

Chronic granulomatous invasive fungal sinusitis: an evolving approach to management

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Background: Chronic granulomatous invasive fungal sinusitis (CGIFS) is rare and a consensus on ideal management is lacking. We present an extensive case managed successfully with a conservative approach.

Methods: Case report and literature review.

Results: The patient presented with unilateral proptosis, papilledema, and headache. Imaging revealed an infiltrative process with extensive intracranial and intraorbital involvement. Biopsy showed fungal elements and granulomatous reaction consistent with CGIFS. The patient was managed with conservative surgery and long-term oral voriconazole.

Conclusion: This case supports a conservative surgical approach in some patients with extensive CGIFS. Oral voriconazole is effective and has significant advantages over more toxic agents administered intravenously. © 2014 ARS-AAOA, LLC.

Key Words:

Aspergillus fumigatus; sinusitis; voriconazole; papilledema; fungus diseases

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Chronic granulomatous invasive fungal sinusitis (CGIFS) is a rare clinical entity in North America. There is no consensus in the literature on the ideal method of surgical and/or medical management of CGIFS, although traditionally aggressive surgical resection and long-term intravenous amphotericin have been used. We present a rare case in which a patient with extensive orbital and intracranial CGIFS was managed successfully with a more conservative approach.

Case report

A 36-year-old African American male with a past medical history of hypertension, asthma, atopy, eczema, and bilateral cataracts secondary to keratoconus status postremoval

at age 17 years presented to the outpatient clinic for evaluation of a sinus mass. The patient had been having intermittent right-sided epistaxis, nasal obstruction, and diplopia with decreased visual acuity in the right eye for 1 year prior to presentation. He additionally reported numbness over his right maxilla for the past 6 months and right-sided head and facial pain for 5 months. The patient was otherwise healthy and was not known to have immune dysfunction, diabetes, or a personal history of cancer. Family history was unremarkable. He denied travel outside of the United States. He was initially treated with antibiotics for sinusitis without resolution. The pain continued to worsen and the patient developed vertiginous spells prompting his referral to our center.

On physical exam, the patient had mild right-sided proptosis. He reported double vision on downward gaze and his visual acuity in the right eye was 20/100 compared to 20/25 on the left. He had decreased sensation in the right V2 distribution. His skin showed diffuse eczematous changes. Nasal endoscopy revealed fullness of the right lateral nasal wall without an obvious mass lesion. Magnetic resonance imaging (MRI) revealed an infiltrating mass with extensive osseous destructive changes in the right maxillary and ethmoid regions. There was extensive dehiscence of the medial and inferior orbital walls with extraconal tumor displacing orbital contents (Figs. 1 and 2). The right orbital apex was spared of disease. Confluent opacification of the sphenoid sinuses was present with a small amount of pneumatization

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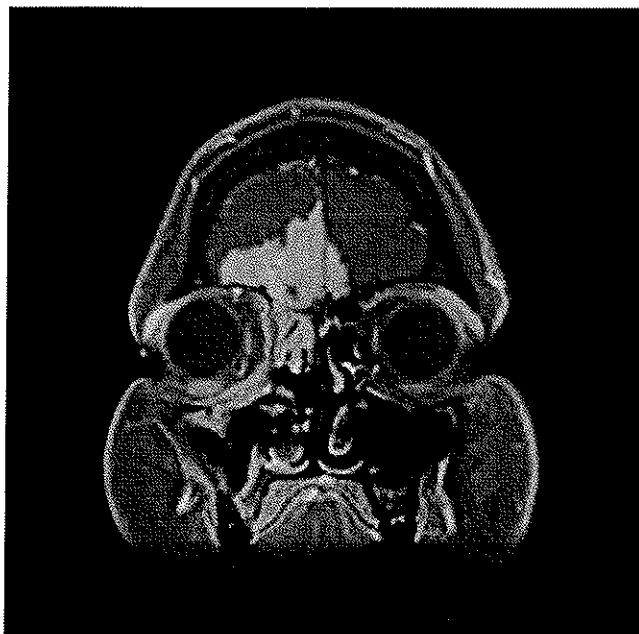


FIGURE 1. Pretreatment T1 coronal postgadolinium image showing involvement of the orbital wall and frontal lobes.

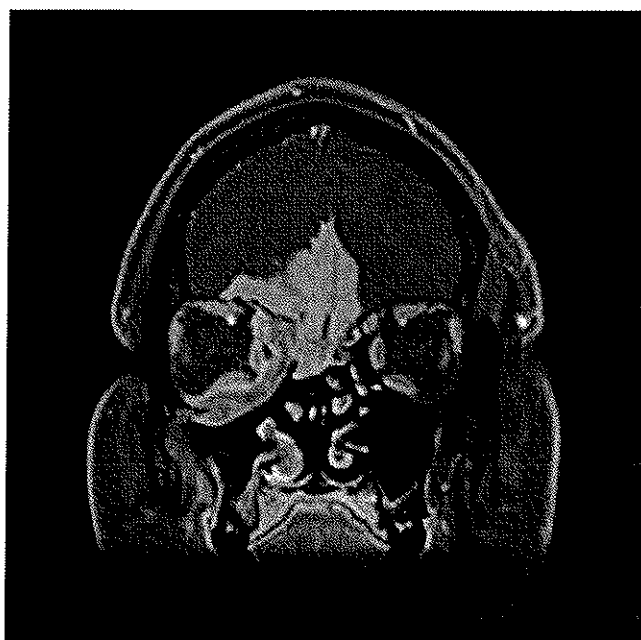


FIGURE 2. Pretreatment T1 coronal postgadolinium image showing displacement of the orbital contents.

suggestive of fluid levels. Also present was extensive skull base involvement with direct intracranial extension and displacement of brain parenchyma with associated bifrontal and right temporal vasogenic edema with right to left midline shift and displacement of the frontal horns (Fig. 3).

A malignancy was suspected and the patient was taken to the operating room for an endoscopic biopsy of the

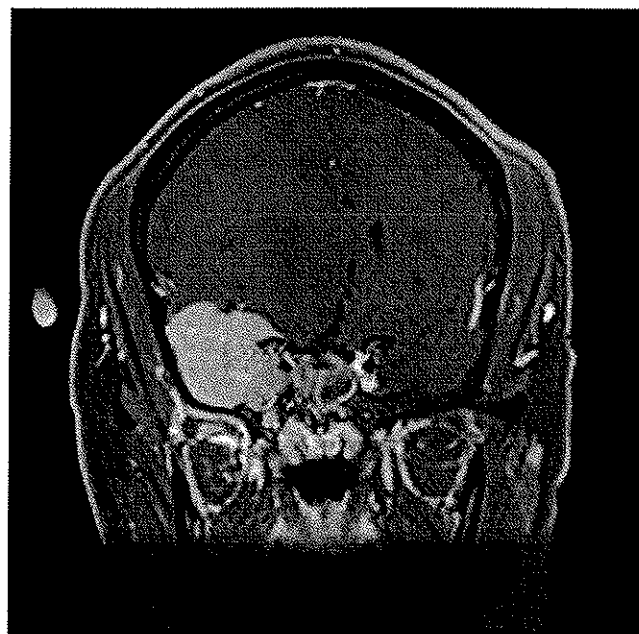


FIGURE 3. Pretreatment T1 coronal postgadolinium image showing involvement of right temporal lobe, right to left midline shift, and displacement of the frontal horns.

lesion. Intraoperatively, the tissue was noted to be friable and inflamed with increased vascularity. Biopsies were sent for frozen section, which showed marked acute and chronic inflammation, fibrosis, and multinucleated giant cells with no definitive neoplasm identified. Based on the frozen pathology, a more extensive debridement including total ethmoidectomy, maxillary antrostomy, sphenoidotomy, and right middle turbinate resection was performed. Final pathology revealed chronic granulomatous inflammation involving mucosa, submucosa, and bone with septate hyphae present on Gömöri methenamine silver (GMS) and periodic acid–Schiff (PAS) stains. No potassium hydroxide test was performed. There was no evidence of vascular invasion by fungus or significant tissue necrosis. No neoplasia was seen. The culture eventually grew *Aspergillus fumigatus*. Fungal polymerase chain reaction (PCR) confirmed this with detection of *A. fumigatus* DNA.

The patient was hospitalized and initially started on 600 mg of amphotericin B intravenously (IV) every 24 hours until the culture returned and *Aspergillus* was confirmed. He remained on amphotericin B for 3 days and was then transitioned to IV Voriconazole 600 mg every 12 hours for a 1-day loading dose. Antifungal treatment was then switched to 400 mg of oral voriconazole twice daily. Voriconazole levels were monitored on a monthly basis and ranged from 2.3 to 5.1 $\mu\text{g/mL}$ (within normal limits) during the course of therapy. Neurosurgery and Ophthalmology were consulted due to the intracranial and intraorbital involvement. Given the degree of vasogenic edema present in the right frontal and temporal lobes, and the presence of papilledema, the patient was started on steroids.

An extensive workup was performed including immunologic testing, which showed elevated immunoglobulin E (IgE) and IgG subclass 4 as well as CD8 T-cell depletion. Neutrophil oxidative burst testing was not consistent with chronic granulomatous disease—either X-linked or autosomal recessive forms. Human immunodeficiency virus (HIV) testing was negative.

The patient's proptosis and headaches resolved shortly after surgery and the initiation of medical therapy. A computed tomography (CT) scan was repeated 2 weeks after the initiation of treatment along with a follow-up appointment with Otolaryngology. Because the CT showed interval decrease of the intracranial extension and vasogenic edema and the patient's symptoms remained stable, the decision was made to continue the oral voriconazole. At 2 to 3 weeks after surgery, his papilledema had resolved and the steroids were tapered and discontinued. One month after the initiation of medical therapy, MRI was repeated and showed marked interval improvement of the sinonasal cavity, orbit, and intracranial components. Again, the patient's symptoms continued to improve or remain stable and, given this, along with the improvement on radiographic imaging, the management team felt confident in continuing the oral voriconazole.

At his 5-month postoperative visit, sensation had returned over the right V2 distribution. MRI 8 months after surgery and the initiation of antifungal treatment showed no residual disease, with resolution of the right frontal and temporal lobe vasogenic edema and no further displacement of orbital contents (Figs. 4 and 5). A 16-month course of 400 mg voriconazole had been completed at the time of this report. Complete metabolic panels were checked on a monthly basis to monitor liver enzymes. Of note, at 6 months after the initiation of treatment, the patient was found to have abnormal elevations of both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) along with elevated amylase and lipase. He was diagnosed with gallstone pancreatitis at this time, and subsequently underwent a cholecystectomy. After surgery, his liver enzymes, amylase, and lipase returned to normal levels and remained so for the remainder of his antifungal therapy.

The patient continues to have regular follow-ups with Otolaryngology, Infectious Disease, Dermatology, and Allergy/Immunology and is symptom free.

Discussion

Patients with CGIFS are typically immunocompetent, and the condition is most commonly observed in Sudan, India, and Pakistan.^{1,2} Rare cases have been reported in the United States.^{3,4} *Aspergillus flavus* is the causative agent in nearly all cases reported in Sudan, India, and Pakistan.^{1,3} A wider variety of fungal species including *Aspergillus fumigatus* have been identified as the causative agent in North American cases.³ The most common presenting symptom in

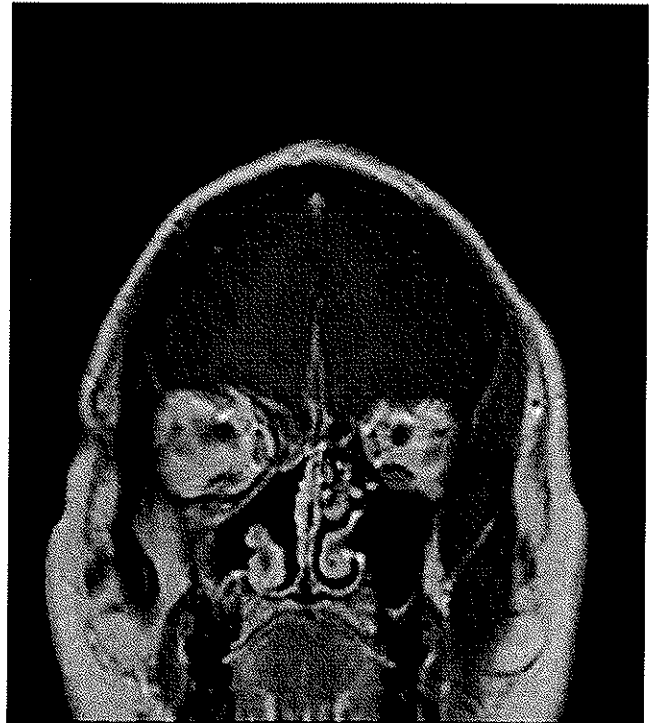


FIGURE 4. Posttreatment T1 coronal postgadolinium image showing resolution of the orbital and frontal lobe disease.

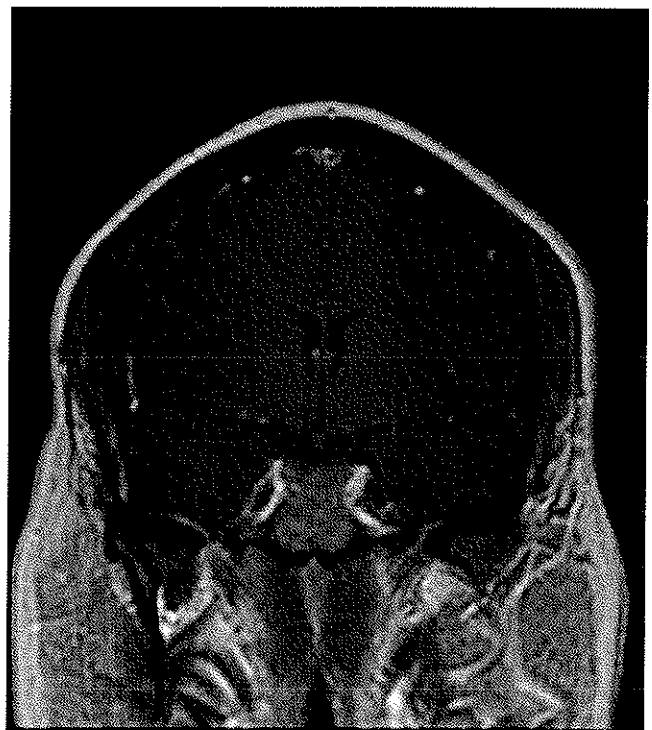


FIGURE 5. Posttreatment T1 coronal postgadolinium imaging showing resolution of temporal lobe. Note the resolution of the right to left midline shift and return of the frontal horns to normal position.

CGIFS is unilateral proptosis.³ Other symptoms at the time of presentation include severe nasal congestion/obstruction, sinus pain/pressure, headaches, and facial numbness.^{3,4} Physical exam findings include unilateral proptosis, numbness over the V2 distribution, congested mucosa, and polypoid changes to the mucosa on nasal endoscopy.

Studies have shown that CGIFS typically is isodense or hyperdense to muscle tissue on CT scans, is unilateral, and generally is present in only 1 to 2 sinuses.^{5,6} As opposed to allergic fungal rhinosinusitis, the appearance is homogenous and extrasinus involvement is greater than intrasinus.⁵ Bony erosion is typically present. MRI should be ordered when orbital or intracranial involvement is suspected. CGIFS is isointense on T1-weighted images and hypointense on T2-weighted images.^{5,6}

Histopathology showing noncaseating granulomas with fungal hyphae within giant cells of the granulomas with invasion into mucosa, submucosa, blood vessels, or bone confirms the diagnosis.^{1,3,7} Surrounding tissue typically shows a mild amount of inflammation consisting of eosinophils, lymphocytes, and plasma cells in a setting of dense fibrosis.^{1,7}

There is no consensus on the best course of treatment for CGIFS; however, most authors agree that both surgery and antifungals play a role. Traditionally, aggressive surgical resection and intravenous amphotericin B have been most widely used. In the case of our patient, aggressive surgery would have required enucleation and significant intracranial resection via craniotomy. In more recent reports, authors have suggested the removal of "as much disease as possible" and concluded that surgical intervention should ultimately be individually based on the extent of disease.^{3,8}

The availability of oral agents for invasive infections owing to *Aspergillus* species as opposed to traditional agents such as intravenously administered amphotericin B is a fairly recent. The largest study to date looking at the response of CGIFS to antifungal treatment was conducted by Gumaa et al.⁸ who had 12 of 19 patients with CGIFS achieve complete remission while on itraconazole at a dose of 100 mg twice daily after surgery. Although no other series looking at treatment response of CGIFS to different antifungals have been done, studies looking at response to voriconazole in patients with both acute and chronic invasive aspergillosis have shown excellent results.^{9,10} Voriconazole is very effective against *Aspergillus* and offers the advantages of a more favorable side-effect profile and the convenience of oral administration. Of particular importance in our case, cerebrospinal fluid (CSF) penetration of voriconazole is good.¹¹

Our patient has remained disease and symptom free for 16 months after surgery and the initiation of oral voriconazole. He did experience elevated liver enzymes at 1 time during his treatment, but as this was in the setting of acute gallbladder pancreatitis, we did not attribute this to the oral voriconazole and therefore feel that our patient did not suffer any long-term side effects of the voriconazole therapy. His continued improvement on radiographic imaging and resolution of symptoms attributed to the CGIFS during close follow-up encouraged the management team that the therapy was effectively controlling his disease. No consensus for the length of treatment with oral antifungals exists, but most papers recommend treatment until complete remission is achieved. In the Gumaa et al.⁸ series, this was anywhere from 6 to 65 weeks.

Conclusion

Cases of CGIFS are rare in North America. Our case represents a patient with extensive disease with both orbital and intracranial involvement who was successfully treated with conservative surgery and long-term oral voriconazole. As no consensus on the best form of treatment for CGIFS exists, we felt it important to report our experience with a conservative approach that lead to an excellent outcome. Given that our patient has remained disease free for 16 months after limited surgery and the initiation of oral voriconazole, we recommend that this treatment regimen be considered in other cases of CGIFS, even for extensive disease. ④

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