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A case of orbital cryptococcosis

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ABSTRACT

Purpose: This report describes a case of *Cryptococcus neoformans* found in an unlikely location, the orbit, in an apparently immunocompetent host.
Observations: A coordinated, multi-disciplinary approach between the ophthalmology, neurosurgery, pathology, and infectious disease departments was integral to saving both vision and life.
Conclusions and Importance: This is the first case of primary orbital cryptococcosis described in the medical literature, to the authors' knowledge. The case draws attention to the possibility that *Cryptococcus neoformans* can indeed invade the orbit and should be considered part of the differential diagnosis for patients presenting with orbital masses of uncertain etiology.

1. Introduction

As far as ophthalmologists are concerned, *Cryptococcus neoformans* can present as vitritis, choroiditis, endophthalmitis, or ocular involvement of meningitis. Orbital invasion by this fungus has never been reported in a patient within the United States, and only twice worldwide. Additionally, the presence of *Cryptococcus* is associated with a variety of cell-mediated immunodeficiencies, most frequently seen as an opportunistic pathogen of patients with AIDS or immunosuppressed transplant recipients. This manuscript describes the case of a 20-year-old otherwise healthy man presenting with eyelid edema who was found to have a primary orbital *Cryptococcus neoformans* abscess with intracranial extension, possibly facilitated by previously undiagnosed immunodeficiency. The radiologic imaging, surgical intervention, pathology reports, and immunology work-up are discussed and emphasize the importance of a multi-disciplinary approach to diagnosis and treatment.

2. Case

A 20-year-old man with obesity (BMI 54 kg/m^2) and past medical history of recurrent sinusitis presented with six weeks of left upper eyelid edema. He had been evaluated at an outside Emergency Department (ED) a month prior, presumed to be suffering from preseptal cellulitis, and prescribed oral trimethoprim-sulfamethoxazole and erythromycin ointment. Over the next two weeks the patient finished his course of oral antibiotics, however, the swelling worsened and became painful. At this point, he returned to the ED where a maxillofacial computed tomography (CT) revealed a 4 × 3x3 cm peripherally enhancing abscess involving the left superolateral orbital wall and orbital roof, exerting pressure on the lateral globe. The abscess extended extraorbitally into the temporalis fossa measuring 2 × 1x1 cm and intracranially into the epidural space through an erosion in the frontal bone measuring 2 × 2x1 cm < Fig. 1A and B>. The patient was transferred to the University of Texas Medical Branch at Galveston for ophthalmologic evaluation.

On arrival, the patient was afebrile with normal vital signs. Visual acuity was 20/50 and intraocular pressure (IOP) was elevated to 28 mmHg in the affected left eye. No rAPD or anisocoria was noted. Color plates were full. There was mild restriction of the superior visual field by confrontation secondary to significant upper eyelid edema. A desmarres retractor was necessary to continue the ocular exam, showing an unremarkable anterior segment without conjunctival chemosis or hypopyon. Dilated fundus exams were normal bilaterally. A complete blood count showed mild leukocytosis and anemia.

The otolaryngology team performed preliminary bedside incision and drainage of the superficial eyelid, draining 1 cc of purulent fluid for culture. It was not evident on CT scan whether this was contiguous with the intraorbital abscess. Considering the intracranial extension seen on CT scan, the patient was taken to the operating room (OR) by the neurosurgical team with a member of the oculoplastics team present to guide any potential orbital components of the surgery. A keyhole approach was taken, starting with a subperiosteal dissection at the

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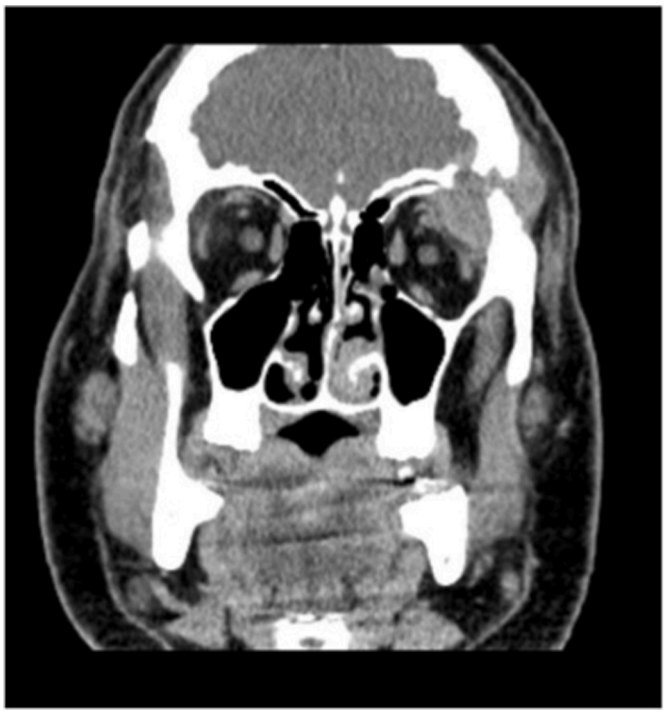

Fig. 1A. Text: Coronal section of initial Maxillofacial CT revealing a 4 × 3x3 cm peripheral enhancing extraconal orbital mass involving the left lacrimal gland and orbital roof with lytic disruption of the frontal bone allowing intracranial extension.

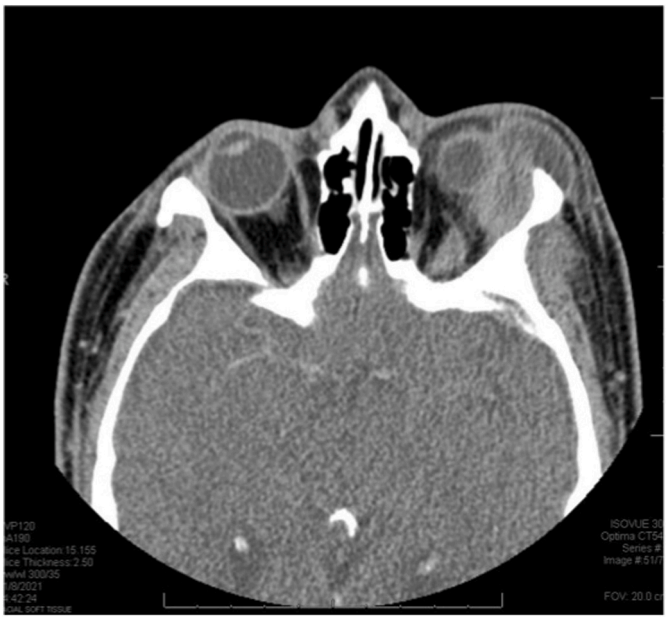

Fig. 1B. Text: Axial section of initial maxillofacial CT showing the orbital mass adhering to the superolateral orbital wall and exerting pressure on the lateral globe.

lateral orbital rim. The temporalis muscle was incised. Necrotic-appearing tissue was encountered immediately and removed. Dissection and debulking was continued down the keyhole until the defect in the frontal bone was reached. It was noted that the bone was frail and fragments of bone were easily removed. Tissue samples and bone fragments were sent to the frozen lab intraoperatively for diagnosis. Preliminary findings revealed thickly encapsulated, narrow-based budding yeast. The decision was made to cease further debulking without entering the orbit out of concern for complications arising from any further damage to the frontal bone. The wound was irrigated with vancomycin saline and closed.

The following day, cultures obtained from the OR grew yeast that was identified via MALDI-TOF as *Cryptococcus neoformans* < Fig. 2A and B, and C>. Per recommendations of the infectious disease team, the patient was started on liposomal amphotericin B 500 mg IV daily and flucytosine 2 g PO every 6 hours.

By the second day post-op, the patient's vision improved to 20/25 and his IOP returned to within normal limits. Lab tests investigating immune function showed the patient had a Hemoglobin A1c of 5.2% and negative fourth generation HIV screening test. IgA was mildly elevated at 362 g/L (ref 70–312), IgG normal at 1430 g/L (ref 640–1600), and IgM low at 54 g/L (ref 56–352). The drainage from the superficial eyelid never grew an organism.

Ten days into his admission, the patient continued to have eyelid pain and swelling. A repeat maxillofacial CT confirmed that the mass was grossly unchanged compared to prior < Fig. 3>. The patient was taken to the OR for debulking by the oculoplastics team. The sub-brow incision made for the initial eyelid drainage served as the entry point. Immediately after the orbital septum was dissected, thick purulence with blood was encountered. Bleeding was profuse and hemostasis was difficult, but ultimately accomplished with cautery. Dissection was continued posteriorly along the orbital roof. Inspection of the orbit through the incision revealed small amounts of necrotic-appearing tissue, which was removed and sent fresh to the pathology lab. The wound was sutured shut, keeping the central portion open for packing with Iodoform Gauze.

Altogether, 400 cc of blood had been suctioned from the relatively shallow wound, a highly unusual amount in ophthalmic surgery. Though the exact cause of the bleeding was not identified, it was proposed either that the abscess itself was saturated with blood or that a small artery, perhaps the lacrimal or the superior palpebral, had been lacerated during the initial incision and was difficult to identify in the ensuing deluge.

No evidence of nerve impingement, orbital compartment syndrome, or systemic dissemination of infection was seen during the patient's course. Lumbar puncture was not performed given the absence of meningismus or neurologic abnormalities. Additionally, the patient's ongoing therapy with high-dose antifungals would have covered central nervous system (CNS) involvement. He was discharged with instructions to complete a six month course of consolidation therapy with fluconazole 600 mg PO twice daily.

The patient followed up two months later in the oculoplastics clinic. Mild left upper eyelid ptosis remained without eyelid edema, visual changes, or neurologic symptoms.

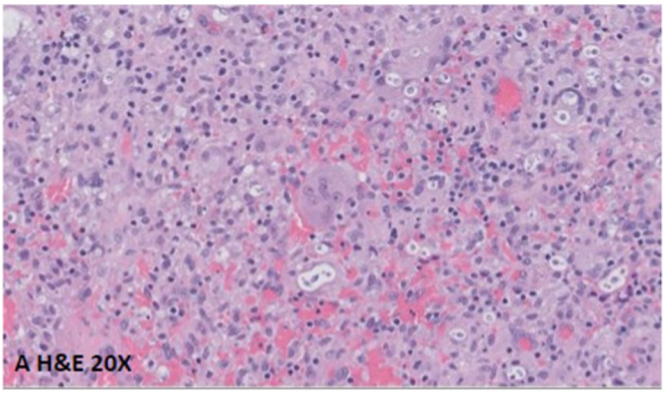

Fig. 2A. Text: Hematoxylin and eosin stain of intraoperative tissue showing granulomatous inflammation with lymphocytes, epithelioid histiocytes, and giant cells.

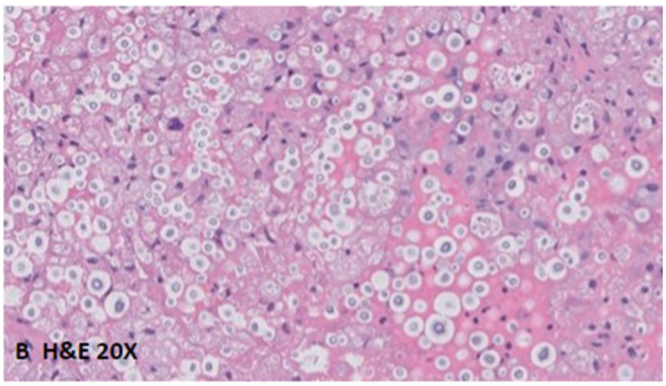

Fig. 2B. Text: Hematoxylin and eosin stain of intraoperative tissue showing numerous yeast forms with variability in size and capsule thickness.

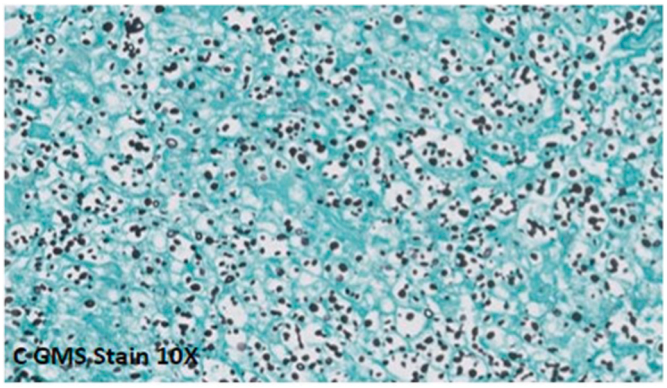

Fig. 2C. Text: Gomori methenamine silver stain of intraoperative tissue positive for narrow-based budding yeast.

3. Discussion

Cryptococcus neoformans is an aerobic, facultative intracellular fungus that grows as a budding yeast. Its primary virulence factor is a thick polysaccharide capsule, classically seen on GMS and India Ink stains, with which it evades host detection, replicates within phagocytes, and suppresses immune responses.[1,2] Typically, the pathogen enters the human respiratory tract via inhalation. Depending on the functionality of the host's cell-mediated immune system, cryptococcosis may manifest as a primary pulmonary syndrome, or disseminate and invade multiple organ systems, or be cleared rapidly by the immune system without disease manifestations. Alternatively, it may lie dormant for years until opportunistic reactivation.

Several factors have precipitated the increased incidence of cryptococcosis in the 20th century, including increased human longevity, the HIV/AIDS pandemic, and the development of chemotherapies and corticosteroid/nonsteroidal immunosuppression.[1] The most common and fatal extrapulmonary manifestation of cryptococcosis is meningoencephalitis. *Cryptococcus* species traverse the blood-brain barrier either as free organisms or within the cells they invade.[3] Within the CNS, fungal replication and capsule turnover obstruct cerebrospinal fluid (CSF) flow thereby increasing intracranial pressure (ICP). This may present clinically to the ophthalmologist as papilledema or sixth cranial nerve palsy.[4]

Given the patient's unusual presentation, the authors undertook a review of the biomedical literature to determine whether *Cryptococcus neoformans* had previously been identified in the orbit. The search terms "invasive fungal rhinosinusitis", "orbital fungemia", and "orbital cryptococcosis" were employed in PubMed and Google Scholar without limits on language or date to ensure a broad list of results.

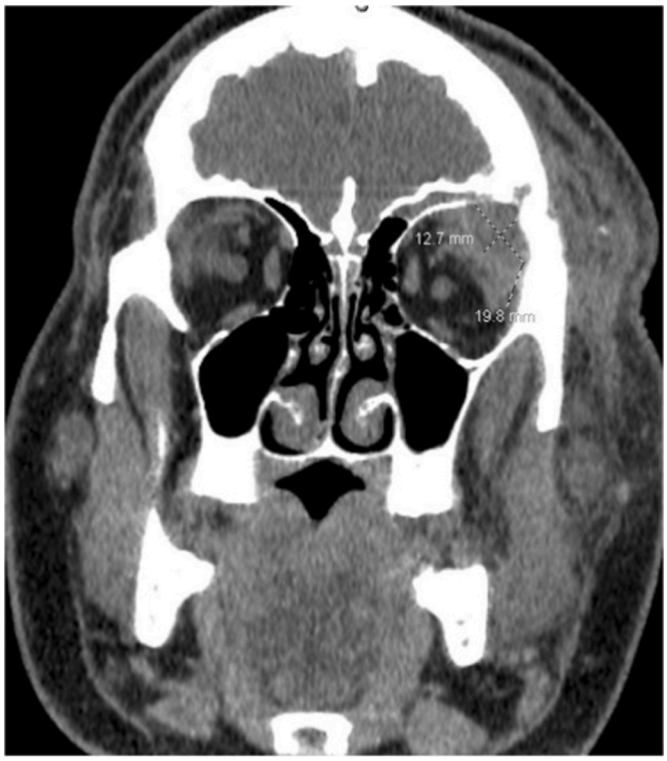

Fig. 3. Text: Coronal cut of second maxillofacial CT showing minimal change from previous in the size of the left orbital abscess involving the lacrimal gland with small left upper eyelid component, frontal bone erosions, and intracranial extension.

Invasive fungal rhinosinusitis (IFRS) is a common medical entity, almost exclusively attacking immunocompromised hosts. Uncontrolled diabetes mellitus is the highest risk factor.[5,6] IFRS extends into the orbit roughly 50–60% of the time and the majority of cases are caused by Rhizopus oryzae.[6,7] Cases of primary orbital fungal infections, however, are an anomaly within medical literature. There has been one case of primary histoplasmosis of the orbit in a 33-year-old immunocompetent female with progressive right eye vision loss and pain with abduction, found to have a right inferotemporal orbital mass with intraconal and extraconal components. She improved with surgical excision and a six-month course of oral itraconazole.[8] Naturally, cases such as this may at first be mistaken for bacterial cellulitis or orbital inflammatory syndrome and illustrate the importance of broadening the differential when there are bony erosions on imaging or lesions are unresponsive to antibiotics or steroids.[9]

With regards to cryptococcal IFRS, a case has been reported of a primary ethmoidal cryptococcal abscess extending into the orbit of a 48-year-old immunocompetent male who underwent endoscopic debridement three times followed by orbital exenteration before histopathology identified the culprit. He was placed on oral fluconazole for three months and followed for 18 months without recurrence.[10]

Alternatively, the skin may be inoculated with cryptococcus through systemic dissemination or trauma.[11,12] A case of orbito-cutaneous *Cryptococcus neoformans* was seen in a 65-year-old immunocompetent female with isolated right sided swelling of the temple and proptosis.[13] CT imaging showed a mass eroding through the greater wing of the sphenoid involving the lacrimal gland and lateral rectus muscles. Fine-needle aspiration detected *Cryptococcus neoformans*, which the authors theorized could have begun as a subclinical pneumonitis with hematogenous dissemination subcutaneously to the area. The infection resolved within two months on 200 mg of daily fluconazole.

The origin of *Cryptococcus neoformans* in our patient is challenging as no evidence of lesions elsewhere were discovered. While he did have

eyelid edema to imply a cutaneous pathway, the drainage did not grow anything on culture. Similarly, there was no extension seen from the maxillary, nasal, or ethmoid sinuses, despite previous sinus infections. Hematogenous spread is possible, although blood cultures were negative at the time of admission, and no respiratory symptoms were reported to suggest inoculation through the airway. While there have been numerous cases of cranial and cutaneous cryptococcosis after percutaneous and traumatic inoculation, our patient denied having had trauma or piercings to his eyelid. Likewise, while the possibility of unintentional inoculation into the conjunctiva remains, our patient denied ocular pruritus or allergic conjunctivitis preceding onset of eyelid edema. As such, to the authors' knowledge, this patient's diagnosis, *Cryptococcus neoformans* as a primary orbital fungal infection, has never been reported in the medical literature.

Considering the organism's tendency to affect immunocompromised hosts, the infectious disease team considered whether this patient had an underlying and previously undiagnosed immunodeficiency. As mentioned previously, an immunologic work-up found relatively normal immunoglobulin levels. However, in an immunocompetent patient, a more robust humoral response would be expected in the setting of fungal invasion. In particular, the importance of IgM in protective immune responses against cryptococcosis has been demonstrated in humans, where IgM-expressing B cells inversely correlate with risk of cryptococcosis.[14] Our patient's IgM was paradoxically low; this meager recruitment may have revealed an abnormality in his humoral defense system. Though a specific deficiency was never identified, this may ultimately have been another case of *Cryptococcus neoformans* in an immunocompromised host.

4. Conclusion

As evident, a primary C*ryptococcus* of the orbit with osteomyelitis through the frontal bone allowing for cranial involvement is not simply a rarity; it posed unique complications for this patient's care. While typical cases cause visual symptoms of central nervous system sources, this patient's infection spread from the orbit itself to the brain. The intracranial extension through bone demonstrated the aggressive lytic potential of the fungus and required an interdisciplinary approach between ophthalmology and neurosurgery for surgical interventions. Adequate debulking alleviated infectious burden and mass effect on the globe. Much of this case depended on a prompt and accurate diagnosis from the pathologists. Immunologic testing indicated that a patient previously thought immunocompetent may have an underlying immunodeficiency without the immunoglobulins necessary to clear this fungus. Finally, proper choice of antifungal therapy by the infectious disease specialists was crucial to ensure resolution.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

None of the authors have financial disclosures.

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