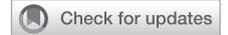


37-Year-Old Man With Headache and Nasal Congestion



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A 37-year-old man with obesity and type 2 diabetes mellitus presented to his primary care physician with 4 days of headache, congestion, and nasal drainage. His headache was dull, aching, and involved his entire head, though there was an occasional throbbing quality pain in his bilateral cheeks (just below the eyes) and forehead. Nasal congestion was his most bothersome symptom, and he felt so “stuffy” that it was difficult to breathe at night. He reported green drainage from the nose with brownish streaks. On review of additional symptoms, he reported chills, an intermittent nonproductive cough, and sore throat. His only home medications were metformin and glimepiride. He was a nonsmoker and worked at the airport as a cargo assistant. He had no recent sick contacts and lived with his wife and several healthy school-age children. Vital signs were all within normal limits: temperature, 36.9°C; heart rate, 75 beats/min; blood pressure, 135/76 mm Hg; respiratory rate, 16 breaths/min; and oxygen saturation, 98%. Physical examination was notable for edematous nasal turbinates and mild pharyngeal erythema without exudates. The maxillary sinuses were tender. There was no palpable cervical, submandibular, or supraclavicular lymphadenopathy. Cardiac examination revealed regular rate and rhythm without murmurs or extra heart sounds. His lungs were clear to auscultation bilaterally without wheezes, rhonchi, or stridor. His abdomen was nontender and nondistended.

1. In addition to testing for coronavirus disease 2019 (COVID-19), which *one* of the following is the *next best* step in evaluation or management of this patient?

- Rapid antigen detection testing for streptococcal pharyngitis
- Dedicated computed tomography (CT) of the sinuses
- Short course of antimicrobial therapy
- Analgesics, nasal steroids, and saline irrigation
- Complete blood count (CBC) with differential

Rapid streptococcal testing is not indicated. Although he presented with an acute-onset sore throat and pharyngeal erythema, his risk of streptococcal pharyngitis is low. This is evident on the basis of his Centor score of 0 (no tonsillar exudate, no tender/swollen lymph nodes, no fever, and present cough). Generally, a Centor score more than 3 warrants testing for *Streptococcus spp* whereas a score less than 2 does not.¹

Dedicated CT of the sinuses is not appropriate. This patient meets clinical criteria for acute rhinosinusitis (purulent nasal drainage, congestion, and headache, lasting <4 weeks), and the most recent clinical practice guidelines from the American Academy of Otolaryngology specifically recommends against performing radiographic imaging in cases of acute rhinosinusitis without suspected complication or alternative diagnosis.² Avoiding imaging will reduce radiation exposure, cost of care, and discovery of incidental findings with uncertain clinical significance.

A short course of antimicrobial therapy is not currently indicated. When managing patients with acute rhinosinusitis, it is most important to differentiate viral rhinosinusitis (VRS) from acute bacterial rhinosinusitis

See end of article for correct answers to questions.

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(ABRS). It is essential to recognize that purulence of nasal discharge and presence/absence of fever do not reliably distinguish between VRS and ABRS. Given his concurrent viral upper respiratory symptoms and short duration of illness, VRS is most likely, and antibiotic therapy will not provide benefit.²

Conservative symptom management with analgesics, nasal steroids, and saline irrigation is appropriate. These interventions are low risk and may improve quality of life while he recovers.

Complete blood count with differential is not necessary. The diagnostic criteria for VRS and ABRS do not include laboratory data, and blood work is neither necessary nor sufficient to differentiate between the 2 most likely etiologies.²

In this patient, testing for COVID-19 was positive. He self-quarantined for 10 days and was afebrile throughout that time. He tried the recommended treatments (analgesics, nasal steroids, and nasal saline) for several days, but did not feel that they were helpful. His cough and sore throat resolved after several days. His headache, nasal congestion, and purulent nasal discharge initially improved, but he unfortunately had recurrence and progressive worsening over several days, which prompted another primary care visit (~14 days after initial symptom onset).

The patient is concerned because his worsening symptoms are limiting his ability to work.

2. Which one of the following next steps will best address his concerns?

- a. Dedicated CT of the sinuses
- b. Five-day course of amoxicillin-clavulanate
- c. Dexamethasone treatment of unresolving COVID-19 infection
- d. Reinforce the importance of adherence to nasal steroids and saline irrigation
- e. Five-day course of levofloxacin

The patient now meets criteria for ABRS (>10 days of symptoms with recent worsening after initial improvement). Dedicated

CT of the sinuses would be indicated if there were signs/symptoms of complicated ABRS with spread to the surrounding tissues or central nervous system such as severe headache, facial swelling, cranial nerve palsy, proptosis, or vision changes. However, the patient had no clinical evidence of complicated ABRS, so advanced imaging is not appropriate. Much like the previous discussion on VRS, avoidance of imaging at this juncture will reduce unnecessary cost and radiation exposure without diminishing the diagnostic yield.

Initiating a 5-day course of amoxicillin-clavulanate is appropriate. Acute bacterial rhinosinusitis is diagnosed in patients who initially meet criteria for VRS, but then go on to have persistent symptoms without any improvement for longer than 10 days or in patients with severe symptoms (fever [temperature, $\geq 39^{\circ}\text{C}$] with purulent nasal discharge or facial pain) for 3 to 4 consecutive days or symptoms that initially improve but subsequently worsen (double worsening). Bacterial infection will complicate VRS in about 0.5% to 2% of cases, and most ABRS infections are caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.² Although not strictly necessary in patients who can ensure close follow-up, antibiotics can shorten the duration of illness. In those without any medication allergy, amoxicillin-clavulanate is the drug of choice because of its efficacy, low cost, and narrow spectrum.²

Initiating dexamethasone is not appropriate. Although some of his initial symptoms may have been attributable to COVID-19, his current symptoms are most consistent with ABRS. Additionally, the use of dexamethasone is limited to inpatients with oxygen requirements or respiratory distress.

Reinforcing adherence to saline irrigation and nasal steroids is not the most appropriate answer. This answer implies that non-adherence to the proposed treatment regimen has contributed to his worsening, which is not accurate. Conservative therapies may help palliate symptoms, but they

do not alter duration of illness. This option may be misleading and does not adequately address this patient's concerns. Instead, he should be offered antibiotics.

Prescribing levofloxacin is not the best option. Although levofloxacin adequately covers the typical microbes involved in ABRS, it is unnecessarily broad and its adverse effect profile is more sinister than that of amoxicillin. Levofloxacin should be considered as a second-line agent for those with beta lactam allergy.²

Although the patient initially had some improvement with antibiotic therapy, his symptoms of nasal congestion and frontal headache persisted and were eventually accompanied by worsening right jaw pain. He remained afebrile, but laboratory evaluation was remarkable for mild leukocytosis, normocytic anemia, and hemoglobin A_{1c} 13.6% (increased from 8.7% 6 months prior). The human immunodeficiency virus test result was negative. He underwent dental extraction owing to concern for dental abscess. Fungal smear from dental extraction exhibited organisms with broad nonseptate hyphae with 90° branching concerning for mucormycosis.

3. Given the most likely diagnosis, which one of the following is the most appropriate next step in evaluation or management?

- a. Endoscopic evaluation of the sinuses and initiation of empirical antifungals
- b. Magnetic resonance imaging (MRI) of the sinuses, brain, and orbits and initiation of empirical antifungals
- c. Serum testing for beta glucan and *Aspergillus* galactomannan
- d. Bronchoalveolar lavage and initiation of empirical antifungals
- e. Intravenous (IV) iron infusion and initiation of empirical antifungals

The patient has pathological evidence of mucormycosis infection in the jaw, and his sinus symptoms are best explained by invasive fungal sinusitis. Endoscopic evaluation of the sinuses is essential for identifying

the extent of disease, acquiring diagnostic cultures, and operative planning. In addition to early initiation of antifungal therapy, prompt surgical debridement has the greatest impact on mortality.³

Magnetic resonance imaging may eventually be required, but it should not be prioritized over endoscopic evaluation of the sinuses. In fact, the preferred first-line imaging modality in patients with rhino-orbito-cerebral mucormycosis is CT, which has a higher sensitivity for bony deformities and can be performed more rapidly than MRI.⁴ In those who have abnormalities on CT, further imaging with MRI may be used to better characterize involvement of the orbits and brain, especially in patients with visual symptoms.

Beta glucan and *Aspergillus* galactomannan have no role in the diagnosis or management of invasive mucormycosis. Although these tests are increasingly used to screen for fungal infection and monitor treatment response, fungal pathogens involved in mucormycosis do not contain the necessary components in their cell wall to yield a positive test result. Importantly, this answer also does not include the initiation of empirical antifungals, which should not be delayed.

Bronchoalveolar lavage is also not appropriate. Although some patients can develop pulmonary mucormycosis, this patient only had mild respiratory symptoms, which are best attributed to a previous COVID-19 infection. These symptoms resolved, and his current presentation is most concerning for rhino-orbito-cerebral mucormycosis.

Intravenous iron infusion is not appropriate. Although there is an association between deferoxamine use and development of mucormycosis, this occurs because deferoxamine somewhat paradoxically promotes uptake of iron by *Rhizopus* species and promotes their growth.⁵ There is some evidence that iron overload itself increases the risk of mucormycosis.

The patient underwent maxillectomy/palatotomy and was admitted to an outside hospital on broad-spectrum antibiotics/antifungals. On endoscopic evaluation, he had widespread necrotic tissue throughout the

sinuses, and CT of the sinuses revealed necrotic bone. Magnetic resonance imaging of the face, brain, and orbits revealed extraconal enhancement within the right orbit and mild thickening/enhancement of the inferior/lateral rectus muscles. He was transferred to Mayo Clinic for coordination of multidisciplinary care, wherein he quickly underwent additional endoscopic surgical debridement of the sinuses. He was initiated on IV liposomal amphotericin B for antifungal coverage.

4. Although this patient is on IV liposomal amphotericin B, which one of the following is most appropriate for avoiding adverse drug reactions?

- a. Close monitoring of bilirubin, transaminases, and international normalized ratio
- b. Intravenous fluids before drug administration and close electrolyte monitoring
- c. Regular use of sunscreen and avoidance of prolonged sun exposure
- d. Close monitoring of CBC with differential to assess for development of neutropenia
- e. Close monitoring of CBC, lactate dehydrogenase, and haptoglobin to assess for hemolytic anemia

Intravenous amphotericin B should be the initial treatment of mucormycosis. Close monitoring of liver tests while taking this drug is not critical. Although it has been associated with mild elevations in liver enzymes in a minority of patients, clinically significant hepatotoxicity is rare.

Intravenous fluids and close monitoring of electrolytes is the most appropriate answer. Amphotericin is famously nephrotoxic and often leads to acute tubular necrosis via direct cellular damage. Electrolyte derangements are extremely common because of both direct renal toxicity and more poorly understood mechanisms leading to renal wasting of potassium, magnesium, and sodium. The best management strategy for amphotericin nephrotoxicity is aggressive hydration and electrolyte repletion. Along with electrolytes, creatinine

and/or cystatin C should be monitored closely.

Unlike some drugs (such as tetracycline antibiotics), amphotericin is not associated with significant photosensitivity and avoidance of sun exposure is not necessary.

Neutropenia is not a reported complication of amphotericin.

Routine CBC monitoring may be useful for monitoring anemia, which can complicate amphotericin treatment because of direct marrow toxicity and suppression of erythropoietin production. However, hemolytic anemia caused by amphotericin has not been reported, and serial monitoring of lactate dehydrogenase/haptoglobin is not warranted.

After initial debridement, the patient had a prolonged hospital stay during which he had serial endoscopic and ophthalmic examinations, all of which were reassuring. He was also treated with adjunctive antifungal irrigation. His amphotericin treatment was complicated by significant renal toxicity and progressive multifactorial anemia (chronic inflammation, serial phlebotomy, and amphotericin toxicity).

5. In the outpatient setting, which one of the following will be most important for preventing future episodes of this condition?

- a. Avoiding occupational exposures
- b. Improved dental hygiene
- c. Basal-bolus subcutaneous insulin with close monitoring of blood glucose
- d. Dietary modification and increased exercise
- e. Enhanced foot hygiene

Although the transmission of mucormycosis is not entirely understood, there is no evidence to suggest that certain environments/occupations place people at higher risk of infection. In fact, Zygomycetes are ubiquitous in the environment and avoidance is neither practical nor recommended.

There is no established relationship between poor oral hygiene and development of mucormycosis.

Diabetes mellitus is the most common risk factor for the development of mucormycosis. Although classically it occurs in severely ill diabetic patients with ketoacidosis, uncontrolled diabetes is a risk factor even in the absence of acidosis. Additionally, elevated blood sugar during treatment of mucormycosis is associated with higher rates of treatment failure. Close monitoring of glucose and adherence to insulin therapy is extremely important for avoiding progression or recurrence of infection.⁶

Lifestyle modifications are an important component of diabetic management. However, this patient requires insulin. His hemoglobin A_{1c} is well above the target range despite adherence to his medications, and he has now suffered a major complication of diabetes that necessitates tight glucose control.

Although many fungal infections originate and spread from the feet, mucormycosis does not have any relationship to foot hygiene.

The patient was transitioned from his prior oral diabetic regimen to a basal-bolus insulin regimen. Final operative cultures with susceptibilities revealed *Rhizopus* species with minimum inhibitory concentrations of 2, 2, and 4 for amphotericin B, posaconazole, and isavuconazole, respectively. Attempts were made to transition to posaconazole. Unfortunately, he proved to be a rapid metabolizer of posaconazole and was not able to achieve therapeutic levels, so he was transitioned to isavuconazole before discharge. He was discharged from the hospital with a prolonged course of oral isavuconazole (weeks to months, depending on clinical/radiographic response) and multidisciplinary follow-up including otolaryngology, ophthalmology, dentistry, infectious disease, and his primary care provider.

DISCUSSION

Our case highlights a relatively indolent presentation of rhino-orbito-cerebral mucormycosis in the setting of poorly controlled type 2 diabetes mellitus and recent COVID-19 infection. The initial presentation was most consistent with acute rhinosinusitis (purulent nasal discharge accompanied by nasal obstruction, facial pressure, or both). Symptoms of acute

rhinosinusitis lasting for less than 10 days without significant worsening are most likely caused by a viral infection and should be managed symptomatically with analgesics, nasal steroids, and saline irrigation. It is important to note that neither fever nor purulence of nasal discharge reliably distinguish viral from bacterial rhinosinusitis. Instead, ABRS should be considered once symptoms of acute rhinosinusitis fail to improve within 10 days, are severe after 3 to 4 days, or worsen after initially improving.² Antibiotics are not always strictly required for patients with ABRS but can shorten symptom duration, and first-line treatment is with amoxicillin-clavulanate because of its effectiveness against pathogens causing ABRS and narrow spectrum. Those who fail to improve with antibiotic therapy should raise suspicion for complications or alternative diagnoses.²

Mucormycosis is a life-threatening invasive fungal infection with a variable presentation that classically affects diabetic patients (particularly during episodes of ketoacidosis) or those with severe immunocompromise (human immunodeficiency virus, hematologic malignancy, and organ transplant recipients).⁶ Additional known risk factors include treatment with corticosteroids or the iron chelator deferoxamine, which stimulates growth and leads to tissue invasion by increasing iron uptake in the fungal species that cause mucormycosis.⁵ Clinical presentation depends on the extent of organ involvement and can range from mild rhinosinusitis to disseminated disease, for which mortality approaches 96%.⁷ There are many recent reports of an association between COVID-19 and invasive fungal sinusitis, though causation is difficult to establish because a large proportion of these patients had preexisting diabetes mellitus and were treated with corticosteroids for their COVID-19 infection.⁸

The most important initial step in the management of mucormycosis is prompt surgical debridement and initiation of liposomal amphotericin B. Treatment with amphotericin B requires close monitoring of renal function and electrolytes due to its risk of renal toxicity and renal

wasting of magnesium/potassium (though the risk is lower in the liposomal formulation relative to the deoxycholate version). There exist only 3 antifungal agents with activity against mucormycosis (amphotericin, posaconazole, and isavuconazole). Other antifungal treatments, such as fluconazole, voriconazole, or caspofungin, should not be attempted. Typically, patients are treated with liposomal amphotericin B until they clinically stabilize and transition to posaconazole or isavuconazole. These oral antifungals are continued for a prolonged course—weeks to months depending on clinical response and follow-up diagnostic imaging/endoscopy.

The general internist plays a vital role in the management of mucormycosis by eliminating risk factors for treatment failure (hyperglycemia and iron overload) and managing complications of antifungal treatment.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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CORRECT ANSWERS: 1. d. 2. b. 3. a. 4. b. 5. c