IBD LIVE Case Series—Case 6: Persistent Skin Lesions in a Patient with Crohn's Disease: You Hear Hoof Beats and Discover a Zebra

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LEARNING OBJECTIVES

After completing this IBD LIVE-CME activity, physicians should be better able to:

1. Explain the side effects of medications used to treat IBD, particularly anti-TNFs.
2. Recognize the various types of skin lesions that may occur in IBD patients, focusing on those that arise among patients on immunosuppressants.
3. Be cognizant of the presentation and treatment of pyoderma gangrenosum in IBD patients.
4. Describe the various types of mycobacterial infections that may occur among IBD patients, especially those that are on anti-TNFs.
5. Describe the risk factors for developing a *Mycobacterial marinum* infection and how it may present dermatologically.
6. Explain how to diagnose and treat a *Mycobacterial marinum* infection.

PRESENTATION

Dr. D. Rajan: University of Maryland, Baltimore, Advanced Inflammatory Bowel Disease Fellow, 2015 to 2016, Presentation date: June 25, 2015.

The patient is a 27-year-old white man with a history of inflammatory ileocolonic Crohn's disease with oropharyngeal involvement and treatment-refractory pyoderma gangrenosum (PG). His medical history is significant for adrenal insufficiency, vertebral fractures due to osteoporosis, and latent tuberculosis treated with isoniazid. Surgical history includes a tonsillectomy. His brother and mother have celiac disease. He is married and works as a lawyer. He is a lifetime nonsmoker, does not use illicit drugs, and rarely drinks alcohol. In 2002, at age 14, he was diagnosed with Crohn's disease after presenting with abdominal pain and diarrhea. After his diagnosis, he was treated with prednisone with an excellent response.

He was gradually tapered off of prednisone and transitioned to budesonide, which he remained on for approximately 1 year

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without recurrent symptoms, at which time the medication was discontinued. The patient was well until about 2007 or 2008, when he developed recurrent abdominal pain, diarrhea, and weight loss. After failing azathioprine and steroids, he was started on adalimumab and responded. In 2010, he developed abdominal symptoms and PG when backpacking in Europe. He was treated with prednisone but could not taper below 20 mg per day. A bacterial superinfection of the PG emerged that was treated with antibiotics and wound care, and his adalimumab was increased to weekly dosing.

In 2011, the patient had a positive PPD and was treated with isoniazid for 9 months. In 2012, he reported worsening abdominal symptoms. The adalimumab that he had been taking regularly was increased to 40 mg subcutaneously, weekly. Soon thereafter, he developed nasal congestion, hoarseness, dysphagia, and odynophagia. An otolaryngology evaluation identified numerous ulcerations at the base of the tongue. Biopsies revealed squamous mucosa with focal necrosis, acute and chronic inflammation, and rare epithelioid histiocytic aggregates, suggestive of oropharyngeal Crohn's disease. Adalimumab was discontinued and, after failing certolizumab pegol, the patient was started on infliximab and methotrexate while his prednisone was increased to 40 mg daily. Nonetheless, the patient had persistent PG lesions, predominantly on his right lower extremity, particularly the foot (Fig. 1).

His prednisone was increased to 60 mg daily, methotrexate and non-steroidal anti-inflammatory drugs (NSAIDs) were discontinued, topical tacrolimus was added, and his PG pain was treated with tramadol. In addition, his infliximab infusions were changed to every 4 weeks at 10 mg/kg. After initially improving, his PG worsened. We again stopped the NSAIDs he had started on his own and tapered his prednisone. We also discontinued his tacrolimus, changed his infliximab schedule to every 6 weeks at 10 mg/kg, and started him on minocycline, cyclosporine, and trimethoprim/sulfamethoxazole. In time, his oropharyngeal symptoms resolved and PG lesions healed (Fig. 2). Unfortunately, the patient developed multiple vertebral fractures secondary to osteoporosis from chronic steroid use. We tapered the narcotics that had been started for his back and PG pain and lowered his prednisone that was started by his community gastroenterologist, but could not reduce it below 10 mg because of adrenal insufficiency. A repeat colonoscopy at this time demonstrated healing of the mucosa.

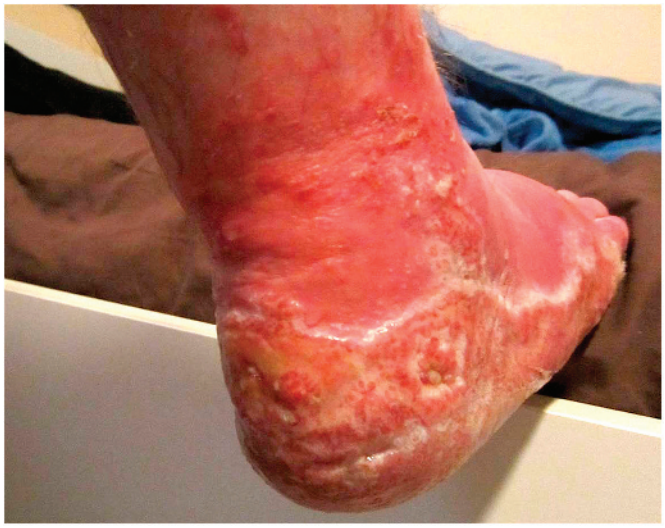

FIGURE 1. Photograph of right ankle and foot demonstrating erythema, edema and crusted, weeping ulcerations in various stages of development and healing (July 2013).

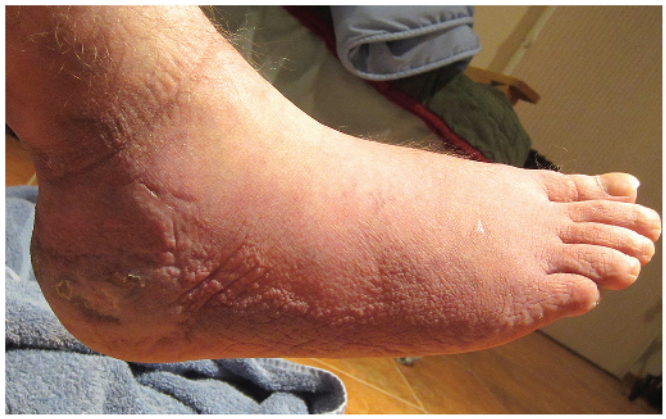

FIGURE 2. Follow-up photograph of right foot showing nearly complete healing after adding antibiotics to his treatment regimen (February 2014).

In May 2014, the patient developed nasal swelling and facial induration treated with oral and topical antibiotics by an otolaryngologist. We discontinued his trimethoprim/sulfamethoxazole secondary to thrombocytopenia and started dapsone, which resulted in an admission to the University of Maryland Medical Center with methemoglobinemia. A shave biopsy of the nose performed during the hospital stay revealed granulomatous dermatitis with features suggestive of acne rosacea or rosacea fulminans (pyoderma faciale). A dermatologist started him on topical metronidazole and desonide, but his lesions worsened. Oral isotretinoin was initiated with significant improvement in his facial and nasal lesions; mild recurrences were treated effectively with the intralesional steroid triamcinolone. His antibiotics were alternated because of a potential drug interaction, but minocycline proved the most effective without causing side effects.

At that time, we stopped the patient's cyclosporine at his request because he was becoming frustrated. Soon thereafter, the patient developed a "flu-like" illness that precipitated an adrenal crisis. A neurologist evaluated him for severe headaches and diagnosed him with pseudotumor cerebri. His isotretinoin was discontinued. Two months later, the patient developed a sore throat, lip swelling, and ulcerations of his lips and oral cavity. A nasal swab showed positive results for *Klebsiella,* and the patient was prescribed gentamicin cream and a methylprednisolone (Medrol Dosepak 2–60 mg/d PO divided q6-24 hr). At this time, the patient's infliximab levels were undetectable at trough but without antibodies. Therefore, he was given an early infusion of 15 mg/kg of infliximab; his cyclosporine was restarted at a dose of 100 mg in the morning and 125 mg in the evening; and he was given

Pneumocystis pneumonia prophylaxis. Despite treatment, the patient's symptoms worsened. In May 2015, the patient was admitted to an outside hospital with a 2 to 3 weeks' history of worsening lip, nose and cheek lesions, and recent-onset fever. He was treated with intravenous (IV) vancomycin and piperacillin/tazobactam and underwent an excisional deep shave biopsy of the left cheek with cultures for bacterial, fungal, viral, and mycobacterial organisms. He was discharged on trimethoprim/sulfamethoxazole.

The patient continued to have intermittent fevers at home and was admitted to the University of Maryland Medical Center from May 30th until June 8th of 2015 where he was noted to be febrile and tachycardic in the emergency department. Physical examination was remarkable for facial edema and crusted, erythematous, fungating nodules with central umbilication on his cheeks, nose, and the upper lip (Figs. 3 and 4). Initial laboratory studies were significant for a white cell count of 11.8×10^3 cells/μL (normal $3.9–10.7 \times 10^3$ cells/μL), hemoglobin of 11.9 g/dL (normal 13–17 g/dL [men]), hematocrit 27.3% (normal 40%–54% [men]), and C-reactive protein of 7.7 mg/dL (normal <3.0 mg/dL). An otolaryngologist performed a laryngoscopy that demonstrated oropharyngeal edema without airway involvement.

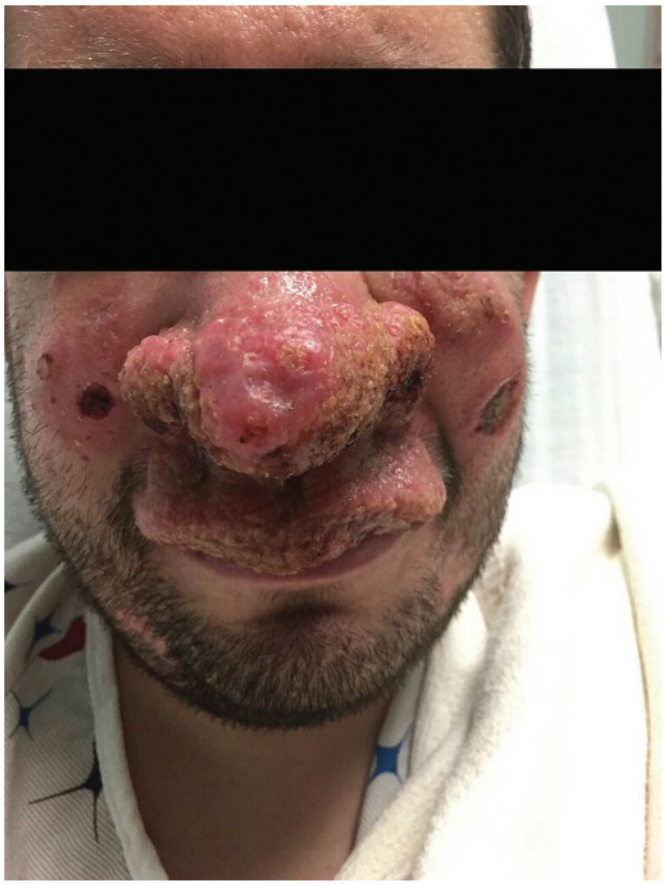

FIGURE 3. At admission, the patient had facial edema with crusted, erythematous, fungating nodules with central umbilication along his bilateral cheeks, nose, and upper lips. Note the deeper ulcerations adjacent to the nose (May 2015).

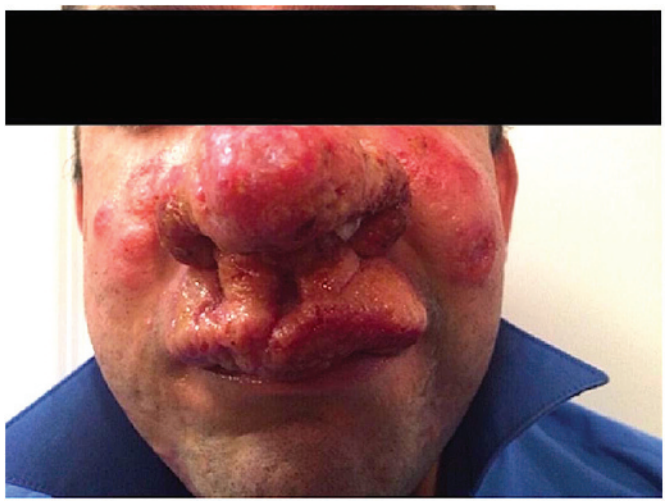

FIGURE 4. Persistent facial edema, erythema, and ulcerations noted despite treatment with vancomycin and piperacillin/tazobactam (June 2015).

On the medical floor, his infliximab and cyclosporine were held while he was treated with vancomycin and piperacillin/tazobactam. Skin lesion cultures revealed *Klebsiella* sensitive to ceftriaxone, and he was treated with ceftriaxone for 10 days. He was given 3 doses of 0.4 mg/kg of IV immunoglobulin (IV IG) daily along with oral hydrocortisone 20 mg bid because of adrenal insufficiency. A repeat shave biopsy of the right cheek revealed fungal folliculitis for which oral fluconazole was initiated. The left cheek biopsy demonstrated pseudoepitheliomatous hyperplasia with parakeratosis and heavy mixed inflammatory infiltrate and exocytosis of inflammatory cells. Special stains for acid-fast bacilli were positive although *Mycobacterium tuberculosis* was not detected on ribosomal RNA. Because of persistent fever, the patient underwent a pan–computed tomography that was remarkable only for an enlarged right submandibular lymph node.

At his follow-up clinic appointment, the patient does not report having fevers or chills, abdominal pain, diarrhea, or extraintestinal manifestations but described having severe nose, lip, and oral pain and poor oral intake secondary to both anorexia and odynophagia/dysphagia.

Dr. Leonard Baidoo (Northwestern, Gastroenterology)

To summarize, this is a patient with Crohn's disease diagnosed in 2002 who was doing relatively well until around 2007 or 2008. He has oropharyngeal involvement and PG that, based on the recent photographs, seems to have persisted and gotten considerably worse. He has become refractory or nonresponsive to virtually all the anti–tumor necrosis factors (TNFs). In fact, his infliximab has been started, stopped, and restarted at various doses. He responded fairly well to cyclosporine, but it was discontinued. So let us go around to the participating sites and get some feedback on how our physicians would manage this complicated patient.

Dr. Hans H. Herfarth (University of North Carolina, Gastroenterology)

It seems to me that the anti-TNFs never really worked, but the patient improved when the cyclosporine was added to the anti-TNF. In the last photographs, the patient looks worse. I am wondering what the patient's cyclosporine level was before it was stopped and also whether you could use tacrolimus to get things under better control. I also would want to know whether this is an atypical mycobacterial infection because there were acid-fast bacilli on staining. I might suggest starting the patient on triple therapy as treatment.

Dr. Raymond K. Cross (University of Maryland, Gastroenterology)

In the past, the patient's oropharyngeal Crohn's was responsive to anti-TNF agents, but the pyoderma was not, and he would get recurrent oropharyngeal symptoms before his infliximab infusions when he was on cyclosporine. This is why he remained on both medications. We do not think this is *M. tuberculosis* because his probe for the ribosomal RNA was negative. Infectious Disease specialists saw him, and they do not think it is typical mycobacteria but, rather, an atypical mycobacterial infection. They have been reticent to start empiric 1-drug or 3-drug therapy until they get it speciated despite his ongoing symptoms.

Dr. Hans H. Herfarth (University of North Carolina, Gastroenterology)

Yes, that was what I thought because we had a similar case with a patient with pyoderma here who was refractory to therapy with steroids, cyclosporine, and anti-TNFs. Then on triple therapy, which is what you would normally do for *M. tuberculosis*, the PG went away. In the end, it was determined that the patient had atypical mycobacteria.

Dr. Myron H. Brand (Yale, Gastroenterology)

We agree with what Hans said. This is likely to be some sort of superinfection in an immunocompromised patient. It is important to get the opinions of the clinicians of Dermatology and Infectious Disease because I think we are dealing with an infectious complication in a patient with Crohn's disease. I do not think that this is just his Crohn's disease. It sounded like his bowel disease was fairly well-controlled but maybe Ray could tell us some more about what was going on with his Crohn's disease. Right now, I do not think I would be immunosuppressing him until I knew for certain what was going on from an infectious point of view.

Dr. Francis A. Farraye (Boston Medical Center, Gastroenterology)

We agree with the statements that have been made. These do not seem to be the typical ear, nose, throat (ENT) and facial manifestations of oropharyngeal Crohn's disease. I think that he needs to have this infection treated, whatever it is. We are thinking outside the box and considering going for a different drug. Ultimately, if he does have luminal Crohn's disease or recurrent pyoderma, may be he should go on ustekinumab or a different agent as opposed to an anti-TNF.

Dr. Emmanuelle (Manny) Williams (Penn State Hershey, Gastroenterology)

We have some experience in treating pyoderma with IV IG although we run into terrible problems in getting insurance coverage for it. However, we have had success with IV IG although, for one of our recent patients, it took a while for it to kick in. Other than that, I think that ustekinumab could be an option although I believe that his infection is what that needs to be treated first.

Dr. Corey A. Siegel (Dartmouth, Gastroenterology)

I agree with many of the previous comments. I think that this infection needs to be sorted out. We are talking about trying all different types of immunosuppressant drugs, but I think that, first, the clinicians from Infectious Disease should give us an idea of what type of empiric drugs might be used for his infectious complications. This patient is in bad shape, and I think that we need to try something. From a bowel standpoint, I like Frank's idea of ustekinumab. There are some limited data that we have discussed in this conference that address the use of ustekinumab for pyoderma with some success. We have also previously discussed using hyperbaric oxygen for some of our patients who have severe disease, and it can also be used for pyoderma. There is almost no downside to using hyperbaric oxygen. I know that Pittsburgh has access to hyperbaric oxygen, but I am not sure whether it is available in Maryland. I would try empiric antibiotics, probably triple-drug therapy, going after mycobacteria. Potentially, I would consider using ustekinumab or hyperbaric oxygen to get his bowel disease under control. The only other thing that has not been raised is orofacial granulomatosis, which is not exactly Crohn's disease but you treat it like Crohn's disease with anti-TNFs in addition to dietary changes, although I do not think avoiding cinnamon and benzoate products is going to make much of a difference for this patient. This might be something to consider when you are waiting for medication to work.

Dr. Alka Goyal (Children's Mercy Kansas City, Pediatric Gastroenterology)

We were wondering whether leprosy (*Mycobacterium leprae*) might be a possibility given this patient's presentation and facial appearance. We were also curious about whether genetic testing might be warranted to evaluate for treatment-resistant Crohn's disease.

Dr. Ioannis E. Koutroubakis (University of Crete—Greece, Gastroenterology)

Personally, I agree that the first thing to do is to treat the potential infectious etiology. This person had latent tuberculosis (TB) in the past. We should take into account that, even if his test results are negative for it, treatment with therapy for tuberculosis or other atypical mycobacteria is warranted. This would be my first priority. Of course, your choices of inflammatory bowel

disease (IBD) medications are limited in that he has not responded to anti-TNFs. Although I do not have experience with ustekinumab, I agree that this agent might be a good choice.

Dr. David G. Binion (University of Pittsburgh, Gastroenterology)

Dhyan, you gave us a little bit of information about his bowel disease but one of the last pieces of objective data that were presented was that the patient had a hematocrit of 27, which, for a male patient, implies that there may be some losses coming from the gastrointestinal tract. If he is in good shape with no obvious damage to the gut, I would be suspicious about gluten sensitivity. I know that you mentioned that both his mother and brother have a history of celiac disease. I do not know whether you have explored an elimination diet or removing gluten from this patient's diet, but I had one patient with similarly severe, treatment-refractory disease that was put on a gluten-free diet, and she had complete resolution of skin lesions that had been previously labeled as pyoderma. The pyoderma involved her abdominal wall at multiple incision sites, and it was highly destructive. Eliminating gluten is a fairly benign potential solution that could be added to the mix.

Realistically, I do think that this is superinfection. There was mention that the patient was put on some typical anti-fungal agents. These medications may not be adequate to cover the potential superinfections that can accompany this type of a picture. Given the severity that he is demonstrating, you might consider expanding fungal coverage to something more potent. I would work with the infectious disease colleagues and would consider anti-fungal agents with broader spectrum of activity, such as caspofungin.

Your patient is presenting with an unusual clinical picture with the need for immunosuppression in the setting of a potential infectious complication. If you need guidance, you could confer with colleagues experienced in Solid Organ Transplantation or Infectious Disease Transplant, because they are likely to have the most knowledge in this area. When I work with our small bowel transplant team and we see these types of profound cellulitis infections, the treatment pathway that is most commonly beneficial is systemic anti-fungal therapy. I am also fully in favor of IV IG given that it has proven efficacy for pemphigus but may also help regarding infectious complications.

Dr. Leonard Baidoo (Northwestern, Gastroenterology)

So Ray, the consensus is that you should push your Infectious Disease colleagues to give this patient some empiric or specific treatment. It seems that he has run the course with the anti-TNFs, and if you need to treat him further for his Crohn's disease, an alternative medication might be a good idea. What are you thinking at this point? Infection? Is this refractory, extraintestinal IBD or something else??

Dr. Raymond K. Cross (University of Maryland, Gastroenterology)

The rationale for the IV IG was that he clearly needed a break from immune suppression, and we were convinced that this was primarily an opportunistic infection that was causing his symptoms. I have been fairly aggressive with our Infectious Disease colleagues about getting a medication started, but they have been hesitant to start any medication for mycobacterial infection.

There is some disagreement between our Dermatology and Infectious Disease specialists where the biopsies do not seem to be completely consistent with a mycobacterial infection, even though the stain is positive. As to David's point about anemia, he has been tested for iron-deficiency anemia many times, and his ferritin is 300 to 400, so he is not iron-deficient. I am not sure whether he has been worked up for celiac disease. We also put him on an enteral diet for 2 to 3 weeks before he re-presented to the hospital as a form of last-ditch, nonimmunosuppressive treatment.

We gave him some topical budesonide respules because he was pleading with us for steroids and with his dermatologists for intralesional steroids, and the respules seemed like a good compromise. Topical therapy also seemed appropriate because I think some of the oropharyngeal lesions are results of his Crohn's disease, whereas the nasal and lip findings are the opportunistic infection. After he completes some treatment for the mycobacterial infection, we will need to transition him to something to treat his Crohn's disease. I think ustekinumab is a good idea. We were also thinking about vedolizumab with the idea that it might be less immunosuppressive. I was trying to think of something less systemically immunosuppressive. The thought was that the IV IG would be temporary treatment until we address his infection and get him back to some sort of baseline. At that point, we could institute monotherapy for his Crohn's disease or for whatever this is.

Dr. Hans H. Herfarth (University of North Carolina, Gastroenterology)

Did you recently biopsy the lip and look for granulomas so that you could be sure that this is Crohn's disease? That would better narrow the therapy.

Dr. Raymond K. Cross (University of Maryland, Gastroenterology)

They swabbed, cultured, and biopsied the left cheek, and it showed acid-fast bacilli. However, they lost the pathology to the left cheek. Within the next day or 2, they biopsied the right cheek and the dermatopathologist thought that the biopsy showed something more consistent with a fungal infection. This is the reason that there is disagreement between Dermatology and Infectious Disease. When I spoke with our gastrointestinal (GI) pathologist, he said that although they were suspicious for a fungal infection, there was no way to exclude mycobacteria as a cause. Personally, I found the biopsies to be more confusing than helpful.

Dr. Douglas J. Hartman (University of Pittsburgh, Pathology)

It can be difficult to identify rare mycobacterial organisms in tissue specimens. Even the presence of granulomas does not always help to separate out these 2 entities. I would recommend that you do a tissue culture of one of the specimens. *Mycobacteria*

do not culture very well, which is another diagnostic problem. Once you start down this atypical mycobacterial wormhole, you can get stuck because the diagnoses can be very difficult to separate. Although you know this is not TB, this does not help you with the other types of mycobacterial organisms. If they can get some culture, they can type it because they are doing more molecular evaluations of mycobacteria. However, I would process the sample through Microbiology and not through Anatomical Pathology or Dermatopathology, because the microbiologists are going to be more likely to give you a treatable organism.

Dr. David Binion (University of Pittsburgh, Gastroenterology)

The problem with the granulomas detected on histology is that they might be a physiologic response to infection. Immune responses to mycobacteria will involve epithelioid granuloma formation. So I am not sure that doing a biopsy of the lip will put things into a clean Crohn's category because there is a hint of mycobacteria that we are hearing about. There has been literature over the past 30 years suggesting that atypical mycobacterial infections, such as *Mycobacterium paratuberculosis,* may contribute to the etiopathogenesis of Crohn's disease. Although organisms like paratuberculosis will not be responsible for most cases of Crohn's disease, in all likelihood, there will be rare patients where mycobacterial superinfection is contributing to the disease.

Dr. Leonard Baidoo (Northwestern, Gastroenterology)

I am curious to know about the patient's ethnicity and recent travel history, given that he had latent TB.

Dr. Ray Cross (University of Maryland, Gastroenterology)

He is white and was born and raised in the United States. His only travel history includes the backpacking in Europe that I mentioned as being when the foot lesions developed. More recently, he was in Paris for his honeymoon. He did not report any other type of travel.

FOLLOW-UP

Mycobacterium marinum was eventually isolated from the patient's lesions. A 6-month medical regimen for the treatment of *M. marinum* was initiated, which included a combination of ethambutol, minocycline, and azithromycin. The therapy resulted in near resolution of the facial lesions (Fig. 5). However, the patient manifested worsening luminal symptoms and migratory arthritis and was therefore restarted on infliximab 10 mg/kg, every 6 weeks. As of November 2015, he was doing well and has had no recurrence of either PG or *M. marinum* infection.

DISCUSSION

PG is a less common but serious, extraintestinal manifestation of IBD.[1,2] PG is a neutrophilic dermatosis with lesions that manifest as deep, painful ulcerations that may be a treatment challenge. Symptoms that often accompany PG include malaise, fever, myalgias, and arthralgias, which are also symptoms of IBD.[1] Similarly, infection of PG lesions may not cause profound changes in a patient's symptoms. The mainstay of treatment for PG is immunosuppressants with anti-TNFs showing significant effectiveness in resolving the lesions.[3–6] However, superinfection of PG lesions often requires stopping immunosuppressants until the underlying infection has been adequately treated. The patient described in this case had been immunosuppressed for many years, receiving infliximab, adalimumab, and cyclosporine, alone or in combination, during the course of his illness.

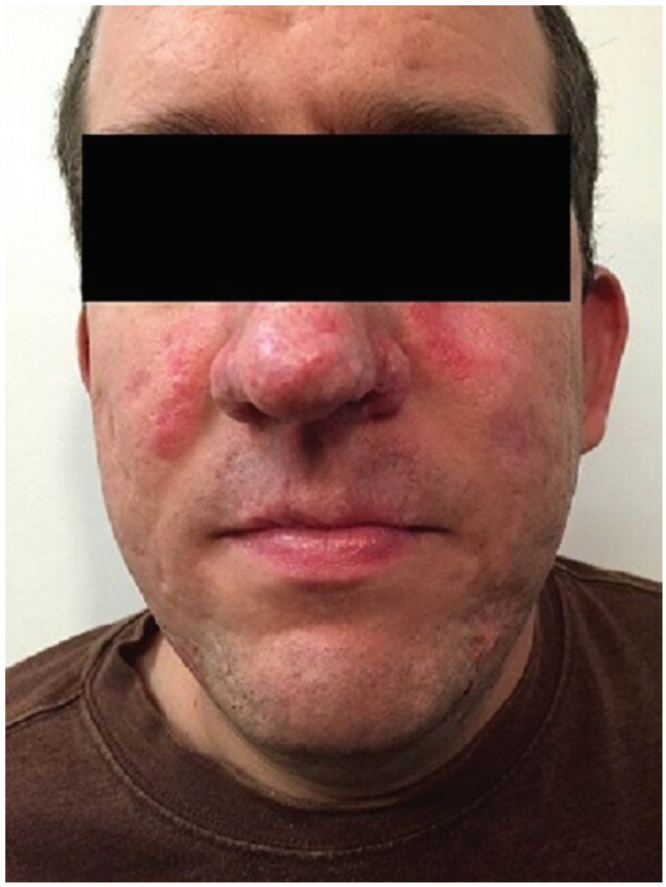

FIGURE 5. Note the near complete resolution of the patient's facial edema and ulcerations after 6 months of medical therapy directed toward *Mycobacterium marinum,* including ethambutol, minocycline, and azithromycin (January 2016).

Although TNF-alpha inhibitors (anti-TNF) therapies have caused a paradigm shift in the management of IBD and other chronic inflammatory disease states, clinicians must be aware of their potentially serious side effects. Infections, drug-induced lupus, serum sickness-like reactions, demyelinating diseases, and skin cancer are examples of more serious adverse reactions that have been observed with anti-TNF therapy.[7–13] Dermatologic manifestations from anti-TNF therapy have been well-documented and can range from simple injection-site reactions to psoriasis, erythema

multiforme, and eczema.[14–17] Dermatologic responses such as Hodgkin-type lymphoproliferative skin disorders and opportunistic infections involving the skin may occur secondary to the immunosuppressive effect of anti-TNF therapy.[15]

Mycobacterial infections are frequently reported opportunistic infections in patients receiving anti-TNFs, and anti-TNF therapy may precipitate their reactivation.[13,18–20] Although *M. tuberculosis* is the most common mycobacterial infection associated with anti-TNF therapy, it rarely causes dermatologic manifestations, even when disease is disseminated. More often, nontuberculous mycobacteria infections are implicated when extrapulmonary infections arise. When nontuberculous mycobacteria cause a cutaneous infection, *M. marinum* is the most likely causative agent although *Mycobacterium chelonae*, *Mycobacterium mucogenicum,* and *Mycobacterium abscessus* have also caused skin infections in patients taking anti-TNF medications.[21–23]

Because TNF serves an important role in maintaining granuloma formation and preventing mycobacterial growth, lymphocutaneous spread of nontuberculous mycobacteria has been increasingly noted among patients receiving anti-TNF therapy over the last 2 decades.[19,24,25] In 2009, Winthrop et al[19] published results of their review of the US Food and Drug Administration MedWatch database reports of nontuberculous mycobacteria infections in patients receiving anti-TNF therapy. During the 9-year period from 1997 to 2006, there were 239 cases of nontuberculous mycobacteria reported in patients receiving anti-TNF therapy. Of these cases, nearly 75 percent were associated with infliximab, and the predominant causative organism was *Mycobacterium avium*. The third most common nontuberculous mycobacteria infection was *M. marinum*, which was also the most likely one to cause skin lesions.

M. marinum is an aquatic mycobacterium whose natural habitat is fresh or salt water, especially reservoirs of water that are not frequently replenished.[16,26] Infection with *M. marinum* in humans typically occurs when the organism is present in contaminated water and inoculates an area of skin break down or puncture; initially, it manifests as sporotrichotic lymphangitis.[24,25,27] Some cases of *M. marinum* infection occur when there is a known exposure to fish fins or water containing fish. For example, in 2010, Ramos et al[28] published a case report of *M. marinum* infection causing painful suppurative papules and nodules on the forearm of a Crohn's disease patient on infliximab that was caring for fish in a domestic aquarium. Although the patient described in this case did not report recreational or occupational exposure to a body of water, infection has been shown to occur at higher rates in those on anti-TNF agents.[16,24,29,30]

Although the prevalence of *M. marinum* is rare, cases of *M. marinum* are increasingly being noted both in immunocompetent and immunosuppressed hosts, such as transplant patients.[27,31] Clinicians should be cognizant of this mycobacterium, particularly in immunosuppressed patients with a history of ulcerative skin lesions, exposure to brackish water, or a history of pyoderma faciale.[6,7] There are no data to support a heightened risk of infection with *M. marinum* in patients on dual immunosuppression, as our patient was. Nonetheless, it is plausible that the combination of cyclosporine and an anti-TNF could have increased the risk and severity of his infection. Health care providers need to be vigilant in monitoring for opportunistic infections in patients with IBD taking immunosuppressants.

Patients with *M. marinum* infection involving the face might be misdiagnosed with pyoderma faciale if appropriate cultures and stains for acid-fast bacilli are not performed. Notably, routine PPD skin testing does not predict infection with or reactivation of the various types of nontuberculous mycobacteria, including *M. marinum*. Misdiagnosis can lead to continuation of potentially detrimental immunosuppressive therapy and failure to initiate appropriate antimycobacterial treatment. Discontinuing immune suppression is recommended when the diagnosis of *M. marinum* is suspected. The decision to resume immunosuppressants depends on the presence and severity of IBD symptoms, the severity of disease course, and whether there is clinical improvement of the *M. marinum* lesions on antimycobacterial therapy.[32,33] In our case, the rapid recurrence of symptoms and severity of the patient's Crohn's disease prompted restarting anti-TNF monotherapy a few weeks after completing treatment for *M. marinum*.

EDITOR'S COMMENT

Dermatologic manifestations are common in patients with IBD, and some centers now have dermatologists who specialize in IBD-related skin problems. When patients with IBD present with skin ulcerations, there is a wide differential diagnosis from familiar PG lesions to rare metastatic cutaneous Crohn's disease.[2,34] Crohn's disease involving the upper GI tract comprises inflammation anywhere from the mouth to the jejunum, typically with concomitant lower GI tract disease.[35] There is significant overlap between orofacial Crohn's disease and PG as well as other confounding entities, such as Bechet's disease, orofacial granulomatosis, lichen planus, herpes simplex virus, and even squamous cell cancer related to human papillomavirus.[36,37] Discerning the etiology of skin lesions in patients with IBD can be difficult, particularly among those with a history of PG. In a study of 95 individuals with skin ulcerations resembling PG, final diagnoses included cancer, vascular occlusive or venous disease, vasculitis, primary infection, drug-induced or exogenous tissue injury, and other inflammatory disorders.[38] Therefore, not all painful skin lesions are pyoderma.

Patients with IBD taking immunosuppressant anti-TNFs have a heightened risk of bacterial, fungal, mycobacterial, and viral illnesses.[39] Because of the increasing numbers of rare mycobacterial infections that are being observed among immunosuppressed patients with IBD, providers should be aware of this, particularly in patients with skin lesions that are not responsive to IBD therapies or that worsen with these treatments. A multidisciplinary approach to managing orofacial/cutaneous IBD and infections may include seeking consultation from Dermatology, Infectious Disease, Microbiology, and Oromaxillofacial specialists.

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CME-MOC EXAM—22.11
IBD LIVE Case Series-Case 6: Persistent Skin Lesions in a Crohn's Disease Patient: You Hear Hoof Beats and Discover a Zebra

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LEARNING OBJECTIVES

After completing this IBD LIVE-CME activity, physicians should be better able to:

1. Explain the side effects of medications used to treat IBD, particularly anti-TNFs.
2. Recognize the various types of skin lesions that may occur in patients with IBD, focusing on those that arise among patients on immunosuppressants.
3. Be cognizant of the presentation and treatment of PG in patients with IBD.
4. Describe the various types of mycobacterial infections that may occur among patients with IBD, especially those that are on anti-TNFs.
5. Describe the risk factors for developing a *Mycobacterial marinum* infection and how it may present dermatologically.
6. Explain how to diagnose and treat a *M. marinum* infection.

1. You have a patient with severe Crohn's disease that you would like to start on the anti-TNF medication adalimumab. Which of the following is **not** a recognized potential side effect of anti-TNF medications that you will discuss with your patient?
   (a) Injection-site reactions
   (b) Osteoporosis
   (c) Increased risk of infections
   (d) Eczema

Please see the following references for further study:

1. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol.* 2003;98:1315–1324.
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2. Which of the following patient factors is a contraindication for initiating anti-TNF therapy?
   (a) Taking a thiopurine concomitantly
   (b) Previously developing antibodies to a different anti-TNF agent
   (c) Having a positive PPD
   (d) Having a history of corticosteroid use

   Please see the following references for further study:
   1. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med.* 2001;345:1098–1104.
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3. Which mycobacterium species is not commonly associated with skin lesions?
   (a) *Mycobacterium leprae*
   (b) *Mycobacterium marinum*
   (c) *Mycobacterium mucogenicum*
   (d) *Mycobacterium tuberculosis*

   Please see the following references for further study:
   1. Brode SK, Jamieson FB, Ng R, et al. Increased risk of mycobacterial infections associated with anti-rheumatic medications. *Thorax.* 2015;70:677–682.
   2. Shehan JM, Sarma DP. Mycobacterium mucogenicum: report of a skin infection associated with etanercept. *Dermatol Online J*. 2008;14:5.
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4. Your ulcerative colitis patient develops PG of the right extremity and responds well to medication. Which of the following agents has shown good efficacy in treating PG and is the medication this patient might be using?
   (a) Caspofungin
   (b) Isoniazid
   (c) Infliximab
   (d) Vancomycin

   Please see the following references for further study:
   1. Regueiro M, Valentine J, Plevy S, Fleisher MR, Lichtenstein GR. Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease. Am J Gastroenterol 2003;98: 1821–6.
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5. Which of the following entities could be misdiagnosed as pyoderma gangrenosum?
   (a) Opportunistic infections involving the skin
   (b) Orofacial granulomatosis
   (c) Behcet's disease
   (d) All the above

   Please see the following references for further study:
   1. Weenig RH, Davis MD, Dahl PR, et al. Skin ulcers misdiagnosed as pyoderma gangrenosum. *New Eng J Med.* 2002;347:1412–1418.
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6. Which of the following individuals would be most susceptible to developing an opportunistic *Mycobacterium marinum* infection?
   (a) A 36-year-old man with Crohn's disease on infliximab for 3 years who is an avid fly-fisherman.
   (b) A 22-year-old woman with ulcerative proctosigmoiditis that is well controlled with budesonide foam.
   (c) A healthy 26-year-old woman scuba diving instructor.
   (d) A 19-year-old man newly diagnosed with Crohn's disease with no medical history that is planning to start treatment with the immunomodulator azathioprine.

   Please see the following references for further study:

1. Ferreira J, Grochowsky J, Krakower D, et al. Mycobacterium marinum: an increasingly common opportunistic infection in patients on infliximab. *Am J Gastroenterol*. 2012;107:1268–1269.
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7. Which of the following is the most reliable method for diagnosing a *Mycobacterium marinum* infection?
   (a) Characteristic crusted, erythematous skin ulcerations
   (b) A positive PPD
   (c) Acid-fast bacillus smear and culture and sensitivity for *Mycobacterium marinum*
   (d) Histology from colonoscopic biopsy showing distorted architecture, numerous crypt abscesses, and granuloma formation.

   Please see the following references for further study:

1. Fallon JC, Patchett S, Gulmann C, et al. Mycobacterium marinum infection complicating Crohn's disease, treated with infliximab. *Clin Exp Dermatol*. 2008;33:43–45.
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3. Ramos JM, Garcia-Sepulcre MF, Rodriguez JC, et al. Mycobacterium marinum infection complicated by anti-tumor necrosis factor therapy. *J Med Microbiol*. 2010;59:617–621.

8. Your Crohn's disease patient was recently diagnosed with a *Mycobacterium marinum* infection. Which medication would not be used to treat the *M. Marinum* infection?
   (a) Ethambutol
   (b) Certolizumab pegol
   (c) Minocycline
   (d) Azithromycin

   Please see the following references for further study:

1. Rallis E, Koumantaki-Mathioudaki E. Treatment of Mycobacterium marinum cutaneous infections. *Expert Opin Pharmacother.* 2007;8:2965–2978.
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