits against radiologists and emergency medicine physicians. The lack of a proper diagnosis and delayed treatment can lead to devastating long-term consequences, which include deformity and disability.

Knowledge of the normal Lisfranc joint anatomy is essential in evading a missed Lisfranc injury diagnosis. The tarsometatarsal joint (TMT joint), or Lisfranc joint, is the "seam" between the midfoot and forefoot. The bony structures include the five metatarsal bases, three cuneiforms (medical, intermediate, and lateral), and the cuboid [3]. The first, second, and third metatarsals articulate with the medial, intermediate, and lateral cuneiforms, respectively. The fourth and fifth metatarsals articulate with the cuboid bone. Inherent stability is provided most importantly by the bony foundation, more specifically the deep position of the base of the second metatarsal and the trapezoidal shape of the middle three metatarsals. Ligamentous structures also play a role in stability. The bases of the metatarsal bones are connected by strong transverse, oblique (Lisfranc ligament), and interosseous ligaments. The Lisfranc ligament, the strongest of the ligamentous structures, traverses the TMT joint and extends obliquely from the medial cuneiform to the base of the second metatarsal. The Lisfranc ligament, along with the groove produced by the base of the second metatarsal, provides important stabilization for the whole TMT articulation (Fig. 18.2).

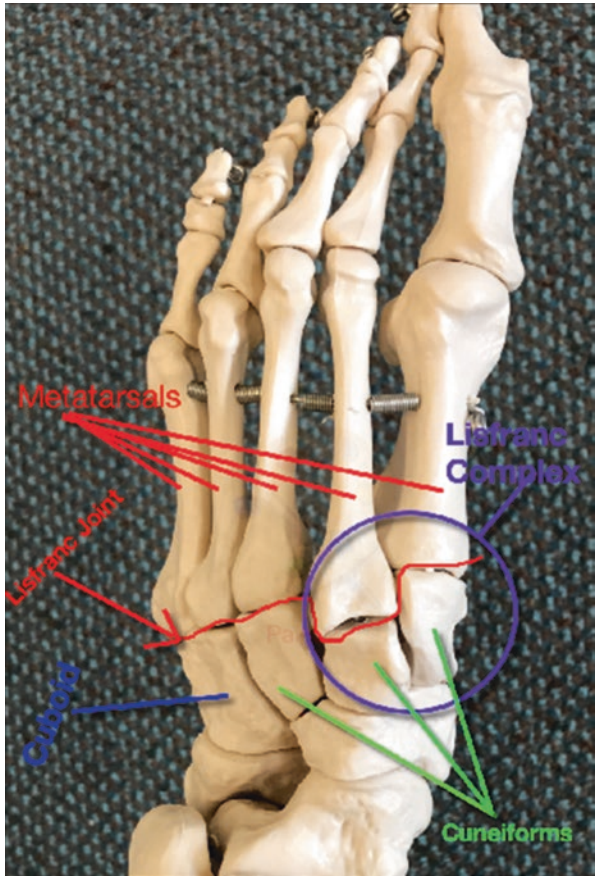

Figure 18.2 Anatomy of the Lisfranc joint complex

Lisfranc injuries are traumatic disturbances to the Lisfranc joint. They can occur in the form of an injury to the ligamentous structures or a bony injury, which is more severe. Two mechanisms can cause this injury: direct or indirect forces/load. Direct forces generally result from crush injuries to the dorsal foot. Indirect trauma, the most common cause, is produced by longitudinal loading of the plantar flexed foot, such as fall on the foot while it is pointing down. Dr. Szema's injury was caused by the indirect load mechanism. Lisfranc

injuries due to indirect forces typically lead to fractures of the metatarsal and tarsal bones, as well as ligamentous injuries (Figs. 18.3 and 18.4).

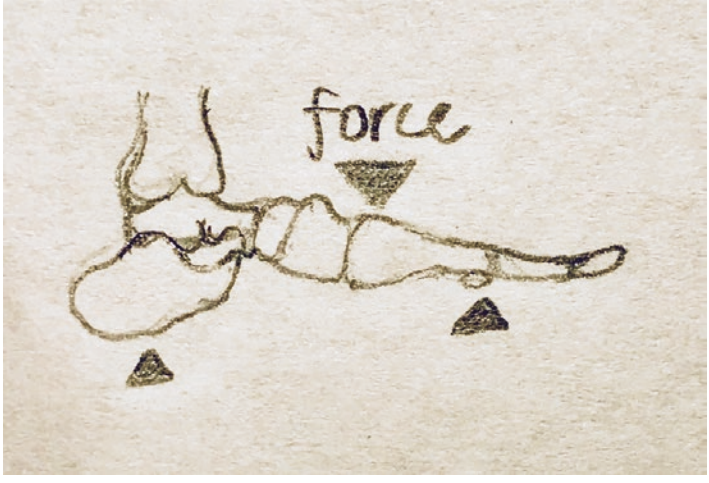

Figure 18.3 Direct force mechanism

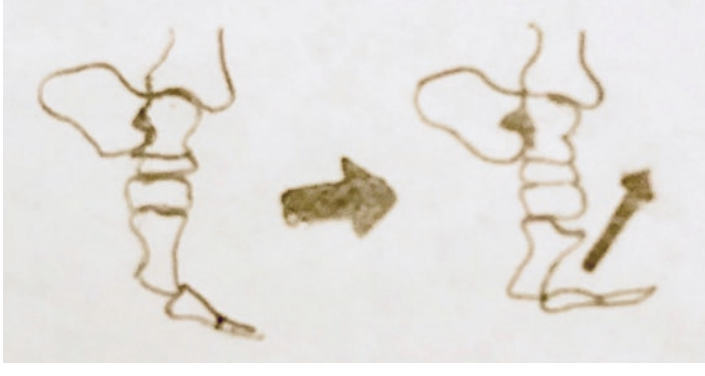

Figure 18.4 Indirect force mechanism

Diagnosis

Clinical diagnosis is based on a detailed physical examination of the injured foot. Lisfranc injuries may present as stable but symptomatic or create a painful, unstable foot. Generally, clinical findings following an acute Lisfranc injury include: midfoot pain (especially on palpation), swelling, planter ecchymosis, and difficulty bearing weight. It is also crucial that the physician immediately check the neurovascular status of the injured foot for possible damage to the deep branch of the peroneal nerve or damage to pedal artery, due to potential compartment syndrome.

Radiographic evaluations are vital in the diagnosis and treatment of Lisfranc injuries [1]. They reveal changes and dislocations in TMT articulation. Dorsoplantar radiographs are typically the first radiological examination performed, after initial history and physical examination. If possible, radiographs performed should include weight-bearing anteroposterior, lateral, and 30-degree medial oblique views [1]. Lateral and weight-bearing radiographs can be very beneficial in evaluating for subtle dislocation and minimizing the effects of overlapping structures at the TMT joint. Stress view radiographs are helpful in unstable lesions. A CT scan is particularly important in identifying fractures and dislocations relevant for maintaining foot stability and function. CT scans are used as a preoperative scan tool, which aids in confirming the injury.

Dr. S received non-weight-bearing dorsoplantar and lateral radiographs, which were unremarkable. He was unable to receive weight bearing or stress views, which limited the radiologist and emergency medicine physician's ability to assess his injury. Fortunately, Dr. S received a CT scan, which revealed Lisfranc fracture dislocation of the left first and second TMT joint, intercuneiform joint, and Lisfranc joint (Fig. 18.5).

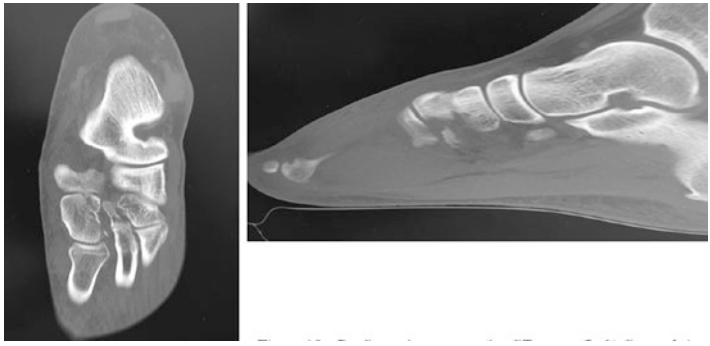

FIGURE 18.5 Dr. Szema's preoperative CT scans. (*Left*) Coronal view showing a Lisfranc fracture dislocation of the L. first and second metatarsals. (*Right*) Sagittal view showing a displaced cuneiform fracture

Treatment

Initial management of Lisfranc injuries is focused around the evaluation of the soft tissue. Operative versus nonoperative treatment is based on displacement involved in the injury. Displacement is described as greater than a 2 mm deviation from normal anatomy. The end goal of treatment is to restore a painless, stable, and functional foot, with precise anatomic reduction necessary in order to reduce future disability. Operative treatment is suggested for injuries that show either a displaced or unstable Lisfranc fracture or if there is displacement on stress views. The orthopedic surgeon may perform an internal or external fixation. Type of fixation used is based on the underlying mechanics of the foot. Lisfranc injuries that show displacement less than 2 mm can be managed with nonoperative measures, such as immobilization for 4–6 weeks with a non-weight-bearing cast.

Dr. Szema's injury required surgical intervention. His orthopedic surgeon successfully performed an open reduction and internal fixation (ORIF) of the first and second TMT joint, Lisfranc space, and intercuneiform joint. The first

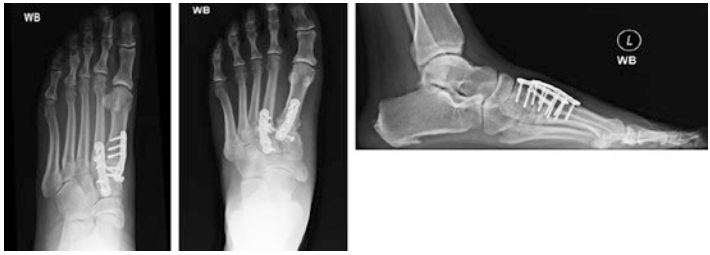

FIGURE 18.6 Postoperative weight-baring X-rays illustrating appropriate reduction of the joints and appropriate placement of the hardware: oblique (*left*), AP (*middle*), lateral (*right*)

and second TMT was fixed with a footplate across the TMT joint. The Lisfranc space was fixed with a 4-0 cannulated screw. This surgery repositions the bones and joints in the mid-part of the foot creating stability during the time needed for ligamentous structures to heal.

After the operating team closed, they placed Dr. Szema's foot in a bulky Jones splint. Possible postsurgical complications include, but are not limited to: infection, nerve damage, chronic pain, nonunion, malunion, and wound dehiscence. Postoperative care includes early immobilization, progressive weight-bearing after 6–8 weeks with the protection of a walking boot, and, in Dr. Szema's case, removal of hardware in 4–6 months.

There is an incidence of posttraumatic arthritis due to damaged articular surfaces, comminuted fractures, or unstable fixation (Fig. 18.6).

Fast Facts

- Lisfranc injuries are commonly overlooked in the emergency department.
- Knowledge of normal Lisfranc joint anatomy is key in diagnosing Lisfranc injuries.
- Displacement greater than 2 mm requires surgical management.

Test Your Knowledge

1. What is the most common mechanism that leads to Lisfranc injuries?

   (A) External rotation
   (B) Direct crush injury to the dorsum of the foot
   (C) Internal rotation
   (D) Longitudinal load applied to a plantar flexed foot

   ANSWER: (D) Although direct crush injuries can cause Lisfranc injuries, it is longitudinal loading of the plantar flexed foot (indirect trauma) that is the most common mechanism.

Suggested Readings

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Chapter 19
The Respiratory Victims of 9/11

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Vignette

The World Trade Center disaster on September 11, 2001, will forever be remembered as one of the worst tragedies in American history. However, out of great hardship sprung equally memorable stories of heroism and humanitarianism, as people nationwide were united in American pride and patriotism. One of the best examples of this outpouring of support was found on Ground Zero itself, where rescue/recovery workers and volunteers toiled day and night to recover remains and clean up seemingly endless Twin Tower debris. Mr. Rodriguez was one such tireless hero. Mr. Rodriguez was a responder on the very day of the attack and continued his courageous efforts for several hours a day, 7 days a week as a janitor on "the Pile." The physical aftermath of the collapse took nearly a year to clear, and Mr. Rodriguez was part of the cleanup crew for 8 months, or a whopping 225 days straight!

Stirring images of the valiant men and women working to clear Ground Zero of the wreckage were captured by various media outlets. Dirt and dust feature prominently in nearly every photo, hanging thick in the air or coating the rubble and workers. Based on the imagery alone, it is unsurprising that Mr. Rodriguez was diagnosed with asthma in 2004 by the World Trade Center Health Program (WTCHP), a program set up by the National Institute for Occupational Safety and Health to provide medical treatment for responders and local survivors [1].

Eleven years later, Mr. Rodriguez's asthma persisted, and he had developed chronic obstructive pulmonary disease (COPD). Now 50 years old, Mr. Rodriguez had been managing his asthma and COPD with a combination of corticosteroid and albuterol inhalers and nebulizers. A corticosteroid suppresses inflammation in asthmatic airways,while albuterol is a bronchodilator, or a medication that that relaxes airway muscles and increases airflow to the lungs [2]. Inhalers and nebulizers are two different mechanisms with the same

purpose: to get medicine to the lungs. With his inhaler, Mr. Rodriguez's medicine was delivered in aerosol form and taken into the lungs with a deep breath. His inhaler was smaller and more portable than a nebulizer, which delivers the medicine as a mist inhaled via mouthpiece. In June 2015, Mr. Rodriguez's formerly manageable ailments suddenly took a turn for the worse despite a clear chest X-ray two months earlier. The WTCHP urgently referred Mr. Rodriguez to Dr. Szema after he reported having suffered recurring cases of hives and dizziness for several months.

Mr. Rodriguez came into Dr. Szema's office with hives present on his upper left thigh, complaining of extreme shortness of breath, dizziness, and general fuzziness. Originally hailing from Ecuador, Mr. Rodriguez reported that he now lived on Long Island, was a non-smoker, and could not think of any recent life changes that might help explain the sudden onset of hives, such as moving to a new home, getting a new pet, or starting any new medication. He explained that he worked as a general laborer whose jobs included painting and gardening. As soon as the words left his mouth, alarm bells went off in Dr. Szema's head. The list of environmental particulates Mr. Rodriguez was likely exposed to on a daily basis was extensive: silica, dust, pollen, weeds...the possibilities were endless! As it turned out, Mr. Rodriguez had never been tested for allergies, which Dr. Szema remedied immediately. An environmental percutaneous skin prick test revealed that Mr. Rodriguez was allergic to mold, dogs, grass, weeds, and white oak and ash trees (Fig. 19.1).

A thorough physical examination uncovered even more red flags. Mr. Rodriguez had expiratory wheezing in the lower left lobe of the lung, along with a constant cough that produced gray sputum. To get a more detailed understanding of Mr. Rodriguez's airway function, Dr. Szema performed impulse oscillometry (IOS) and fractional exhaled nitric oxide testing to determine the extent of his airway obstruction and inflammation, respectively. The IOS test revealed an abnormal X5 reading, which measures the lungs' distal capacitive resistance. An abnormal X5 reading meant that Mr. Rodriguez had twitchy, or hyperresponsive, airways that

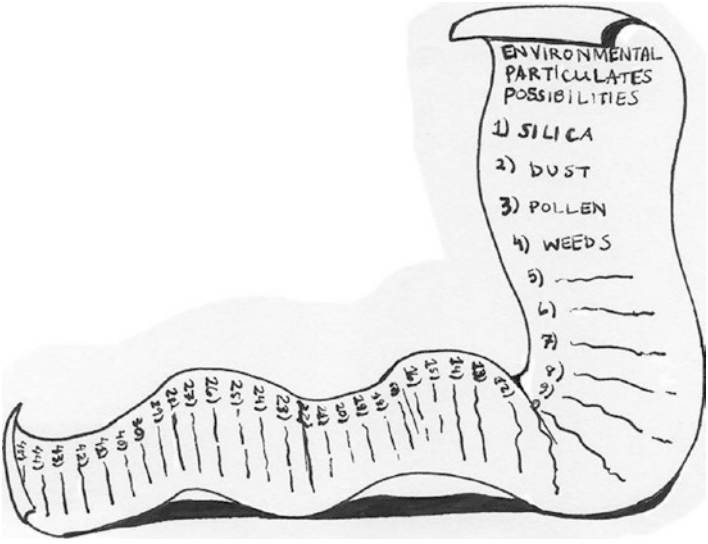

Figure 19.1 The list goes on…

readily narrowed to the point where he felt like he was breathing out of a straw. The exhaled breath condensate nitric oxide (NO) test measured eosinophilic inflammation (eosinophilia), which, along with airway hyperresponsiveness, is a characteristic feature of asthma. The NO test revealed a fractional exhaled nitric oxide (FeNO) level of 46 ppb (parts per billion), which was just shy of the abnormal level of 50+ ppb for adults. But wait! There was a catch. Mr. Rodriguez was on his current asthma medication when he performed the test, so his results were better than they should've been. The result meant he was living with inflamed airways on a daily basis *even* while medicated. It is no wonder his respiratory condition was affecting his ability to perform his job and live a comfortable life.

Mr. Rodriguez returned to the office 7 months later in January 2016, complaining of difficulty breathing while at rest, lying down, and sleeping, despite taking his regular medication. Now that it was winter on Long Island, Mr. Rodriguez had also

noticed that his symptoms worsened whenever he was outside in the cold. Dr. Szema ran a bronchodilator study, which measures airway function prior to inhaling a bronchodilator and performs the same test immediately afterward. The pre- and post-bronchodilator results are compared to determine whether the medication is sufficiently effective. Of the four pulmonary measurements recorded as part of the test, Mr. Rodriguez showed an insignificant improvement in two and a decrease in the other two. The bottom line: Mr. Rodriguez had small airway dysfunction that did not improve after the use of a bronchodilator. It was clear this was not your usual case of asthma. So far, no medication had helped him find a reprieve from the symptoms that haunted him since he volunteered his efforts on 9/11.

Background/Salient Features of Case

In the days, weeks, and months immediately following 9/11, the Environmental Protection Agency (EPA) and the FDNY's Bureau of Health Services made it an urgent priority to assess air quality and the potential health concerns for those in the vicinity [3]. Some of the earliest findings confirmed that the plumes of smoke and dust lingering in the air contained myriad toxic particulates: cement, glass, leaded paint, soot, pesticides, dioxins, jet fuel, carbon monoxide, nitric oxide, and asbestos, to name a few [4]. The thousands of firefighters, police officers, rescue/recovery, and other cleanup workers who flocked to Ground Zero were exposed to this noxious atmosphere for prolonged periods of time. The deleterious effects manifested almost immediately. Within one week of the attack, 99% of exposed NY firefighters reported acquiring a new respiratory symptom they had never before experienced [5].

Within a month, the NY Times and NY Daily News were publishing stories about the chest pain, breathing difficulties, and other respiratory issues running rampant among the Ground Zero workers. The FDNY WTC Medical Monitoring and Treatment Program identified the "World Trade Center cough syndrome" in October 2001, which was the first official

diagnosis directly related to post-9/11 air exposure. The syndrome was defined as a chronic cough, thought to be a consequence of upper and lower respiratory disease typically including chronic asthmatic bronchitis, chronic rhinosinusitis, and/or chronic gastroesophageal reflux [6].

The WTC cough was one of many respiratory maladies uncovered by medical studies that lasted for years after 2001 and continue even today. Many of the discoveries regarding post-9/11 health deterioration are exemplified by Mr. Rodriguez's case. First, lung function abnormalities were significantly related to WTC exposure intensity, which was based on how soon after initial impact responders arrived on scene. Mr. Rodriguez was present on the very day of the attack, which certainly helps explain the wheezing located in his lower left lobe. Additionally, the WTC registry noted that for those who arrived on the day of the attack and continued working for the duration of the cleanup (sound familiar?), using masks or respirators did nothing to mitigate the risk of new asthma diagnoses. A significant relationship was also found between increased respiratory symptoms, persistent airway hyperreactivity, asthma, and decreased lung function with earlier arrival to Ground Zero. Is it any wonder, then, that Mr. Rodriguez's asthma and respiratory symptoms were so debilitating and persistent? Unfortunately for Mr. Rodriguez and so many others, immediate and extended service correlated with more severe medical distress.

Ultimately, Mr. Rodriguez's symptoms were just few of many WTC-related injuries that responders and local inhabitants continue to struggle with today. A plethora of studies have found that WTC related health problems are generally persistent, sometimes progressive, and often a lifelong burden [7]. Fortunately, ongoing research by Dr. Szema and others focuses on long-term analysis of the individuals exposed to the toxic air at Ground Zero. The continued efforts of these doctors are critical to the medical community's ability to understand and treat the respiratory victims of 9/11.

Diagnosis

In addition his preexisting asthma and COPD, Mr. Rodriguez was diagnosed with unspecified lung injury and acute severe exacerbation of moderate persistent asthma. Many studies now refer to pulmonary cases like Mr. Rodriguez's, where asthma and related respiratory issues were developed due to inhalation of particulates post-9/11, as "World Trade Center Lung Injury" [8]. The acute severe exacerbation diagnosis meant that Mr. Rodriguez suffered from random bouts of worsening asthma symptoms, including shortness of breath, coughing, wheezing, or chest tightness. The episodes could be caused by any number of external or internal factors, such as exposure to one of the allergens identified by the patch test or a respiratory infection [9]. The fact that his exacerbations were classified as severe meant they were potentially life-threatening and required close care, observation, and frequent medication.

Treatment

After Mr. Rodriguez's first visit, Dr. Szema prescribed a new aerosol inhaler, complete with a spacer. A spacer is an important addition to an aerosol inhaler because it is designed to ensure that the asthma medication is delivered directly into the lungs and not lost along the way in the mouth or throat. Patients with poorly controlled asthma often fail to inhale medication directly into the lungs, but the use of a spacer makes a significant difference. Dr. Szema also prescribed budesonide mixed with albuterol via nebulizer. The combination of a budesonide, a corticosteroid used for chronic asthma maintenance, with albuterol, a fast-acting bronchodilator, targeted airway inflammation and narrowing simultaneously (Fig. 19.2).

The next step for a patient who is unresponsive to varied and repeated courses of asthma medication is to deter-

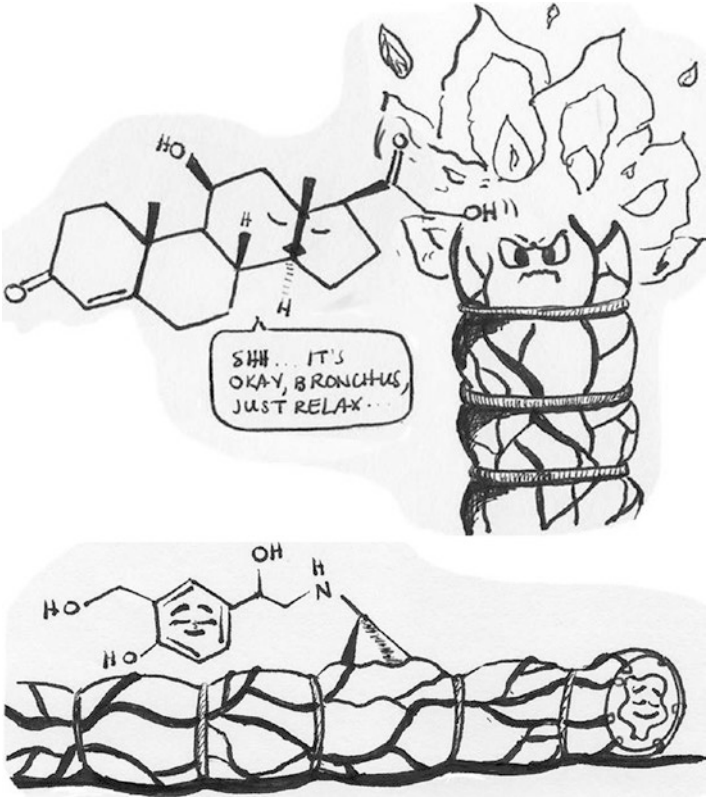

FIGURE 19.2 Budesonide (*top*) and albuterol (*bottom*) relaxing inflamed bronchus

mine his or her IgE, or immunoglobulin E, levels via a blood test. IgE is an antibody that is overproduced by the immune system in response to an allergen and subsequently sets off a sequence of events that produces allergic reactions. The IgE test is specifically used in cases when symptoms are acute and often triggered by specific scenarios, like exposure to cold air in Mr. Rodriguez's case. Lowering IgE levels requires treatment with omalizumab, a non-human antibody that is modified in a

laboratory for the specific purpose of binding to and neutralizing excess IgE in patients with allergic asthma [10]. In November 2015, mepolizumab was FDA approved as the first medication to treat severe asthma in patients specifically with a high eosinophil count, as opposed to IgE-targeting omalizumab [11]. As of March 2016, the FDA approved the use of reslizumab for treatment of severe asthma with eosinophilia. Though manufactured by different pharmaceutical companies, both mepolizumab and reslizumab are antibodies that block the activation site on the cytokine IL-5, ultimately blocking the proliferation of the problematic eosinophils [12].

Future treatment of lung injuries as exemplified by Mr. Rodriguez may very well include the use of vasoactive intestinal peptide (VIP). Though not yet FDA approved, extensive lab testing has already proven VIP's efficacy as a neurotransmitter, immune regulator, vasodilator, and secretion promoter [13]. These specific characteristics make VIP a thrilling prospect for those suffering from such pervasive and debilitating conditions as pulmonary hypertension, erectile dysfunction, sarcoidosis, and allergic asthma. In 2006, Dr. Szema and colleagues published a groundbreaking study revealing that mice whose VIP gene was removed suddenly started exhibiting airway responsiveness and inflammation, the two foremost symptoms of allergic asthma. These results suggested that the presence of VIP was crucial to maintaining a normal, nonallergic environment. Furthermore, when VIP was gradually reintroduced into the VIP-deficient immune systems, all abnormal symptoms eventually subsided, and the mice made a full recovery! These fascinating and critical discoveries have been further supported with additional research from Dr. Szema and others over the past ten years [14]. The medical community is hopeful that VIP's successful treatment of lab mice will soon translate to the successful treatment of human patients like Mr. Rodriguez. VIP may be nothing short of life changing for all who suffer from as-yet-incurable lung injuries, especially the thousands of new cases that cropped up in wake of 9/11.

Fast Facts

Studies show that the vast majority of Ground Zero responders and clean-up workers acquired respiratory illnesses that they did not have prior to 9/11/2001.
NY-based researchers have identified brand new ailments specifically linked to 9/11 air pollution, such as World Trade Center Cough Syndrome and World Trade Center Lung Injury.
Omalizumab, reslizumab, and mepolizumab are some of the medications currently available to help alleviate symptoms seen in many Ground Zero responders. Looking toward the future, VIP is an extremely promising candidate to help those suffering from lung injury.

Test Your Knowledge

1. Which statement is false?

   (A) Eosinophilic inflammation and airway hyperresponsiveness are characteristic of asthma.
   (B) An abnormal exhaled breath condensate nitic oxide result for adults is less than 50 ppb.
   (C) A corticosteroid is an anti-inflammatory.
   (D) Adding a spacer to an inhaler helps asthma medicine reach the lungs more efficiently.

   Answer: (B) An abnormal exhaled breath condensate nitric oxide reading is 50 ppb or *above*, not below! The less nitric oxide present in your exhaled breath, the less inflamed your airways are.

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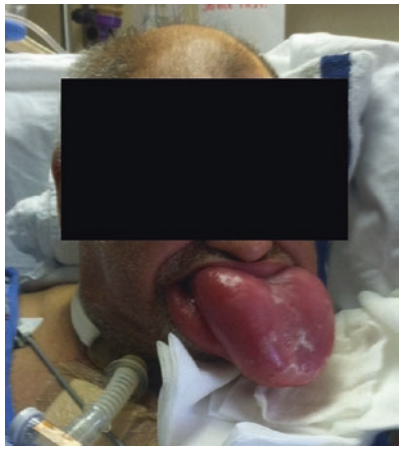
Chapter 20
Angst and Drama: A Tale of Angioedema

Sophia Dang and Jonathan C. Li



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A.M. Szema (ed.), *Unusual Diseases with Common Symptoms*, https://doi.org/10.1007/978-3-319-58952-7_20

Vignette

"Nurse! Nurse!" she cried. "Something's not right. Look! Look at my husband's tongue." Mrs. B watched in horror as her sick, unconscious husband's tongue grew bigger and bigger, while he laid in his hospital bed. It was now easily visible in his slightly ajar mouth. The nurse left quickly to inform Mr. B's physician about his condition. Mrs. B suspected that this was due to an adverse reaction to a medication given the night before for her husband's rising blood pressure. Three weeks later on a Friday afternoon, Dr. Szema received a phone call from a medical intensive care unit (MICU) resident for an immediate consultation on Mr. B. Dr. Szema was not able to fulfill the resident's request for immediate consultation since Fridays were his clinic days, normally booked with patients until 9:00 PM, and instead opted to perform the consultation after a 14-h day at 10:30 PM.

Mrs. B, who wore the unmistakable signs of grief and loss across her face and in her sunken eyes, greeted Dr. Szema and his premedical student. She had spent every possible moment in the hospital with Mr. B, who now rested in his hospital bed with a 4 × 4 piece of gauze futilely covering his tongue that was now the size of a chicken cutlet. It was hard not to notice his tongue or the grimace across his face. He was supposed to be unconscious, but he still bore a facial expression of pain and discomfort. Before examining Mr. B, Dr. Szema asked Mrs. B about the chain of events leading to his current state.

Four weeks prior, Mr. B drove home after work on Route 347, a major highway traversing Suffolk County, Long Island. At home, he sipped a beer as he conversed with his wife and decompressed after another long day at work. Excusing himself momentarily, Mr. B went to use the bathroom, all the while talking with his wife. Mrs. B kept talking, but Mr. B stopped responding. She quickly got up, sensing something was off, and hurried toward the bathroom where she found Mr. B collapsed on the floor. She called 911, and he was rushed to the hospital. Mr. B was admitted to the ICU, his diagnosis: herpes encephalitis, a rare manifestation of a com-

Figure 20.1 The collapse

mon cold sore viral infection. There are two variants of herpes virus, HSV1, common cold sores, and HSV2—genital herpes. In Mr. B's case, whatever variant he had found its way into his brain and robbed him of his consciousness (Fig. 20.1).

One week into his hospital stay, his blood pressure began to rise. In an effort to prevent complications to Mr. B's health, he was administered an intravenous (IV) dose of lisinopril, an angiotensin-converting enzyme (ACE) inhibitor class of blood pressure-lowering medication. An uncommon side effect of ACE inhibitors is angioedema, a condition where

spontaneous swelling occurs in a specific part of the body. The location of swelling varies among individuals and is usually a hereditary disease due to inherited genetic deficits. The culprit responsible for hereditary angioedema and ACE inhibitor-induced angioedema is a protein called bradykinin. Bradykinin mediates swelling reactions in the body and is mostly broken down in the lungs by ACE. ACE inhibitors work by stopping ACE from working and prevent the production of angiotensin II, a peptide that raises blood pressure. Inadvertently, this causes in increase in bradykinin. The medical world doesn't yet understand why some individuals are more susceptible than others, but it could be possible that since bradykinin is also produced in the inflammatory state, he was at higher risk to experience angioedema than the average individual on ACE inhibitor medication (Figs. 20.2 and 20.3).

Despite his increased risk, his state (see image) could very likely have been avoided if the medication was immediately

Figure 20.2 Through the roof

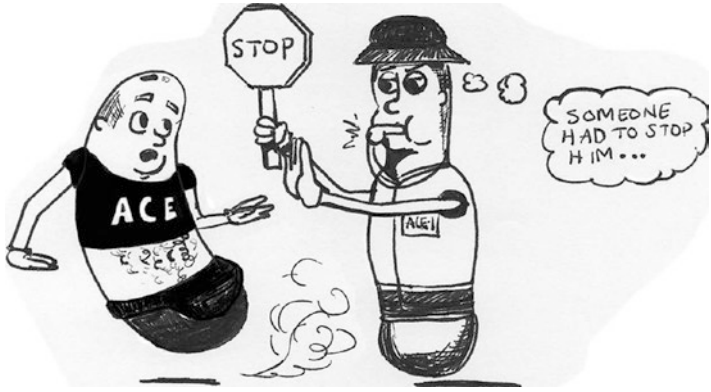


Figure 20.3 ACE-I enzyme patrol

stopped. As Mrs. B continued her story, Dr. Szema learned that somewhere between Mrs. B notifying the nurse about Mr. B's swelling tongue and changing the orders in the system, a communication mishap occurred. Mr. B continued to receive lisinopril, which successfully controlled his blood pressure but impeded his body's capacity to breakdown bradykinin. His tongue continued to swell to a point where it completely obstructed his airway. The intensive care staff was unable to intubate Mr. B and had to resort to performing a tracheostomy, an emergency procedure where an incision is made in the front of the throat to gain access to the main airway leading to the lungs. Only then were they able to prevent Mr. B from suffocating on his own tongue. Dr. Szema and his premedical student were shocked! If only he had been called for consultation earlier! Fortunately, as an allergist/immunologist, Dr (Fig. 20.4).

Szema was used to seeing patients with bona fide hereditary angioedema and had an emergency dose of a medication called icatibant which comes in a pre-loaded syringe—similar to an epinephrine injector for serious allergic reactions. Icatibant is a powerful drug when it comes to stopping bradykinin-induced swelling. Bradykinin works like a key and opens many doors that allow water to move into areas of the

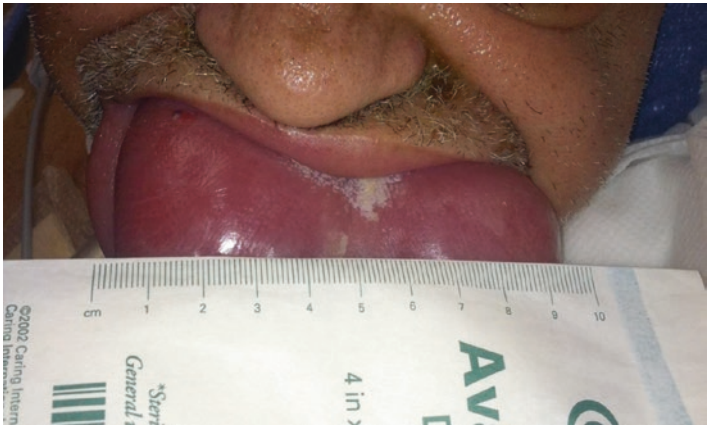
FIGURE 20.4 A nasty decision

body that aren't supposed to have lots of water, which is what causes the swelling. Icatibant will fit perfectly into the hole that bradykinin uses to open the doors and keeps more doors from opening and thus prevent bradykinin from working. Unfortunately, icatibant is supposed to be injected within 30 min of an angioedema attack to be most effective, and Mr. B was 3 weeks beyond that time frame.

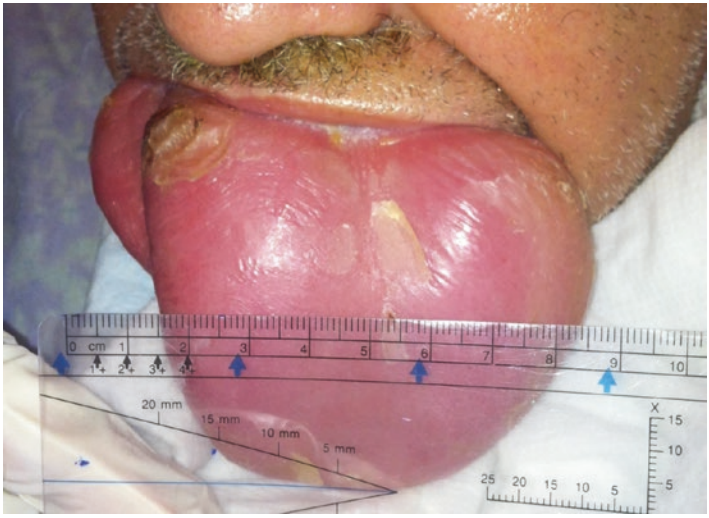
Dr. Szema explained to Mrs. B how the icatibant injection worked and how it was supposed be used within 30 min. He also explained to her why her husband's tongue was swelling and that nobody had ever tried using icatibant for an angioedema attack this long after it had begun. Despite the uncertainty, it was worth a shot and the right thing to do. Dr. Szema moved swiftly, quickly introducing himself to the unconscious Mr. B while listening to his lungs and heart. His premedical student, having been trained on how to use the medication in the office, donned gloves and prepared the medication and alcohol swab. Dr. Szema completed his examination of Mr. B and began cleaning below the umbilicus (belly button) where the injection was to be administered. The premedical student narrowed his vision on to the seconds hand of the clock hanging overhead and began counting down out loud from 60… 59… 58…. The monotonous drone of his counting filled the room until he reached 0, and Dr. Szema removed the

now-empty syringe from Mr. B's body, carefully depositing the needle into the red sharps container. Dr. Szema reiterated to Mrs. B that this administration was purely experimental and beyond the scope of how the drug had ever been used in the past. She nodded. Softness returned to her eyes as she smiled and thanked the duo for visiting at such a late hour.

Three days later, Dr. Szema received a phone call from the overnight attending. Mr. B had awoken in the middle of the night! He was answering very specific, personal questions accurately. Unfortunately, his bout of consciousness was transient, but this gave the overnight attending physician, Dr. Szema, and Mrs. B hope that Mr. B may still be able to make a recovery. Dr. Szema speculated that perhaps the angioedema had contributed to Mr. B's condition by causing an additional source of pressure that was pressing on his brain. That night, Dr. Szema returned to the hospital. Mr. B's tongue on initial examination was rough in texture, whereas 4 days prior, it was taught and turgid like the surface of a tomato. Using the ruler printed on the edge of a 4 × 4 gauze wrapper, with Dr. Szema and his student measured Mr. B's tongue—it had decreased in size across all three dimensions.



(Before injection: approx. 9 cm width)



(One week after injection: approx. 7.3 cm width; note the change in texture between photos)

Mr. B awoke again, 3 days after a second dose of icatibant. Again, he answered the attending's questions correctly. It couldn't have been just by chance anymore. The attending physician requested for a neurology consultation to reevaluate Mr. B. Despite two awakenings, their diagnosis, of a persistent vegetative state, held firm. By definition, transient bouts of consciousness are expected to occur in patients in a persistent vegetative state. Further icatibant injections stopped improving his condition; Mr. B remained unconscious, and his tongue remained swollen. After a few more weeks in the ICU without improvement and much deliberation, Mr. B was transferred to a long-term care facility.

Diagnosis

ACE inhibitor-induced angioedema.

Background/Salient Features of Case

Current medical literature reports ACE inhibitor-induced angioedema in about 0.1–0.7% of recipients and accounts for 20–40% of all angioedema-related emergency department visits each year [1]. This swelling is not due to an allergic reaction and usually affects the lips, tongue, face, or intestines. Frequently, patients who experience this medication side effect are switched to an alternate medication to help control their blood pressure, e.g., angiotensin receptor blockers (ARBs). ARBs may still elicit angioedema in patients, but the risk is much lower (0.07–0.1%). Most patients who stop taking ACE inhibitors after experiencing angioedema continue to experience symptoms and may have had an unknown risk that was made apparent due to the medication.

Herpes encephalitis (encephalitis = brain infection) is most commonly caused by herpes simplex virus type 1 (HSV-1). It is the most common cause of fatal sporadic encephalitis in approximately 10–20% of annual cases in the USA. If left untreated, the fatality can approach 70%. Even with appropriate diagnosis and treatment, the mortality rate is as high as 20–30%. Survivors typically have significant neurological deficits [2].

Bradykinin is produced naturally in the body to produce vasodilation, widening of the blood vessel, at sites of injury and infection to allow the body to protect and heal itself [3]. This is a necessary process because immune cells travel in the blood and exit into other parts of the body at these dilated regions. Since Mr. B had a severe viral infection, we can postulate that his body was producing large amounts of bradykinin to assist his immune system. Then, as soon as the ACE inhibitor entered his system and shut down his ability to breakdown bradykinin, their levels went through the roof! This resulted in the unfortunate outcome we saw above.

Treatment

Icatibant: a bradykinin B2-receptor blocker [4].

Fast Facts

Spontaneous swelling is a medical condition called angioedema. Allergists/immunologists are specialist physicians trained to recognize and treat this condition.
The most common causes are inherited (hereditary angioedema) and side effects due to blood pressure medication (ACE inhibitors).
Acute angioedema attacks can be suppressed through administration of icatibant—which can only be obtained through careful diagnosis and evaluation by a physician.

Test Your Knowledge

1. Icatibant works by blocking the effect of?

   (A) Herpes simplex virus (HSV)
   (B) Angiotensin-converting enzyme (ACE)
   (C) Encephalitis
   (D) Bradykinin
   (E) Lisinopril

   ANSWER: (D) Icatibant is a bradykinin B2 receptor blocker.

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Chapter 21
The Not So FUNgi

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Vignette

Getting up from bed, walking to the bathroom, and making breakfast, simple tasks, right? Unfortunately for Ms. Chalke, it was not that easy. Forty-eight years old, a health enthusiast, and the mother of a teenage daughter, Ms. Chalke was by no means a sedentary person. Able to run 5 miles with ease, she made the 20 something year-olds working at our clinic look like chump change! Based on this history, you would think she was fine. However, the supermom described above was not the person that entered our office. Instead, we got a version of Ms. Chalke that was severely short of breath, plagued with a series of recurring respiratory infections, and dying to know what was going on! Having seen five doctors in the past 8 months, Ms. Chalke needed someone who was more than a doctor. She needed a sharp team of young investigators ready to crack the case! (Fig. 21.1).

Looking through her case file for the first time, we realized we were in for another long night. With over a hundred pages of old case notes, lab results, and CT scans to sift through, we did what any great investigative team does: we laid out all the evidence. Starting with her blood tests, she had persistent eosinophilia or an abnormally high eosinophil level of about 663 cells/μl. Should we be worried? Not really, since eosinophilia is a fairly broad symptom associated with your run-of-the-mill asthma. Given that she was diagnosed with asthma at a young age, we were not surprised at this abnormality. Pretty vanilla stuff so far.

However, according to one of her most recent blood tests, she had abnormally high levels of IgE specific to the airborne fungus, *Aspergillus fumigatus*. Gee willikers what does that mean? Thank you for asking, I thought you'd never ask. Well, basically all it means is that Ms. Chalke's immune system has encountered the fungus once before and is likely sensitized to the mold [1]. In normal people like you and I, this immune response is not present because special cells in our lungs eradicate the fungal spores pretty quickly [1].

FIGURE 21.1 *Aspergillus* infection in the arm

FIGURE 21.2 Confused

However, for people who have cystic fibrosis or chronic underlying asthma, the immune system is not functioning at its best, thus leaving the lung vulnerable to an ambitious young spore ready to germinate into a big brash fungus (Fig. 21.2) [1].

Although we had our first lead, we weren't ready to break out the whiskey just yet. We had a whole series of tests to conduct before we could claim allergic bronchopulmonary

aspergillosis (ABPA)—a severe form of asthma associated with mold hypersensitivity—was guilty of the crime [1]. Because the medical community has widely varying guidelines for diagnosing ABPA, we stuck to the criteria defined by the International Society for Human and Animal Mycology (ISHAM) to crack the case (Fig. 21.3) [2].

Looking through the chart, almost everything was on track for making a specific diagnosis. As discussed earlier, she had underlying asthma and an eosinophil level of 663 cells/μl, which was over the 500 cells/μl upper limit according to the ISHAM Criteria (Fig. 21.3). Additionally, she tested positive for IgE's specific to *A. fumigatus,* and her arm blew up when we conducted an intradermal skin test using *Aspergillus* antigen. Lastly and arguably the hallmark symptom of ABPA, her prior CT's revealed the presence of transient pulmonary infiltrates in the form of ground glass opacities. As the name suggests, "ground glass" is simply a fancy term used by radiologists to describe a hazy area in the CT that preserves visibility of vascular/bronchial landmarks [3]. What's unique in the case of ABPA is that the infiltrates are *transient*, in the sense that they disappear and reappear in different places over time (*example of ground glass pulmonary infiltrates below*) (Fig. 21.4).

Now here is where things get tricky. According to other sources, the patient typically has a total IgE serum concentration of about 1000 IU/ml to qualify for ABPA [4]. With an IgE serum concentration of 144 IU/ml, Ms. Chalke did not meet this criterion. At one point, this made us question the culpability of ABPA in the first place. In fact, we considered a new suspect, "severe asthma and fungal sensitivity syndrome" or SAFS. At first glance, SAFS seemed like the perfect weapon. The symptomology was pretty much the same as ABPA, and the patient didn't need an IgE serum concentration of over 1000 IU/ml to qualify [4, 5]. I guess we can finally break out that whiskey now? Wrong again! In order to be SAFS, there must be *no* pulmonary infiltrates on the CT [4, 5]. ABPA would have gotten away with it too, if it wasn't for those pesky radiologists and their pulmonary infiltrates! That being said, we chose to adopt the ISHAM criteria for ABPA,

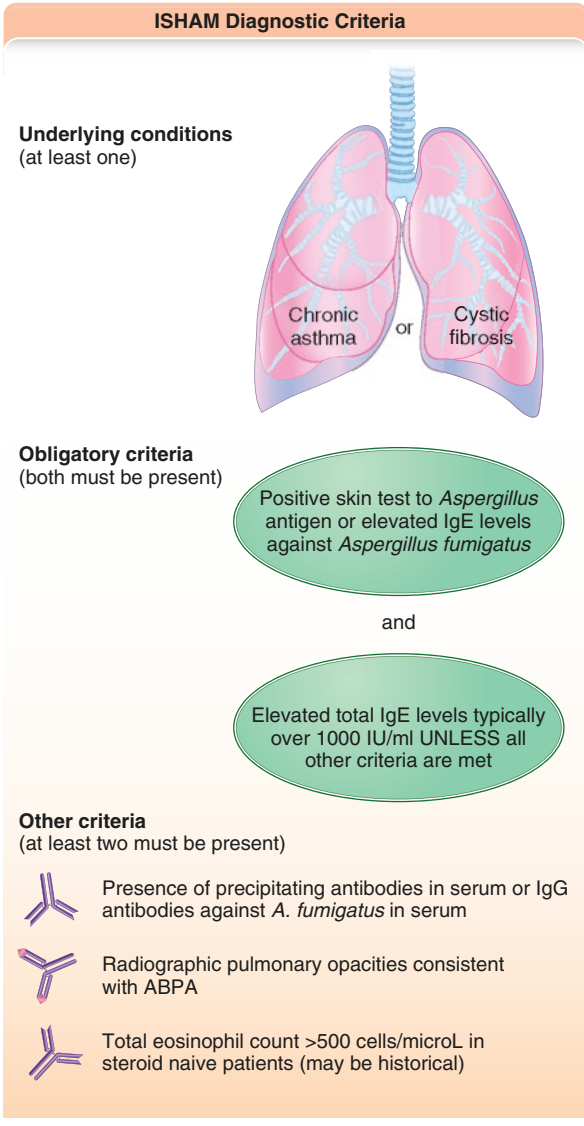

FIGURE 21.3 Diagram based on ABPA diagnostic guidelines. Source: Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al (2013)

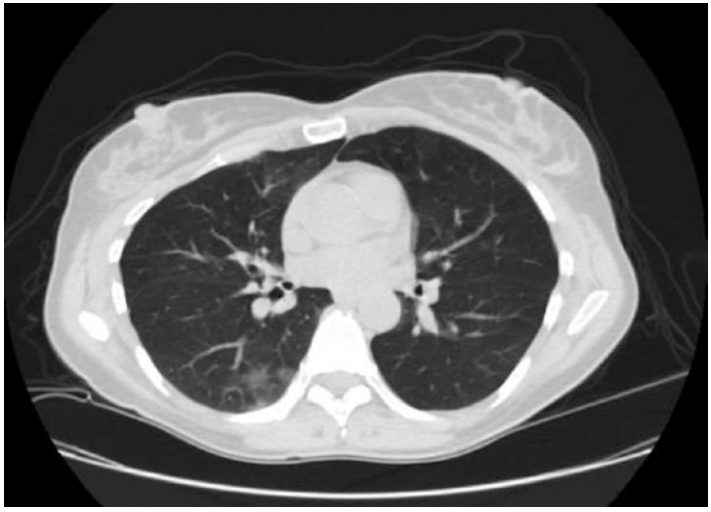

FIGURE 21.4 CT scan indicating transient pulmonary infiltrates

which DIDN'T require an IgE concentration level of over 1000 IU/ml as long as all the other criteria were met [2].

Now that ABPA was finally in custody, we had to find his accomplice responsible for Ms. Chalke's persistent sinusitis. Standard protocol would normally suggest that the sinusitis was bacterial in nature. However, a good patient history goes a long way! She was not only on antibiotics for an extended period of time, but she was also on levofloxacin—the nuclear standard in antibiotics! In consideration of such facts, we knew the culprit was most likely fungal in nature, thus suggesting the presence of allergic fungal rhinosinusitis (AFRS). Like ABPA, the symptoms associated with AFRS are the result of the body's hyperimmune response to a fungus occupying the body [6]. In the case of AFRS, the fungus is found in the sinuses rather than the lungs [6]. In other words, Ms. Chalke was robbed by ABPA and mugged by AFRS. She was targeted twice by the same gang: the notorious fungal fighters!

Now that the culprits were caught and found guilty, it was time for sentencing. Being the troublemakers they were, we decided to go for the maximum sentence: the death penalty.

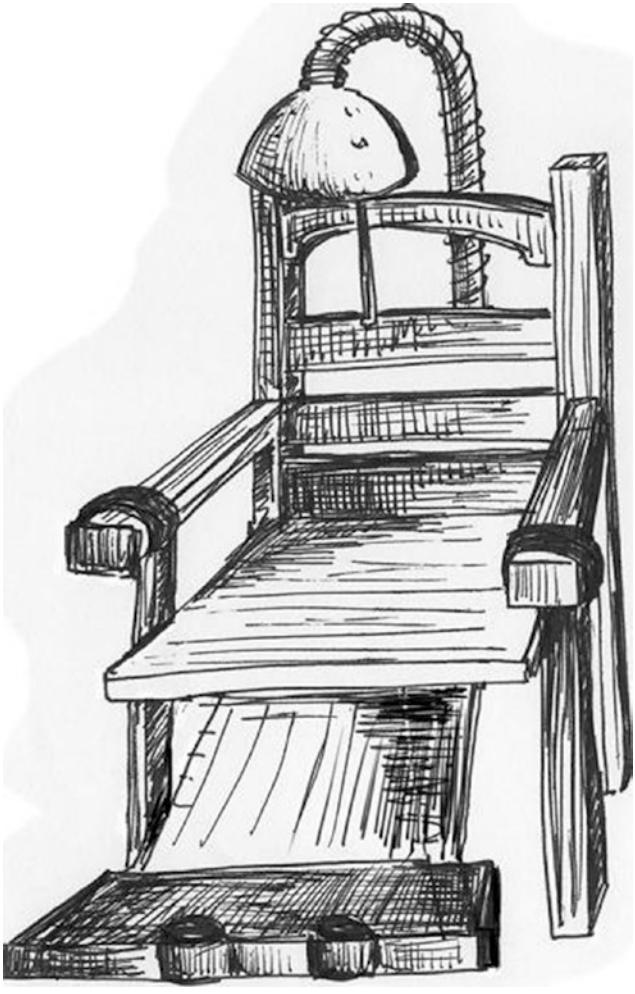

FIGURE 21.5 Death sentence

Through a lethal concoction of systematic steroids and antifungal medication, we hoped to not only to stop the symptoms but also to destroy the fungus itself (Fig. 21.5).

Background/Salient Features of Case

ABPA describes the body's collective response to the colonization of *Aspergillus fumigatus* in the airways of the lung. The fungus that causes ABPA is typically *A. fumigatus,* since it is one of the most common airborne fungi [4]. In the rare case that it's not *A. fumigatus,* it's often a fungus from the *Aspergillus* genus, such as *A. niger* or *A. ochraceus* [1]. In these special cases, the disease is referred to as allergic bronchopulmonary mycosis or ABPM. Symptoms for ABPM [1] are very similar to ABPA [1].

Colonization of *A. fumigatus* is usually due to an exposure of the airborne fungus in immunocompromised patients. The body's immune system reacts by increasing levels of special interleukins, or signaling compounds, which are critical in proliferating eosinophils and exacerbating preexisting asthmatic inflammation [1]. However, instead of getting an asthma attack once in a while due to a transient exposure to the antigen (i.e., walking outside in a field with pollen), the antigen is always around you. On top of that, the colonized fungus also releases proteases that chew away at the structural proteins in the delicate lung tissue, therefore reducing gas exchange and increasing the likelihood of bronchiectasis, which is when the airways in the lung lose their elasticity and become scarred [1]. If left untreated, the breakdown of airways in the lung, in concert with the inflammation from the eosinophils, can evolve into pulmonary fibrosis and compromise day-to-day pulmonary function of the patient [7].

As mentioned before, the line between ABPA and SAFS is still hazy. Unlike ABPA, patients with SAFS don't necessarily have fungus colonizing the lungs. Rather, the symptomology found in SAFS can be due to a fungal hypersensitivity reaction from environmental fungi or fungi colonized in another part of the body (i.e., sinuses). As a consequence, many characteristic features of ABPA are not present, such as the transient pulmonary infiltrates, mucous plugs in the airways, and an IgE count of over 1000 IU/ml [4, 5].

Diagnosis

Mrs. Chalke was diagnosed with allergic bronchopulmonary aspergillus (ABPA) according to the guidelines set by the International Society for Human and Animal Mycology (ISHAM). She was also diagnosed with allergic fungal rhinosinusitis (AFRS) and Sensitivity to Fungi Syndrome (SFS).

Treatment

Ms. Chalke was treated with a combination of steroids and long-term antifungal medication under standard protocol according to her age, weight, and gender. The steroid used was a prednisone 10 mg tablet taken four times a day for 2 weeks. The antifungal used was itraconazole 200 mg tablets taken once daily for a year. She also initiated allergy immunotherapy with mold.

Steroids are generally used to reduce acute symptoms associated with asthma, while antifungal medications aim to eradicate the colonized fungi, ultimately reducing exacerbations in the long term [7]. For those with acute ABPA, standard protocol usually suggests that the patient is treated with tapered oral glucocorticoids first [7]. Because antifungal medications, such as itraconazole, are demanding on the liver and can last from months to years at a time, a combination therapy is usually recommended on those where ABPA exacerbations are great and glucocorticoids are not effective [7]. One alternative to itraconazole is Voriconazole, if itraconazole is not tolerated well by the patient [7].

Fast Facts

ABPA can be tricky to diagnose. *Transient* pulmonary infiltrates are highly characteristic of ABPA when seen with eosinophilia, positive skin tests, and the presence of mucous plugs in the CT [2, 4, 5].

An IgE level over 1000 IU/ml is not necessary for a diagnosis of ABPA. Simply an elevated level of IgE under a 1000 IU/ml can suffice as long as all other diagnostic criteria are met (Fig. 21.3).

In the absence of transient pulmonary infiltrates and mucous plugs, SAFS should be considered, as long as other symptoms remain consistent with ABPA (eosinophilia, dyspnea, and positive skin test to *Aspergillus*) [4, 5].

Test Your Knowledge

1. Which of the following statements about ABPA is *not* true?

   (A) People with chronic asthma and cystic fibrosis are more susceptible to ABPA than those who are not.
   (B) Standard protocol recommends that those with acute ABPA should first be treated with a combination of antifungal medication and steroids.
   (C) A patient coming in the hospital with severe dyspnea, positive skin test to *Aspergillus*, preexisting chronic asthma, high blood pressure of 140/80 mmHg, an absolute eosinophil count of 300 cells/μl, and no transient pulmonary infiltrates probably does not have ABPA.
   (D) Colonization by other species of *Aspergillus*, such as *Aspergillus niger* is referred to as allergic bronchopulmonary mycosis (ABPM).

   ANSWER: (A) TRUE: It is true that those with chronic asthma or cystic fibrosis are at a greater risk for ABPA. This is the case because cystic fibrosis and asthma are specific pathologies that weaken the lungs' ability to fight off the fungal spores [1, 2].
   (B) FALSE: Those with acute ABPA are recommended to be first treated with steroids alone. A combination therapy is only recommended if the patient continues to experience exacerbations despite administration of steroids [7].

(C) TRUE: Consulting Fig. 21.3 in the vignette, one can see that all the conditions are not met. Specifically, two of the three sub-conditions for condition three are not met: the absolute eosinophil count is below 500 cells/μl and there are no transient pulmonary infiltrates.

(D) TRUE: ABPA refers to colonization and hypersensitivity specifically to *Aspergillus fumigatus*. On the other hand, colonization by other members of the *Aspergillus* genus is referred to as ABPM and is seen in a minority of patients [1, 2].

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Chapter 22
Beauty Comes with a Price

Tram Nguyen

A.M. Szema (ed.), *Unusual Diseases with Common Symptoms*, https://doi.org/10.1007/978-3-319-58952-7_22

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Vignette

As spring was turning to summer, 55-year-old Dina came to Three Village Allergy & Asthma with a cough, bloodshot eyes, and itchy, red rashes all over her body. Her throat was also irritated, limiting her to simple nonverbal gestures during check-in, prompting the receptionists to send her in without delay.

Dina's medical history revealed high blood pressure and an allergy to shrimp. While getting acquainted with Dina, Dr. Szema learned that she had no recent exposure to seafood, but she did dye her hair just the day before. In embarrassment, Dina mentioned the rashes were so severe they had descended to her genitals. Upon detecting numerous mucosal lesions (mouth, throat, genital, and anal), Dr. Szema began to suspect Steven Johnson's Syndrome. A hairdresser's panel from Dormer Laboratories was ordered, containing samples of common hair product components, to test the extent of Dina's allergies.

Dina returned 4 days after her initial consultation with Dr. Szema. With assistance from a nurse and a student volunteer, Dr. Szema adhered a 16-chamber patch on Dina's back; each chamber contained either a compound or a mixture of compounds from a hair dye sample. Atransparent film dressing was placed over the patch to secure it in place and prevent moisture from sneaking inside. Dr. Szema advised Dina not to shower for 3 days until the results from the patch test could be read (Fig. 22.1).

Patch testing normally requires 2–3 days before allergic contact dermatitis can be detected [6]. Dina, however,

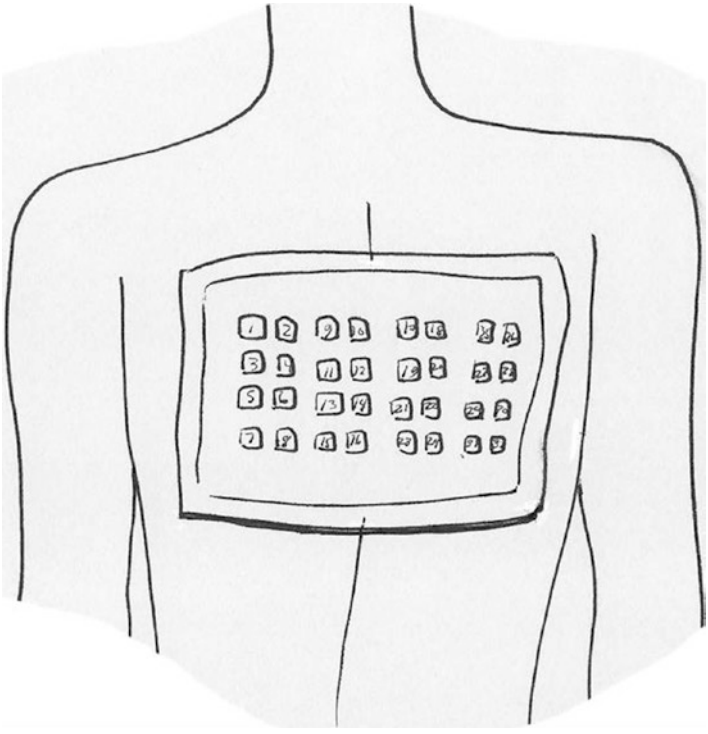

FIGURE 22.1 Patch test

could feel this reaction just a few short hours after the patch was placed. She called the clinic around noon, complaining of itchy, burning sensations on her back. Dr. Szema asked her to come right away so he could thoroughly examine the reaction. Dina quickly left work and headed for Dr. Szema's office, driving an hour and a half through traffic.

Dina entered the clinic flashing her usual brilliant smile, yet her smile couldn't mask the irritation she clearly felt. Dina was escorted to the exam room, and her vitals were taken. When Dr. Szema came to read the patch test, he peeled

off the transparent film dressing and saw wheals (raised, red skin bumps) staring back at him.

"This is definitely not normal, Dina," Dr. Szema said as he examined the wheals. "Usually, it would take two to three days to see a reaction with patch testing, but the severity of this reaction suggests this is not a usual case of delayed allergic contact dermatitis."

Dina sighed with relief as the nurse then applied an ice pack to the tested skin area. "This is the best I've felt all day!" Dina said. "That was unbearable!"

"So, Dina," said Dr. Szema as he began applying a steroid cream to relieve the itchy, burning sensations on Dina's back. "It looks like you have to say good-bye to these hair dyes forever."

"But Dr. Szema, you don't understand…" Dina replied quietly. "My job is to be on TV. I can't afford to have any grey hair. I have to look my best day in and day out!"

"There must be other hair dyes that are better for you," said Dr. Szema. "Why don't you ask your hairdresser for some samples from different brands, and we'll do the test again to see which ones don't irritate you?"

"Absolutely!" said Dina. "I will ask her to pick out some brands, and I will bring them in."

In addition to patch testing at Three Village Allergy & Asthma, Dina also tested some hair dyes on her arm at her hairdresser's as well. After a couple of trips back to Dr. Szema's office, Dina finally found a hair dye kit that did not irritate her (Fig. 22.2).

"So Dr. Szema, does that mean I could recommend this brand to my girlfriends if they are allergic to hair dyes like me?" Dina asked, excited as she finally found her go-to brand.

"Well," Dr. Szema hesitated, "this one works for you, but everyone is different. I would advise your friends get tested like you did to see which one works best for them. There is no "one-size-fits-all" solution for everyone."

FIGURE 22.2 Breakup text

Background/Salient Features of Case

Patch testing is an allergy skin test that is based on the principles of type IV (delayed) hypersensitivity, which is when the immune system develops exaggerated responses to a foreign substance [6].

It is important to note that these responses are typical defense mechanisms but can be problematic when they are hyperactive. Patch testing is useful for determining which allergens should be avoided. Patch testing involves suspected allergens being placed on top of the skin instead of being "pricked" into the skin like the skin prick test (percutaneous test) that tests for immediate responses. Patch testing requires discontinuation of oral antihistamines and topical corticosteroids usage at least a week prior to the patch placement day [4]. Moisture might interfere with patch test results; therefore, patients are advised to refrain from showering and doing activities that lead to sweating. The results of the test can be read 48–72 h after the patch placement.

In principle, patch testing allows time for the body to develop a localized response at the area of exposure to aller- just hours after the patch replacement. This severe immediate allergic contact dermatitis suggests that Dina has a hypersensitivity to the ingredients of the various hair dyes that she used and was tested for.

In literature, hair dye has been reported to cause severe reactions in some patients. Specifically, p-Phenylenediamine (PPD) and toluene-2,5-diamine are the most common hair dye allergens [3]. Another alarming conclusion from one study also indicated the concentration of allergens in hair dye was tenfold lower than the legal (European) standards, yet they still induce clinical reactions. Both the literature and our observations at Three Village Allergy & Asthma suggest that formal regulations might not be extensive enough to protect consumers. Therefore, a preventive approach is needed before using beauty products with common allergens.

Diagnosis

Dina was diagnosed with severe delayed allergic contact dermatitis to several hair dyes and immediate allergy to others, as well as Steven Johnson's syndrome, as she presented a relevant collection of symptoms.

FIGURE 22.3 Bloodshot eyes

Allergic Contact Dermatitis (ACD) is a cell-mediated, antibody-independent inflammatory skin condition following exposure to an allergen [5]. The allergen penetrates the skin, reacts with haptens (non-protein chemicals), which activate T cells, and ultimately leads to a localized immune response on the skin [1]. In other words, ACD occurs when an allergen comes in contact with the skin and causes the exposed area to develop itchy, red bumps.

Steven Johnson's syndrome (SJS) is a rare disorder, affecting five individuals per million in the population [2]. Symptoms of SJS include flu-like symptoms (cough, sore throat, fever, etc.) as well as blisters, red rashes, and mucosal lesions affecting the oral cavity, genitals, anus, and conjunctiva (watery/bloodshot eyes). SJS is usually a hypersensitivity reaction to allergens/drugs or infections. Due to its severity, SJS is considered an emergency and should be treated immediately by discontinuing any drug/allergen of suspect and administering antihistamines and steroids (Fig. 22.3).

Treatment

The treatment plan consisted of patch testing various hair dye components and compounds from different brands to see if Dina could use her hair dye again without suffering through an allergic reaction. Apart from several hair dyes that induced allergic contact dermatitis, Dr. Szema was able to track down p-Phenylenediamine (PPD), nickel, and toluene-2,5-diamine sulfate (2,5-diaminotoluene sulfate) as the specific agents that Dina was allergic to. Out of all the hair dyes

tested, Dina's body only tolerated one specific brand. This, however, does not suggest that all the other hair dyes are bad; in fact, there was another patient at our practice who had a positive patch test to the very same dye brand that Dina tolerated! Therefore, it is important to note that different people could respond differently to the same chemicals. It is best to test beauty products on a small skin area for any reaction prior to using them.

On a side note, if you ever forget to test a product on yourself before using it (I'm personally guilty of this), you might be able to able to secure compensation from the manufacturer. Penni, another patient who developed allergic reactions to a specific brand of hair dye, tried contacting a manufacturer, insisting that their products were toxic to her. After much back and forth through mail and phone, the manufacturer agreed to reimburse Penni for medical fees (co-pays and medication) provided documentation from her physician. However, keep in mind this is not always guaranteed, so it is still best to test and avoid any known allergen.

Fast Facts

- Certain agents, hair dyes, for example, can induce Steven Johnson's Syndrome, a collection of severe allergic reactions.
- Patch testing is a type of allergy test that is based on the principles of delayed contact dermatitis. Unlike skin prick tests that test for immediate reactions to certain allergens, patch tests are usually read 48–72 h following the patch placement.
- Testing a beauty product before using should always be practiced, especially in people who have a history of allergies to certain ingredients found in such products. Avoid using any product that induces a reaction.

Test Your Knowledge

1. Which of the following is true?

   (A) The patch-tested area needs to be kept dry throughout the duration of the test.
   (B) Patch testing relies on the principles of Steven Johnson's syndrome.
   (C) Delayed allergic contact dermatitis is a type I hypersensitivity.
   (D) Hair dyes are toxic and should be avoided at all cost.

   ANSWER: (A) This is a correct statement. Moisture from showering, bathing, and sweating can cause the patch to come loose and the ink markings to fade.
(B) This is a false statement. Steven Johnson's syndrome, as aforementioned, is a rare condition that could be life threatening. If patch testing relied on the principles of Steven Johnson's syndrome, it would not be a safe procedure! Instead, patch testing is based on the principles of delayed contact dermatitis, which explains the typical wait time of 72 h since patch placement to read results.
(C) This is an incorrect statement. Delayed allergic contact dermatitis is a type IV hypersensitivity reaction. As you can guess from the name, type I hypersensitivity is immediate, not delayed. Another difference is Type I IgE (antibody) mediated, whereas type IV is independent of antibodies. Anaphylaxis, a life-threatening condition, is an example of type I hypersensitivity.
(D) This statement is too extreme of a claim. Utilizing products to enhance appearance is a validated need; there are regulations and standards to try to protect consumers' health, even though they do not always indicate complete safety. Research is continuously conducted to confirm and adjust regulations in product formulas to increase safeness. In this chapter, we explored a case of allergy to hair dye, but it should not be assumed that hair dyes in general are toxic (to draw an analogy, just because

allergy to peanut is common, it doesn't mean peanut butter is toxic!). However, as hair dyes, and beauty products in general, are mainly made of artificially synthesized compounds, it is best to take precaution and test them before using. Ultimately, if a product causes reactions, it should be avoided altogether.

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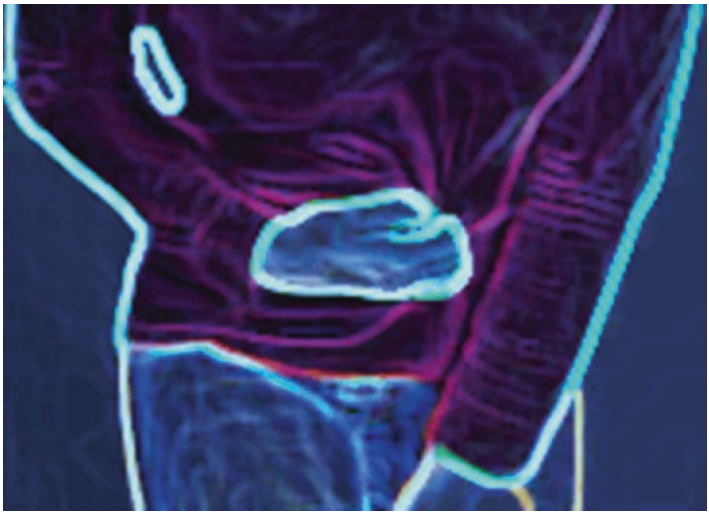
Chapter 23
Shocking Sex!!!

Gregory Smith



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Vignette

Seven years ago, Ms. Cheveu had a normal sex life. One night, however, tears streamed down her face. Excruciating pain coursed through her body, searing through her nerve endings. "I can't breathe," she exclaimed, "it feels like I've been shot!" Such intense torment would normally be associated with being stabbed or giving birth—not having sex! Cheveu's vision deteriorated while eyeing her husband—and soon a waning darkness enveloped. She passed out. Later that month, in the context of her duties as a nurse practitioner, Mrs. C. collapsed in the middle of the ICU on rounds. "Code blue" rang throughout the hospital floor. A team of physicians and nurses rushed to her side and implemented resuscitation techniques, including defibrillation. Ten minutes later, light entered her eyes and she regained consciousness.

Ms. Cheveu's past medical history includes Hashimoto's thyroiditis and attendant hypothyroidism, an autoimmune disorder whereby the body's immune cells damage the thyroid cells. Symptoms of a damaged thyroid include fatigue, sore muscles, drowsiness, weight gain, dry skin, and hair loss, just to name a few [1]. Could that impact her collapse and pain? Or could there be another factor at hand? Ms. Cheveu also had a procedure performed known as the permanent birth control coil that inserts a small device composed of Nitinol (nickel-titanium alloy), stainless steel, polyethylene terephthalate (PET) fibers, platinum, silver, and tin into the fallopian tubes [2]. Ever since then, Ms. Cheveu would endure painful hypotension—shock during sex! What could possibly be the cause of this? Could a small birth control device designed to block sperm be the culprit behind this magnitude of pain?

Background/Salient Features of Case

The permanent birth control coil procedure is non-surgical [2]. An permanent birth control coil insert, composed of the aforementioned materials, is inserted into the fallopian tubes [2].

This 4-cm-long expanding spring extends 0.8-mm in diameter and ultimately causes the fallopian tubes to inflame and thicken [2]. Blockage of the fallopian tubes—an inflammatory then fibrotic response—ultimately prevents sperm from fertilizing the respective egg cell. A study conducted by Al-Safi et al. (2013) showed that the 1-year success rate of the permanent birth control coil procedure was 86.7% to prevent pregnancy [3]; however, pre-marketing studies for permanent birth control coil did not follow up with all participants beyond 1 year, if at all, because of device placement failure, or participant dropout or exclusion (for various reasons) [4]. In this study, no long-term complications were registered [5]. The benefits of the procedure are cited as being minimally invasive, having a 3% rate of incorrect placement, requiring no general anesthesia, incisions, long recovery time, or hospital visits [5]. Truth be told, this procedure does appear to be an alternative to laparoscopic tubal sterilization.

As per procedure, a hysterosalpingography, or an imaging technique used to look at the fallopian tubes and uterus, is conducted after three months to confirm placement and occlusion [3]. In 2015, Dhruva et al. revisited the effectiveness of the permanent birth control coil procedure. Even after permanent placement of the metal coil, there was still an estimated 5.7% annual risk of pregnancy [4]. Nine years later, the risks besides pregnancy have included: tubal perforations; intractable pain; and bleeding, which necessitated hysterectomies [3]. Adverse side effects such as allergy to the device have not been fully characterized.

Diagnosis

Allergy testing for nickel was negative. However, nickel, as part of Nitinol, is just one of the main components. Other metals include titanium, steel, PET, platinum and tin. Several months after the negative nickel patch test, additional allergy tests were ordered. Subsequent chemotechnique patch testing revealed one key allergen that showed inflammation on Ms. Cheveu's skin—titanium. Titanium 3-oxalate was tested

with a Finn chamber and the results were positive. During the examination, her skin was raised, red, inflamed, itchy, and irritated within the confines of the Finn chamber. Whereas testing was conducted on the back, her foreign metal coil was placed in her fallopian tubes—which were now presumably inflamed and irritated. Could this be her a cause of agony? Ms. Cheveu's symptoms and allergy test confirmed a Gell-Coombs delayed type IV hypersensitivity or contact dermatitis to the titanium in the permanent birth control coil coil. As the cause of her pain and agony came into view, tears rushed down Ms. Cheveu's face. Initially, the tears were in response to finally discovering the cause of her ailments. Then reality settled in. The next step would require having a hysterectomy performed, or a procedure involving removing the uterus. Her original decision to avoid the O.R. from tubal ligation came back to haunt Ms. C., since now she was back!

The allergy test confirmed the root cause of the issue. However, what would be the cause of coding in the hospital? The thickening of tissue requires new tissues to grow. Where there are tissues, there are blood vessels. As this foreign metal spring is inserted into the fallopian tubes, new blood vessels develop through a process known as neovascularization, which was confirmed using ultrasound imaging. In the presence of an allergen, such as the titanium, the fibrosis is further coupled with inflammation. Now let's revisit Ms. Cheveu's case. She coded on the hospital floor. For Ms. Cheveu, it appears that the development of new blood vessels diverted blood away from the body, leading to a drop in blood pressure. While walking in the ICU, the increase in heart rate may have induced hypotensive shocks, leading to her collapse. If left untreated, hypotensive shocks may even be lethal.

Seven years later, Ms. Cheveu finally learned the root cause—the titanium. However, the reality of the nurse practitioner requiring seven years to discover the root of her ailments is alarming and raises several questions. If Ms. Cheveu failed to receive proper patch testing to detect potential

allergens, how many other women could be receiving the permanent birth control coil without proper screening? How many other women can be in a state of chronic inflammatory response and not know that this is from the permanent birth control coil insert? Could there be an adverse reaction rate heretofore underreported? Are there more negative aspects of the neovascularization from the fibrosis that have still not been observed?

Treatment

For Ms. Cheveu's Hashimoto's thyroiditis, 100 μg of Synthroid was prescribed in order to stabilize her hypothyroidism triggered from the Hashimoto's thyroiditis. For the permanent birth control coil procedure, the best option was clear: remove the device. The tissue had been badly damaged and the device required urgent removal. However, such inflamed and damaged tissue cannot possibly be salvaged. Otherwise, the risk of infection sets in as the device is removed. The safest route is to removal the permanent birth control coil insert in concert with removal of the uterus. If the device remained, the pain and shock would simply increase in frequency.

Fast Facts

- The permanent birth control coil procedure performed on Ms. Cheveu induced neovascularization, inflammation, and fibrosis.
- This patient was additionally diagnosed with pelvic congestion syndrome (PCS). However, we have not been able to confirm a link between the Gell-Coombs delayed type IV hypersensitivity and the PCS. Nonetheless, having both contact dermatitis and PCS can lead to capillary leakage while attenuating a hypotensive shock due to the diversion of blood flow. The hypotension may have been exacerbated due to a setting of hypothyroidism.

Patch testing revealed that Ms. Cheveu has a delayed contact dermatitis to titanium (Gell Coombs Type IV Immune Reaction). She is allergic to one of the main metals in the Essure insert: titanium.

Test Your Knowledge

1. The development of new functional blood vessels is known as:

   (A) Angiogenesis
   (B) Neovascularization
   (C) Glycosylation
   (D) Clearance

   ANSWER: (B) Neovascularization is characterized by the formation of new blood vessels. In Ms. Cheveu's case, the titanium induced a state of chronic inflammation because of the allergic response. The permanent birth control coil functions by inducing fibrosis, which can be coupled with neovascularization. The new blood vessels then divert blood away from the core of the body thus placing a strain on the heart by increasing cardiac output.

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