A unique case of phaeohyphomycosis subretinal abscess in a patient with arthropathy and lung pathology

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A 67-year-old former gold miner with rheumatoid arthritis, treated with steroids and methotrexate, presented to eye casualty with a painful right eye. Examination revealed an anterior uveitis and despite an initial response to topical steroids, the intraocular inflammation worsened with anterior and posterior uveitis development. Re-examination showed a white mass in the peripheral nasal retina initially suspected of being active Toxoplasmosis infection and anti-toxoplasmosis treatment commenced. After improvement and tapering of this treatment, the intraocular inflammation reoccurred. Cytopathological examination of a pars plana vitrectomy obtained vitreous sample that showed a non-diagnostic non-infectious chronic vitritis. The vitreoretinal surgeons elected to do a direct biopsy of the white subretinal mass in the peripheral nasal area. This revealed, quite unexpectedly, an abscess containing pigmented phaeohyphomycosis fungi. This case report documents the multidisciplinary approach that assisted in clinching a final diagnosis and the role of sub-retinal biopsy in this unprecedented scenario.

Key words: Phaeohyphomycosis, pigmented fungi, subretinal abscess, subretinal biopsy

Sub retinal abscesses are a rare occurrence. Whilst most are due to bacteria, reports of fungal subretinal abscess are extremely rare and only a handful of cases have been documented, in the setting of generalised sepsis, immunocompromised states and intravenous drug abuse.[1] Here, we report a unique case of subretinal phaeohyphomycosis abscess and the role of subretinal biopsy in securing a firm diagnosis when other testing modalities proved non-diagnostic.

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Case Report

A 67-year-old male presented to the emergency eye centre (EEC) complaining of a painful right eye of 5-day duration. The medical history included active rheumatoid arthritis. His regular medications included sulfasalazine, prednisolone, and methotrexate for his rheumatoid disease.

Clinical examination revealed a visual acuity (VA) of 6/9 with minimal conjunctival injection, anterior chamber (AC) cells 1+ and posterior synechiae (PS). A diagnosis of anterior uveitis was made and the patient was commenced on topical prednisolone 1% and topical cyclopentolate 1%. The response to this treatment was good and the steroids were slowly tapered over 1 month; however, before cessation of treatment, the anterior segment inflammation worsened. The patient represented with VA 6/36 and AC cells 3+, extensive PS and a posterior vitritis. Immediate management included a subconjunctival injection of mydricaine No. 2, the topical treatment was increased and an urgent referral was made to the uveitis service.

At review, 4 weeks after presentation, the anterior and posterior segment inflammation remained and a white mass was noted in the peripheral nasal retina [Fig.1 upper plate], almost at the ora serrata. A diagnosis of presumed *Toxoplasma* chorioretinitis was made and treatment with pyrimethamine and sulfadiazine followed by oral clindamycin was initiated. On further questioning, it was discovered that there was the possibility of a previous pulmonary tuberculosis (TB) infection. The patient's previous employment was gold-mining. A chest X-ray showed apical lung scarring on the right. He had had no previous treatment for active tuberculosis. In view of concern over possible reactivation of TB with an increase in oral steroids, further investigations were performed. HIV testing was negative. Quantiferon and induced sputum sampling were also performed (all negative) and the dose of prednisolone was increased to 60 mg daily. Blood cultures were also negative and there was no serological evidence of *Toxoplasma* infection (toxoplasma latex <16).

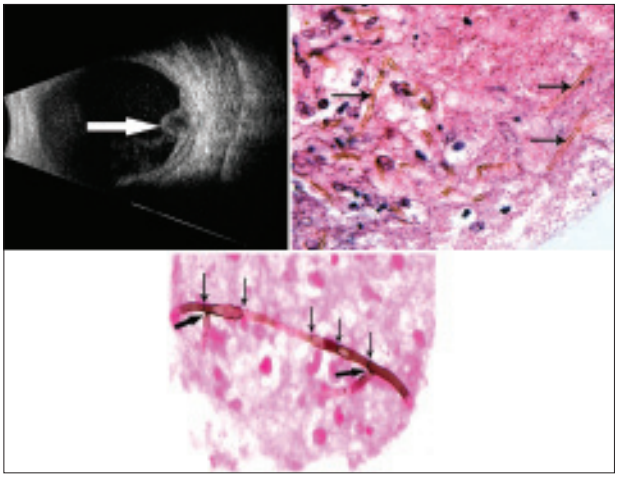

Figure 1: (Upper Plate) 10 MHz B-scan ultrasonography of subretinal mass (nasal peripheral retina-white arrow) (Middle Plate) Hematoxylin and Eosin stained section of the retinal biopsy showing brown fungal hyphae (black arrows) coursing through the abscess.(Lower Plate) Masson Fontana stain showing a positive melanin brown reaction. Thin arrows showing fungal septae and thick arrows indicate dichotomous branching of hyphae

The patient responded to oral steroids and clindamycin, with a reduction in intraocular inflammation and improved VA of 6/18 after 2 weeks treatment. However, when the oral prednisolone was gradually reduced and the clindamycin stopped (after 5 weeks treatment), there was an increase in intraocular inflammation and VA reduced to 3/60. A diagnostic pars plana vitrectomy was therefore performed with vitreous sampling, which revealed a chronic vitritis without infectious agent or neoplasia. No herpes family viruses or toxoplasma organisms were identified on polymerase chain reaction testing.

In order to clinch the diagnosis, combined cataract surgery, retinal biopsy, and intraocular oil tamponade was performed. The combined procedure facilitated access to the anteriorly located subretinal mass. Surgery was performed 4 months after the patient initially presented with acute anterior uveitis. The nasal sub-retinal mass was biopsied using a 23-gauge (23G) vitrector hand piece and samples sent to histopathology and microbiology. Haematoxylin and eosin stained sections revealed an abscess with occasional granulomata. Close inspection showed brown pigmented septate branching hyphae that stained strongly with Masson Fontana melanin stain and with a Periodic Acid Schiff (PAS) and silver stain [Fig.1 middle and lower plates]. The presence of a melanin containing, septate, branching, and mycelial fungus on histopathology was diagnostic of phaeohyphomycosis infection, on morphology alone. Prolonged fungal culture of the biopsy was negative and 18S ribosomal subunit polymerase chain reaction (PCR) was also negative (most likely due to the presence of PCR inhibitors in the sample). The absence of a culture and PCR result did not permit precise speciation of the phaeohyphomycosis fungus. The patient was referred to the infectious diseases department and oral voriconazole therapy initiated. The patient remained under joint care and was treated with antifungal therapy for 6 months; however, no primary source of fungal infection was identified. Following retinal biopsy the patient developed a retinal fold secondary to proliferative vitreoretinopathy (PVR), which extended from the biopsy site to the optic disc. Vitrectomy, removal of silicone oil, epiretinal membrane peel, subretinal PVR removal and retinectomy were performed with laser retinopexy and intraocular gas tamponade. Unfortunately, the patient required two further operations for rhegmatogenous retinal detachment. Currently, the retina is flat with heavy silicone oil tamponade and the VA is 2/60. Further retinal biopsy taken during vitrectomy for retinal detachment revealed no fungal elements on microscopy and intravitreal amphotericin B was also injected perioperatively.

Discussion

Phaeohyphomycosis is a collective term that describes infection caused by darkly pigmented mycelial fungi, a feature secondary to the presence of melanin within their cell walls. These organisms may also be described as dematiaceous.[2]

The most common phaeohyphomycosis genera pathogenic to humans include *Exophilia, Phialophora, Wangiella, Bipolaris, Exserohilum, Cladophialophora.*

Aureobasidium, Cladosporium, Curvularia and Alternaria.[2] Morphology by histopathology is sufficient to make a diagnosis of phaehyphomycosis, characterized by branching, septate hyphae with confirmation of melanin by tinctorial staining (Masson Fontana or an equivalent)[3]. Whilst histopathology permits a clear diagnosis of phaeohyphomycosis, the precise species does require PCR and cultures.

Infection is presumed to be as a result of implantation following superficial trauma and exposure to contaminated soils or organic matter. Systemic infections result either from direct invasion from a more superficial site, such as the paranasal sinuses or by means of haematogenous dissemination. The central nervous system is most frequently affected but other sites including lung, bone, and joint or peritoneum may also be involved.[4] Most life threatening fungal infections are associated with immune compromise. However, primary cerebral phaeohyphomycosis seems to ignore this rationale with more than half of cases being fully immunocompetent.[4] Melanin within the cell walls of dematiaceous fungi may provide the reasons for this disparity; it has been extensively investigated as a virulence factor.[5]

Phaeohyphomycosis can cause keratitis[5] endophthalmitis,[7] orbital[8] and periorbital skin[9] infection. However, this is the first time a subretinal abscess caused by phaeohyphomycosis has been documented in the medical literature. The most plausible theory involves a haematogenous route (metastatic infection) transmission from a peripheral nidus to the subretinal space, which in turn initiated a posterior and anterior segment uveitis. Patients with underlying lung disease appear to be at a increased risk of pulmonary phaeohyphomycosis.[2] It is possible that, in this patient, the lung parenchyma may have been a source of infection, in the setting of chronic, low level immune suppression/ modulation by the methotrexate therapy with reactivation of a previous self-limiting respiratory phaeomycotic infection, with subsequent dissemination.

This unique case highlights the multidisciplinary nature of modern ophthalmology. Posterior segment pathology is usually diagnosed by characteristic clinical signs, extensive systemic investigations and non-invasive ocular investigations such as fluorescein angiography. However, it is not uncommon for vitreoretinal surgeons to aid in the diagnosis of a posterior uveitis of unknown aetiology by sampling vitreous, retina or choroidal tissue,[10,11] leading to increased diagnostic accuracy and prompt treatment.

Johnston *et al*.[12] reported 13 cases of retinochoroidal biopsy in unclear uveitis seven of the cases tissue biopsy helped direct specific treatment. Intraocular lymphoma, recurrence of lymphoblastic leukaemia, chronic scleritis, toxoplasmosis, and metastasis were diagnoses confirmed as a result of the tissue biopsies performed. Malignancy was also excluded in several cases, which allowed for a trial of medications such as oral steroids and anticytomegalovirus agents.

In this case, it is difficult to postulate whether the final VA and outcome have been improved by surgical intervention. It is clear that the patients intraocular inflammation was increasing rapidly and only high dose steroids subdued the response. Without sub-retinal biopsy, the specific treatment of this patient's phaeohyphomycosis with antifungal medication would not have been possible and years of treatment for idiopathic uveitis may have ensued.

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