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Chronic mucocutaneous candidiasis presenting as *Candida* endophthalmitis

A 38-year-old female from Montreal, Canada, consulted for sudden, painless vision loss in her left eye 5 days before presentation. Her medical history was known for bipolar disease, hypothyroidism, and clinically diagnosed truncal tinea versicolor (Fig. 1).

Her history was largely unremarkable except for occasional ingestion of beef tartar. She denied any chills or fever and was afebrile upon physical examination. At initial visit, her visual acuity was 20/20 OD and counting fingers OS. Slit-lamp examination of the left eye showed 1+ cells and 1+ flare in the anterior chamber as well as 2+ vitreous cells and 1+ vitreous haze as per the Standardization of Uveitis Nomenclature working group grading scheme.[1] Dilated fundus examination revealed an exophytic white lesion in the macula (Fig. 2).

A clinical diagnosis of panuveitis caused by probable ocular toxoplasmosis OS was established. Baseline uveitis workup was initiated while empirical therapy with pyrimethamine (25 mg PO daily), folinic acid (10 mg PO every second day), and clindamycin (300 mg PO QID) was started on the day of the initial presentation. The patient also received routine topical uveitis treatment (prednisolone 1% q1hr, dexamethasone ointment 0.1% qHS, and homatropine 2% BID) in her left eye and oral prednisone 60 mg daily, started 48 hours after the initiation of antiprotozoal treatment. Her initial workup was notable for mild absolute eosinophilia and negative *Toxoplasma gondii* serology (immunoglobin [Ig]M and

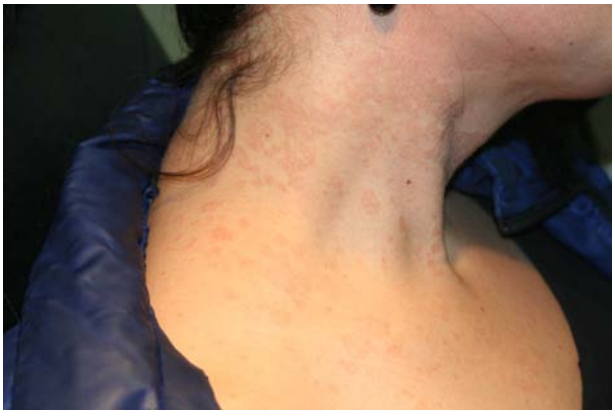

Fig. 1—Tinea versicolor lesions of neck.

Fig. 2—Coloured fundus photograph of the left eye at initial presentation showing a white, exophytic macular lesion.

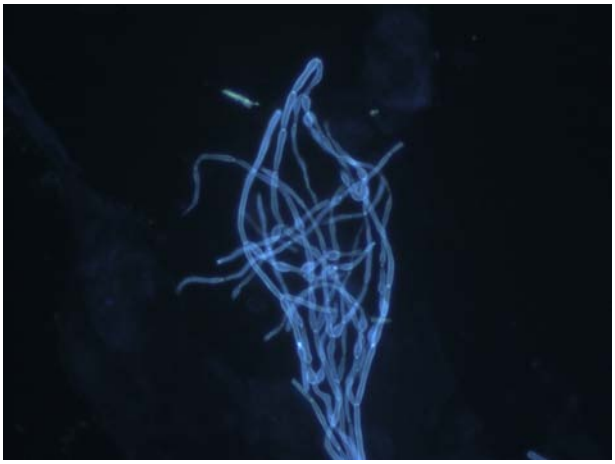

Fig. 3—Calcofluor-white stain of the vitreous showing presence of pseudohyphae.

IgG). Results of screening for HIV, syphilis, cytomegalovirus (IgG), and tuberculosis (interferon-gamma release assay) were negative. Baseline workup was done for sarcoidosis even though the clinical picture was more suggestive of an infectious etiology; both chest x-ray and angiotensin-converting enzyme level were within normal limits.

After 2 weeks of clinical stability, the patient's vision deteriorated and the fundus lesion had worsened significantly. Prednisone was suspended and a diagnostic vitrectomy was performed promptly. Calcofluor-white stain showed presence of pseudohyphae in the vitreous a few hours after the vitrectomy (Fig. 3). The vitreal culture subsequently confirmed *Candida albicans* growth the next day.

Upon further questioning, in addition to her chronic skin lesions, the patient also reported chronic white buccal lesions, as well as recurrent vulvovaginitis. Furthermore, on review of systems, she described symptoms suggesting left-sided neglect for the last few weeks.

On subsequent investigations, direct examination of skin lesion scrapings showed pseudohyphae consistent with *Candida* species, and buccal culture grew *Candida albicans.* Serum (1 to >3) β-D-glucan, a marker of invasive fungal infection, was elevated at >500 pg/mL though blood cultures remained negative. Cerebral magnetic resonance imaging (MRI) showed multiple active right parietal microabscesses (Fig. 4) and an old frontal lesion suggesting previous infection. Spinal MRI was consistent with spondylodiscitis at the level of L4–L5. The diagnosis was established as chronic mucocutaneous candidiasis (CMCC) complicated by invasive candidiasis, with the eye as the presenting infection site.

Intravenous liposomal amphotericin B (5 mg/kg/day) was started but had to be stopped 2 weeks later due to renal toxicity. This was followed by oral fluconazole (800 mg daily) for 1 year, leading to complete resolution of mucocutaneous symptoms and of the cerebral and spinal lesions on subsequent MRIs. The daily dose of fluconazole was then reduced to 400 mg daily for the following 6 months before further being tapered to 200 mg daily. She will likely continue on this prophylactic dosage for life. In addition to the systemic treatments, the patient also received 4 weekly intravitreal antifungal injections (amphotericin B, 5 μg/0.1 mL, $n = 1$; voriconazole, 100 μg/0.1 mL, $n = 3$) OS, quieting down the panuveitis. However, her visual acuity stayed at counting fingers as a result of extensive macular scarring. Her right eye remained free of disease with normal visual acuity.

In light of her unusual clinical presentation, the patient was referred for genetic testing, which revealed bi-allelic *CARD9* mutations (manuscript in preparation).

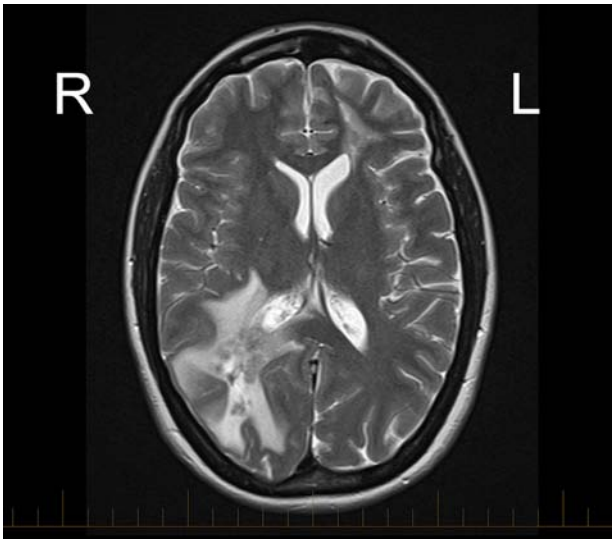

Fig. 4—Cerebral magnetic resonance imaging (T2, axial) demonstrating multiple right (R) parietal microabscesses as well as a left (L) frontal lesion suggesting previous infection.

The clinical presentation of ocular candidiasis spans over a continuous spectrum. Whereas chorioretinitis involves only the chorioretinal layers, manifesting as cotton wool spots, Roth spots, retinal hemorrhages, or deep retinal focal white infiltrates, the diagnosis of *Candida* endophthalmitis also requires the presence of vitritis and/or fluffy vitreal lesions extending from chorioretinal infiltrates.[2] In addition to ocular candidiasis, the differential diagnosis of a focal chorioretinal lesion with associated vitreous cells includes toxoplasmosis, toxocariasis, tuberculosis, cat-scratch disease, onchocerciasis, cysticercosis, sarcoidosis, syphilis, and masquerade syndrome.[3] Toxoplasmosis is by far the most common infectious cause of such lesions in both adults and children.[3] However, when necessary, diagnostic vitrectomy should be performed for microbiological testings.

Candida species are the leading cause of endogenous endophthalmitis.[2] Risk factors associated with ocular candidiasis overlap with those associated with invasive candidiasis in general, including surgery due to solid tumor[4] and immunosuppression.[5] In the context of established *Candida* infection, prolonged candidemia and specific *Candida* species (*C. albicans* and *C. parasilosis*) are associated with a higher risk of eye involvement.[2]

By definition, endogenous *Candida* endophthalmitis occurs in association with transient or persistent candidemia, yet it remains an infrequent complication of invasive candidiasis. Even though the aforementioned wide spectrum of signs of ocular candidiasis was detected in up to 26% of patients with proven candidemia,[6] full-blown endophthalmitis involving the vitreous was reported in only 0% to 1.6% of patients with invasive candidiasis.[2,6]

Conversely, not all *Candida* endophthalmitis have proven candidemia at presentation. The reported rates of positive blood culture in patients diagnosed with *Candida* endophthalmitis are highly variable, ranging from 11% to 100% depending on the population.[7,8] Even when bloodstream infection is not demonstrated, most reports involve processes or procedures pathologically consistent with transient candidemia such as intravenous drug use,[9] contaminated intravenous infusion,[10] and childbirth,[11] as well as lithotripsy of renal calculi in the presence of fungal urinary tract colonization.[12] Reports of *Candida* endophthalmitis associated with superficial candidiasis such as vaginal infection or onychomycosis are rare.[13,14] To our knowledge, our patient is the first reported case of endophthalmitis associated with CMCC, a condition characterized by persistent or recurrent superficial candidal infection of skin, mucous membranes, and nails.

Finally, this case emphasizes the importance of performing an in-depth workup and of screening for immunodeficiencies when managing atypical cases presenting with "spontaneous" deep *Candida* infections such as endophthalmitis. Multiple genetic mutations, including *CARD9*, have been reported to cause impaired Th17 immunity against *Candida* species, predisposing to superficial and/or deep infections.[15] The presence of CMCC and its associated genetic susceptibilities are often overlooked but are important for several reasons. Recognition of such susceptibilities not only ensures prompt short-term and long-term treatments for patients, but also provides the opportunity for novel adjunctive therapy targeting specific mutations.[16] Furthermore, as some of these mutations are inheritable, appropriate genetic counselling would also be beneficial and necessary.

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Pyoderma gangrenosum of the eyelid

Pyoderma gangrenosum (PG) is a rare inflammatory skin condition of unknown etiology. In rare cases, it affects the eyelid, where it can have devastating visual consequences. We describe a case of severe eyelid PG, successfully managed with aggressive chronic immunosuppression.

PG is one of the neutrophilic dermatoses—a group of dermatological diseases characterised by skin infiltrate with mature polymorphonuclear lymphocytes in the absence of an infection or true vasculitis.[1] PG has an incidence of approximately 6 per 1 million person-years in the United Kingdom. The characteristic clinical feature of PG is the formation of sterile pustules that rapidly develop into an ulcer with a purulent base that undermines its elevated, violaceous edge.[2] PG often affects the legs and trunk and is associated with chronic gastrointestinal, endocrine, or hematological conditions. We add a further case to the few reports of eyelid PG and review the literature to investigate clinical features, treatment strategies, and outcomes. We wish to highlight that cases with preservation of the eyelid posterior lamellae appear to have a good prognosis, whereas cases with lagophthalmos or orbital involvement have a poorer prognosis. In addition, we highlight that treatment with infliximab infusions and high-dose oral prednisolone has been highly successful in our case.

A 40-year-old female with poorly controlled type 2 diabetes mellitus and a 10-year history of PG presented with a painful, swollen, inflamed left upper lid, which was diagnosed as being a chalazion. The PG was usually controlled with monthly infliximab, but she had missed the infusion 3 weeks before presentation. She presented again 2 weeks later describing the lesion to have "burst" 1 day before. On examination she had a horizontal fissure through skin and orbicularis oculi muscle, at the skin crease of the left upper lid, with surrounding erythema (Fig. 1A). Additionally, she had a single 1-cm-diameter abdominal follicular skin lesion.

She was treated with oral antibiotics, but over the subsequent 2 weeks the disease process completely destroyed the left upper lid anterior lamella (Fig. 1B). The levator function, extraocular movements, and cornea were unaffected. The result of blood testing was unremarkable except for positive anti-neutrophil cytoplasmic antibody immunofluorescence with a 2+ perinuclear pattern. A computed tomography scan showed no postseptal extension of the inflammation, and swabbing of the lesion cultured

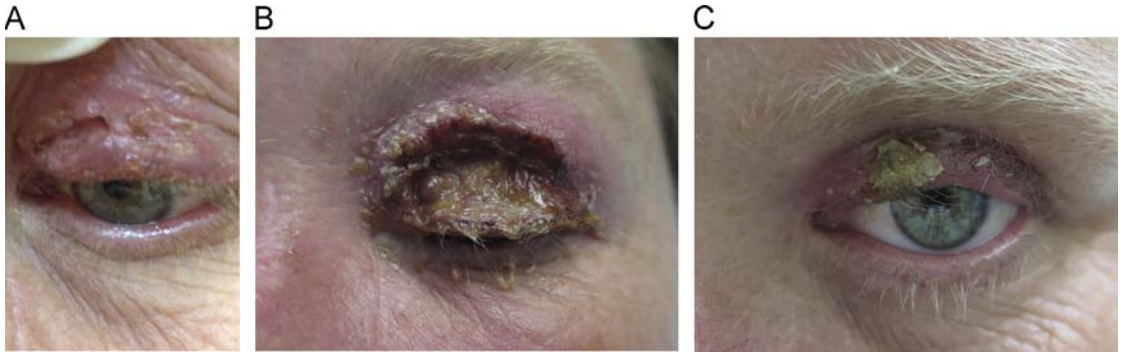

Fig. 1—(A) Left upper lid appearance at second presentation, with a horizontal upper lid fissure in the upper through the full depth of the anterior lamella. (B) Two weeks later, extensive ulceration of the anterior lamella. The ulcer has a violaceous rim and an undermined border. (C) Four weeks later, the lesion granulated and has almost completely healed with high-dose oral prednisolone and infliximab infusion.