

## CLINICAL CARE CONUNDRUMS

## “Different Strokes for Different Folks”

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.



This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A 35-year-old woman presented to her primary care physician complaining of left post-auricular pain, swelling, and redness. She described the pain as 8 out of 10, constant, sharp, and nonradiating. She denied fever or chills. A presumptive diagnosis of cellulitis led to a prescription for oral trimethoprim-sulfamethoxazole. Left facial swelling worsened despite 4 days of antibiotics, so she came to the emergency department.

Noninfectious causes of this woman's symptoms include trauma, or an inflammatory condition such as polychondritis. Key infectious considerations are mastoiditis or a mastoid abscess. Herpes zoster with involvement of the pinna and auditory canal may also present with pain and redness. In the absence of findings suggestive of an infection arising from the auditory canal, cellulitis is a reasonable consideration. With the growing incidence of community-acquired methicillin-resistant *Staphylococcus aureus* infections, an agent effective against this pathogen such as trimethoprim-sulfamethoxazole may be used, usually in combination with an antibiotic that provides more reliable coverage for group A streptococcus.



Her past medical history included poorly controlled type II diabetes mellitus and asthma. She reported no previous surgical history. Her current medications were insulin, albuterol inhaler, and trimethoprim-sulfamethoxazole, although she had a history of noncompliance with her insulin. She was married with 1 child and was unemployed. She smoked 1 pack of cigarettes daily, drank up to 6 beers daily, and denied use of illicit drugs.

Her history of diabetes increases her risk of malignant otitis externa. Both diabetes and excess alcohol consumption are risk factors for herpes zoster. Smoking has been shown to increase the risk of otitis media and carriage by *S. pneumoniae*, a common pathogen in ear infections.



She was ill-appearing and in moderate respiratory distress. Her temperature was 39°C, blood pressure 149/93 mmHg, pulse 95 beats per minute, respiratory rate of 26 times per minute, with an oxygen saturation of 96% while breathing ambient air.

She had swelling of the left side of the face extending to the left forehead and lateral neck. Examination of the external ear and auditory canal were unremarkable. The swelling had no associated erythema, tenderness, or lymphadenopathy. She had no oropharyngeal or nasal ulcers present. Her pupils were equal, round, and reactive to light and accommodation with normal sclera. Her trachea was midline; thyroid exam was normal. The heart sounds included normal S1 and S2 without murmurs, rubs, or gallops. Her lung exam was remarkable for inspiratory stridor. The abdominal examination revealed no distention, tenderness, organomegaly, or masses. Cranial nerve testing revealed a left-sided central seventh nerve palsy along with decreased visual acuity of the left eye. Strength, sensation, and deep tendon reflexes were normal.

While there are many causes of facial nerve palsy, distinguishing between a peripheral palsy (which causes paralysis of the entire ipsilateral side of the face) and a central palsy (which spares the musculature of the forehead) is important. The most common type of peripheral facial nerve palsy is Bell's palsy. Infections such as meningitis or tumors of the central nervous system can cause central facial nerve or other cranial nerve palsy. Important infections to consider in this case would be viral such as herpes zoster or simplex, or atypical bacteria such as *Mycoplasma* and *Rickettsia*, which may explain the neurologic but not all of the other clinical findings in this case. It is also critical to determine whether she has an isolated seventh cranial nerve palsy or if other cranial nerves are involved such as may occur with basilar meningitis, which has a myriad of infectious and noninfectious causes. The decreased visual acuity may be a result of corneal dryness and abrasions from inability to close the eye but may also represent optic nerve problems, so detailed ophthalmologic exam is essential. Her ill appearance coupled with facial and neck swelling leads me to at least consider Lemierre's syndrome with central nervous system involvement. Finally, facial swelling and the inspiratory stridor may represent angioedema, although one-sided involvement of the face would be unusual.



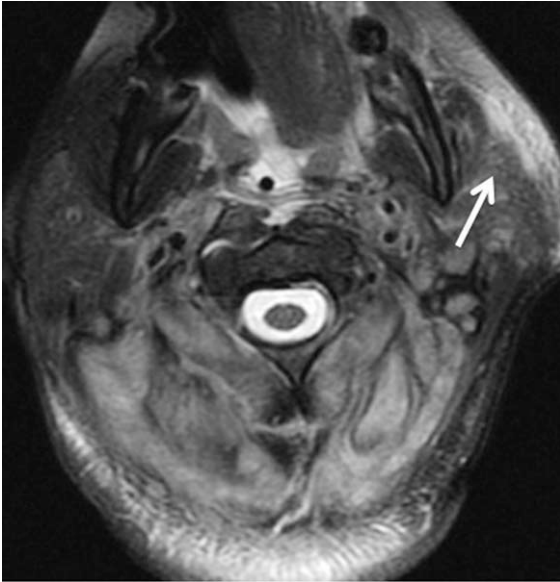
The results of initial laboratory testing were as follows: sodium, 138 mmol/L; potassium, 3.4 mmol/L; chloride, 109 mmol/L; bicarbonate, 14 mmol/L; blood urea nitrogen level, 19 mg/dL; creatinine, 1.1 mg/dL; white cell count, 23,510/mm<sup>3</sup>; differential, 90% neutrophils, 1% bands, 7% lymphocytes, 2% monocytes; hemoglobin level, 12.5 g/dL; platelet count, 566,000/mm<sup>3</sup>; hemoglobin A1c, 11%; albumin, 1.6 g/dL; total protein, 6.2 g/dL; total bilirubin, 0.8 mg/dL; alkaline phosphatase, 103 U/L; alanine aminotransferase

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**FIG. 1.** Magnetic resonance imaging (MRI) showing enlargement and enhancement of the left parotid gland (arrow).

level, 14 U/L; international normalized ratio of 1.2; partial thromboplastin time, 29 seconds (normal value, 24–34 seconds); erythrocyte sedimentation rate, 121 mm/hr; creatine kinase, 561 U/L (normal value 25–190). Arterial blood gas measurements with the patient breathing 50% oxygen revealed a pH of 7.34, a partial pressure of carbon dioxide of 28 mmHg, and a partial pressure of oxygen of 228 mmHg.

I am concerned that this patient has sepsis, likely due to an infectious trigger. With her clinical presentation localized to the head and neck, her history of diabetes, and the accelerated sedimentation rate, malignant otitis externa would explain many of her findings. Empiric anti-infective therapy directed toward *Pseudomonas aeruginosa* should be initiated, and imaging of the head and ear should be undertaken.

The patient required intubation due to increased respiratory distress and stridor. Her physicians used intravenous vancomycin, clindamycin, and piperacillin/tazobactam to treat presumed cellulitis. Her abnormal neurologic exam led to magnetic resonance (MR) imaging and MR angiography of her neck and brain, which showed evidence of multiple regions of ischemia in the left occipital and inferior parietal distributions, as well as bilateral cerebellar distributions and enhancement of the parotid gland and mastoid air cells (Figure 1). A cerebral angiogram revealed irregularity and caliber reduction in multiple cervical and intracranial arteries, associated with intraluminal thrombi within the left intracranial vertebral artery, consistent with either vasculitis or infectious angioinvasion (Figure 2).

The angioinvasive nature of the findings on imaging leads me to suspect fungal infection. The patient's history of diabetes mellitus and acidosis are risk factors for mucormycosis. *Aspergillus* and *Fusarium* may also be angioinvasive but would be much more likely in neutropenic or severely immunocompromised patients. *S. aureus* may cause septic emboli mimicking angioinvasion but should be readily detected in conventional blood cultures. At this point, I would empirically begin amphotericin B; tissue, however, is needed for definitive diagnosis and a surgical consult should be requested.

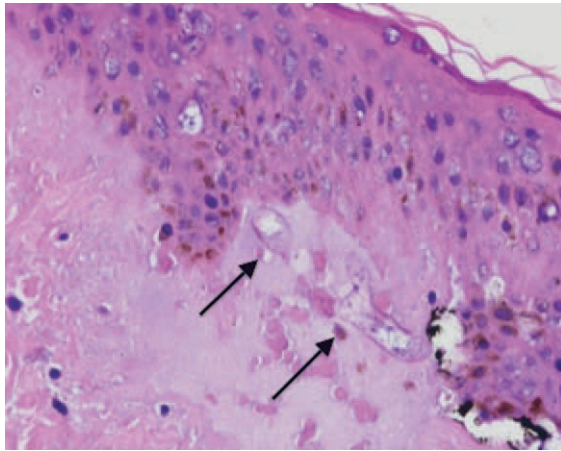


**FIG. 2.** Cerebral angiogram showing multiple areas of vessel irregularity (arrows) in the left internal carotid artery.

After reviewing her imaging studies, an investigation for vasculitis and hypercoagulable states including antinuclear antibody, anti-deoxyribonucleic acid, anti-Smith antibody, anti-SSA antibody level, anti-SSB level, antineutrophil cytoplasmic antibody, activated protein C resistance level, factor VIII level, human immunodeficiency virus antibody, homocysteine level, cardiolipin antibody testing, lupus anticoagulant, prothrombin 20210 mutation, and protein C level was done, and all tests were normal. Protein S level was slightly low at 64% (normal value 65%–140%). Given the enlarged parotid gland and the enhancement of the left parotid bed on magnetic resonance imaging, she underwent a parotid biopsy that revealed sialadenitis.

Systemic vasculitides can result in tissue damage, mediated by the release of endogenous cellular contents from dying cells, known as damage-associated molecular patterns, sufficient to cause systemic inflammatory response syndrome (SIRS). This patient presented with acute symptoms but has negative laboratory studies for autoantibodies. The parotid biopsy also did not reveal evidence of vasculitis. All these findings make the diagnosis of vasculitis much less likely.

She remained in the medical intensive care unit on mechanical ventilation, with minimal symptomatic improvement. On hospital day 10, the patient developed necrosis of the left external ear. A punch biopsy of the necrotic area of her left pinna was performed; the pathology report read: “Sections of punch biopsy of skin show an unremarkable epidermis. There is dermal necrosis involving the stroma and adnexal structures. Intravascular thrombi within the deep dermis are seen. Within superficial dermis there are broad, elongated, nonseptated hyaline structures reminiscent of *Mucor*. Special stains (periodic acid-Schiff stain and Grocott Gomori methenamine silver stain [GMS]) performed with appropriately reactive controls fail to highlight these structures” (Figure 3). The infectious disease team reviewed the pathology slides with the pathologist. As there was inconclusive evidence for zygomycosis, ie, only a few hyaline structures which failed to stain with GMS stain, the consultants recommended no change in the patient's management.



**FIG. 3.** Punch biopsy of the patient's left external ear showing broad elongated, nonseptated hyaline structures which failed to stain with Grocott Gomori methenamine silver stain (GMS) (arrows).

The gross and microscopic evidence of necrosis and areas of intravascular thrombi are nonspecific but compatible with a fungal infection in a patient with risk factors for zygomycosis. The GMS stain is a very sensitive stain for fungal structures, so a negative stain in this case is surprising, but additional testing such as immunohistochemistry should be pursued to confirm or refute this diagnosis. While *Rhizopus* species can be contaminants, the laboratory finding of these organisms in specimens from patients with risk factors for zygomycosis should not be ignored.

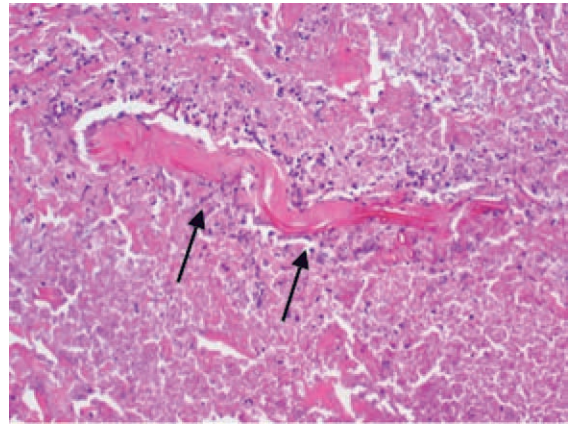
On hospital day 12, the patient was noted to have increased facial swelling. A computed tomographic (CT) angiogram of the neck revealed necrosis of the anterior and posterior paraspinal muscles from the skull base to C3–4, marked swelling of the left parotid gland, and left inferior parieto-occipital enhancing lesion. An incisional parotid biopsy was performed. Special stains were positive for broad-based fungal hyphae consistent with mucormycosis (Figure 4).

Given these findings, the patient should be started on amphotericin B immediately. Medical therapy alone generally does not suffice, and aggressive surgical debridement combined with intravenous antifungal therapy results in better outcomes. The longer the duration of symptoms and the greater the progression of disease, the less favorable the prognosis.

The patient was started on amphotericin B lipid complex and micafungin. However, after 16 days of therapy, repeat imaging of the neck showed worsening necrosis of the neck muscles. At this time, she underwent extensive debridement of face and neck, and posaconazole was added. After prolonged hospitalization, she was discharged to a rehabilitation facility on posaconazole. She resided in a nursing facility for 6 months. One year after her hospitalization, she is living at home and is able to ambulate independently, but requires feeding through a percutaneous endoscopic gastrostomy (PEG) tube because she remains dysphagic.

## COMMENTARY

Infections caused by the ubiquitous fungi of the class *Zygomycetes* typically take 1 of 5 forms: rhinocerebral, pulmonary, gastrointestinal, disseminated, and cutaneous. The pre-



**FIG. 4.** Parotid tail excisional biopsy with broad fungal hyphae (arrows).

sentation varies widely, ranging from plaques, skin swelling, pustules, cellulitis, blisters, nodules, ulcerations, and ecthyma gangrenosum-like lesions to deeper infections such as necrotizing fasciitis, osteomyelitis, and disseminated infection.<sup>1</sup> Infections typically occur in immunocompromised hosts, including transplant recipients and patients with hematologic malignancy, but also occur in patients with diabetes mellitus, intravenous drug users, and patients on deferoxamine therapy.<sup>2</sup> Deferoxamine and other iron-binding therapy is thought to predispose to zygomycetes infections because of improved iron uptake of the fungal species and, thus, stimulation of growth.<sup>3</sup> Pulmonary and rhinocerebral infections are the most common clinically encountered forms, and 44% of cutaneous infections are complicated by deep extension or dissemination.<sup>4</sup>

The articles cited above describe the more typical presentations of this rare disease. However, this patient had an unusual presentation, as parotid involvement due to zygomycosis has only been described once previously.<sup>5</sup> Her inflammatory vasculitis and ensuing strokes from involvement of the carotid artery are recognized complications of zygomycosis, and in 1 case series of 41 patients with rhinocerebral mucormycosis, carotid involvement was seen in 31% of patients.<sup>6</sup> After the punch biopsy of the patient's pinna showing nonseptated hyphae "reminiscent" of *Mucor*, why did her physicians delay administering amphotericin?

There are 2 likely possibilities: anchoring bias or error in medical decision-making due to inaccurate probability estimates. Anchoring bias describes a heuristic where the initial diagnosis or gestalt biases the physician's process for assigning a final diagnosis.<sup>7,8</sup> This bias creates cognitive errors by limiting creativity in diagnosis. In this case, the infectious disease team carefully weighed the information obtained from the first biopsy. Given their low pretest estimate of this virtually unreported presentation of a rare disease, they decided to evaluate further without beginning antifungal therapy. Of note, there were few hyaline structures, and those structures lacked uptake of GMS. Since they considered the diagnosis yet rejected the diagnosis due to insufficient evidence, it is unlikely that anchoring bias played a role.

Was there an error in medical decision-making? The physicians in this case faced a very common medical dilemma: whether or not to start a toxic medication empirically or wait for diagnostic confirmation prior to treatment.<sup>9</sup> To solve this dilemma, one can apply decision analysis. Moskowitz et al



described 5 phases of medical decision analysis by which a probabilistic “right” answer to clinical scenarios can be deduced mathematically.<sup>10</sup> To solve this problem, probabilities must be assigned to the risk of giving a drug to a patient without the disease versus the risk of not giving a drug to a patient with the disease. For example, amphotericin deoxycholate causes acute renal failure in 30% to 47% of patients. Newer formulations of amphotericin, such as liposomal amphotericin and lipid complex, result in lower rates of nephrotoxicity (27% vs 47%). The risk of not giving amphotericin to a patient with zygomycosis is death. Even in patients treated with amphotericin, the mortality rate has been shown to be 66%, and up to 100% in those with strokes related to zygomycosis.<sup>2,6,11</sup> Simply looking at these probabilities, decision analysis would favor empiric treatment.

The physicians caring for this patient did not have the luxury of retrospective speculation. After looking at all of the data, the equivocal skin biopsy and rare clinical presentation, the question to ask would change: What is the risk of giving amphotericin empirically to someone who, based on available information, has a very low probability of having zygomycosis? When phrased in this manner, there is a 47% chance of nephrotoxicity with amphotericin versus the very small probability that you have diagnosed a case of zygomycosis that has only been described once in the literature. Mathematically and—more importantly—clinically, this question becomes more difficult to answer. However, no value can be placed on the possibility of death in suspected zygomycosis, and the risk of short-term amphotericin use is much less than that of a course of treatment. As such, empiric therapy should always be given.

Physicians are not mathematicians, and dynamic clinical scenarios are not so easily made into static math problems. Disease presentations evolve over time towards a diagnosable clinical pattern, as was the case with this patient. Two days after the aforementioned biopsy, she worsened and in less time than it would have taken to isolate zygomycosis from the first biopsy, a second biopsy revealed the typical nonseptated hyphae demarcated with the GMS stain. Even appropriate diagnostic testing, thoughtful interpretation, and avoidance of certain cognitive errors can result in incorrect diagnoses and delayed treatment. It is monitoring the progression of disease and collecting additional data that allows physicians to mold a diagnosis and create a treatment plan.

The primary treatment of zygomycosis should include amphotericin. However, there are limited data to support combination therapy with an echinocandin in severe cases, as in this patient.<sup>12</sup> Posaconazole is not recommended for monotherapy as an initial therapy, but there is data for its use as salvage therapy in zygomycosis.<sup>13</sup> This case highlights the difficulties that physicians face in the diagnosis and treatment of rare diseases. Cerebral infarction in a hematologic malignancy, uncontrolled diabetes, or iron chelation therapy could be the initial presentation of rhinocerebral zygomycosis. There truly are different strokes for different folks. Recognizing this and similar presentations may lead to a more rapid diagnosis and treatment of zygomycosis.

## TEACHING POINTS

1. Zygomycosis has a wide range of clinical presentations ranging from skin lesions to deep tissue infections. As it is an angioinvasive organism, it can also present as cerebral infarcts and brain abscesses.
2. Zygomycosis infections should be suspected in patients with uncontrolled diabetes, hematologic or oncologic malignancies, and patients on iron chelation therapy with a potentially compatible clinical picture.
3. If zygomycosis infection is suspected, rapid histologic diagnosis should be attempted. However, as histologic diagnosis can take time, empiric therapy with amphotericin should always be administered.
4. Amphotericin remains the primary medical therapy for this disease; however, there is limited emerging evidence to suggest that echinocandins can be used in combination with amphotericin for improved treatment of severe rhinocerebral zygomycosis. Posaconazole has a role as salvage therapy in zygomycosis, but should not be used as the sole primary treatment.

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