MYCOBACTERIUM

Mycobacterium tuberculosis usually causes pulmonary disease, but adnexal involvement can rarely occur, usually by lymphatic or haematogenous spread, or by direct extension from the paranasal sinuses. Disease patterns in the orbit are generally divided into periostitis, soft tissue tuberculoma (with or without bony involvement), orbital spread from the paranasal sinuses, or TB dacryoadenitis.

Rose et al recently reported a cohort of 8 patients presenting to a London specialist orbital clinic with periocular or orbital tuberculosis, although no ‘typical’ presentation was observed, most patients reported ocular discomfort on eye movement, and none had intraocular disease. Such non-specific features often lead to diagnostic delays, and the clinician should be lead by clinical suspicion, and not a positive culture result.

Where extrapulmonary TB is strongly suspected, patients should be investigated with a chest X-ray and triple anti-tuberculous therapy (ATT) commenced. A positive culture for M. Tuberculosis is the diagnostic ‘gold standard’, but where this is negative, supportive tests such as tuberculin skin tests, PCR-based analysis and Interferon-Y release assays (IGRA) should be considered. Although surgical intervention can alleviate symptoms and prevent visual loss, a complete course of ATT is paramount to control the disease.

Finally, atypical mycobacteria and Mycobacterium hominis infections of the orbit can also occur, but are rare. These organisms can involve any periorbital or orbital tissue (including the periosteum and bony walls), can extend into the adjacent sinuses or...
intracranial cavity,\textsuperscript{[3,7]} and can also occur in the absence of pulmonary disease.\textsuperscript{[4,8]} Clinical features include a “cold” orbital abscess, a discharging cutaneous sinus, or, rarely, optic neuropathy complicating sphenoidal osteomyelitis.\textsuperscript{[9]}

**FUNGAL INFECTIONS**

Although rare, opportunistic fungal infections of the orbit should be considered in debilitated or immunocompromised patients. Such organisms include the Phycomycetes (\textit{Mucor} and \textit{Rhizopus} spp.), Ascomycetes (\textit{Aspergillus} spp.), Blastomyces,\textsuperscript{[10]} \textit{Sporothrix} spp.,\textsuperscript{[11,12]} and Phaeohyphomyces (\textit{Bipolarina} spp.),\textsuperscript{[13]} the most common of which are \textit{Mucor} and \textit{Aspergillus} spp. Ubiquitous in the environment, these organisms reach the orbit by direct extension from the sinuses and, unless the underlying risk factor(s) are addressed, the prognosis for sight and even life may be dire. In recent years, a new strain of \textit{Mucor} infections (\textit{Apophysomyces elegans}) has been reported in healthy immunocompetent patients with grave sequelae or death as a consequence. This strain of \textit{Mucor} has a high mortality rate in immunocompromised patients, with 100% mortality reported in rhino-orbital-cerebral disease. This species of \textit{Mucor} is found in warm climates and is generally transmitted through a traumatic break in the skin or by an insect bite.

**Orbital Fungal Infection: Phycomycetes**

\textbf{Overview}

\textit{Mucor}is, a genera of the order Mucorales, and a subset of the class Phycomycetes, are ubiquitous spores that are pathogenic among debilitated patients [Table 1]. Their pathogenicity is due to their ability to invade blood vessels, leading to endothelial damage, ischemia, and necrosis. Half of all patients with \textit{Mucor} infections develop rhino-orbital-cerebral disease, presenting with facial pain, sinusitis, pharyngitis, or nasal discharge, and the characteristic necrotic nasal eschar may even be absent. Management includes treatment with lipid formulations of amphotericin B and thorough debridement of necrotic tissue, although mortality rates remain in the region of 30%. Finally, iron chelation with deferasirox may play a critical role in the future, although clinical experience remains limited.\textsuperscript{[14]}

\textbf{Pathophysiology}

With increasing numbers of immunosuppressed patients, rhino-orbital-cerebral fungal infections are a growing cause of morbidity and mortality,\textsuperscript{[15,16]} although infection rarely occurs in immunocompetent patients.\textsuperscript{[17]} rhino-orbital-cerebral invasion begins in the nasal passages and spreads to the maxillary and ethmoid sinuses, before involving the orbit.\textsuperscript{[18-20]} Intracranial involvement occurs as a result of extension via the orbital roof and apex through the cribriform plate.\textsuperscript{[18,21]}

Understanding this pathogen and its mechanism of invasion is essential in managing the disease. Being angioinvasive, the fungus dissects the internal vascular lamina from the media, causing extensive endothelial damage, with thrombosis, ischemia, and infarction, thus limiting the efficacy of systemic medical treatment and allowing the fungus to invade the surrounding tissues. In addition, these fungi have the facultative ability to grow in both aerobic and anaerobic conditions.\textsuperscript{[19,21]} Tissue ischemia and infarction result in lactic acidosis, which reduces phagocytosis, thus promoting fungal invasion outside the vessels.

**Clinical Presentation and Diagnosis**

The systemic and orbital features of rhino-orbital mucormycosis infection are shown in Tables 2 and 3, Table 1. Predisposing factors for \textit{Mucor} infection

| Predisposing factors for \textit{Mucor} infection |
|-----------------------------------------------|
| Uncontrolled diabetes mellitus (particularly patients with ketoacidosis) |
| Solid malignancies |
| Hematological malignancies with neutropenia |
| Extensive burns |
| Iron overload (hemochromatosis)\textsuperscript{[19]} |

Table 2. Systemic features of rhino-orbital phycomycete infection

| Systemic features of rhino-orbital phycomycete infection |
|--------------------------------------------------------|
| Fever |
| Lethargy |
| Facial pain and paresthesia |
| Sinusitis |
| Pharyngitis |
| Oral or dental pain |
| Seropurulent nasal discharge |
| Anosmia |
| Necrotic intranasal or intraoral masses |

Table 3. Orbital symptoms and signs in rhino-orbital phycomycete infection

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|---------------------------------------------------------------|
| Reduced visual acuity |
| Trigeminal insensitivity |
| Proptosis |
| Ophthalmoplegia |
| Afferent pupillary defect |
| Orbital apex involvement leading to internal and external ophthalmoplegia, ptosis, and periorbital paresthesia |
| Although rare, bilateral orbital involvement has been reported |

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respective. Although characteristic of the disease, necrotic black nasal or oral eschar resulting from vascular thrombosis and tissue infarction is a late finding and is occasionally absent [Figures 1 and 2].

Investigations
Blood tests occasionally identify a raised erythrocyte sedimentation rate or white blood cell count, but blood cultures are typically non-contributory. Histological specimens show broad hyposetoate hyphae that branch irregularly and, when folded, give a characteristic twisted-ribbon appearance [Figure 1]. Relevant stains include Gomori’s methenamine silver stain, potassium hydroxide preparation, and hematoxylin and eosin stain, and cultures are most likely to be achieved on Sabouraud’s agar without inhibitors. The extent of disease is determined with computed tomography (CT) or magnetic resonance imaging (MRI). CT may show mucosal thickening, bony destruction, and venous filling defects suggestive of thrombosis [Figure 2] and MRI of the sinuses typically identifies mucosal thickening or even obliteration of the sinus cavity with a hyperintense signal on T2-weighted images [Figure 2].

Management of Mucormycosis
The keys to successful management include a high index of suspicion, prompt diagnosis, and addressing the underlying systemic disease. Prompt diagnosis can be achieved through early nasal endoscopic examination with biopsy of any areas with suspected mucosa. In addition, urgent biopsy of orbital tissue should be performed to determine the necessity of debridement or orbital exenteration. Early wide debridement of devitalized tissue and adjunctive antifungal therapy are essential and lifesaving. Medical treatment includes liposomal amphotericin B (a fungistatic agent active against most yeasts and molds) at a dose of 3–10 mg/kg/d, with recent experience suggesting a role for posaconazole, a new triazole antifungal agent with a wide in vitro spectrum of activity that can be used for patients with elevated creatinine secondary to amphotericin B. Repeated and extensive tissue debridement may be necessary; however, despite limited mucormycosis having been managed successfully without exenteration, the indications for this destructive procedure remain uncertain because of the rarity of the disease. Orbital exenteration is justified for more posterior disease, but may not always be indicated for more anterior involvement. Recently, it was proposed that serial debridement should be performed in addition to endoscopic follow-up evaluation each week. Augmentation of systemic antifungal therapy and surgical debridement, including hyperbaric oxygen and local amphotericin B packing in the area of disease involvement, are reported to exert a major beneficial clinical effect, although the literature contains no prospective studies supporting this impression. It is logical and likely that these will become part of the recommended therapy in the treatment of this disease. Future therapies are likely to
Rare Orbital Infections; Hamed-Azzam et al

include granulocyte-macrophage colony-stimulating factor therapy, and iron chelation.\textsuperscript{[14,34,39-41]}

Prognosis

Historically, the prognosis of rhino-orbital phycomycete infection has been very poor, although, with the introduction of amphotericin B, overall survival rates have risen from 10% to approximately 70%. These figures reflect both the aggressive nature of Mucor and Rhizopus, and the frequent delay in diagnosing a debilitated patient who may be simultaneously receiving treatment for other life-threatening diseases.\textsuperscript{[18,21,22,24]} Hematologic malignancy, advanced age, and extension to the cranium or orbit are among the negative prognostic factors. Early diagnosis and awareness of this disease among diabetic and immunocompromised patients improves the prognosis. The infection should be suspected in immunocompromised patients with facial discomfort, pain, paresthesia, facial swelling, cellulitis, fever, and new-onset progressive sinusitis over a period of hours or days. Immediate management with biopsy, antifungal therapy, and prompt surgical debridement should improve the prognosis and potential for survival.\textsuperscript{[38]}

Aspergillus

Overview

Aspergillus is a saprophytic, ubiquitous fungus that causes both invasive and non-invasive sinus infections.\textsuperscript{[39,40]} The non-invasive form occurs in immunocompetent patients, presenting with allergic sinusitis or sinonasal fungal ball,\textsuperscript{[41-44]} whereas the invasive form occurs in immunocompromised patients. The latter is associated with arteritis and secondary thrombosis (because Aspergillus can invade vessel walls), as well as aneurysm formation, with mortality rates of approximately 28% despite intensive treatment.\textsuperscript{[45,46]}

Pathophysiology

Although Aspergillus typically occurs in compromised patients, it also occurs in healthy patients.\textsuperscript{[47]} In debilitated patients, the invasive disease often extends posteriorly through the orbit into the cavernous sinus and brain. Frequently, coexistent hematological diseases are present, such as leukemia, lymphoma, or HIV infection\textsuperscript{[48-50]}, however, invasive aspergillosis very rarely occurs in healthy patients.\textsuperscript{[51]} By contrast, although the non-invasive form causes chronic sinusitis, or isolated aspergillomas, orbital involvement is infrequent.\textsuperscript{[52]} Aspergillus requires specific conditions to proliferate and invade, including a previous mucosal lesion caused by a previous infection or manipulation, mucosal hypertrophy, and chronic bacterial sinusitis.\textsuperscript{[53]}

Clinical Presentation and Diagnosis

Aspergillus infections frequently occur in warm, humid climates (with the exception of Mucor and Rhizopus occurring equally in both warm and cold climates), and tend to be relatively indolent, generally progressing over many weeks, months, or even years. Nevertheless, it can lead to blindness and death. Isolated reports have highlighted the diagnostic dilemma that arises with such a slow process, with one case of steroidresponsive optic neuropathy, and another describing Aspergillus infection of the orbit following dental infection, both ultimately resulting in death.\textsuperscript{[54,55]}

Colonization of the sinuses occurs from the nose, with invasion continuing both through the orbital apex and into the brain, and into the infratemporal fossa via the inferior orbital fissure. However, when isolated sphenoid sinus disease is present, optic neuritis can lead to visual loss without direct orbital involvement.\textsuperscript{[56]} When the orbit is involved, gradually progressive proptosis occurs, with visual loss resulting from chronic fibrosing granulomatous disease of the sinuses.\textsuperscript{[57]} An accurate and timely diagnosis requires a high index of clinical suspicion, and histology demonstrating a typical branching septate hyphae (often at 45° angles) on Gomori methenamine silver and periodic acid–Schiff stains. Cultures on Sabouraud’s agar without inhibitors remain the gold standard for diagnosis.

Imaging with CT identifies a hyperdense mass expanding or destroying the paranasal sinuses, and extending into the orbit or cranium [Figure 3]. On MRI, Aspergillus lesions are hypointense on T2-weighted images, and isointense on T1-weighted images.

Figure 3. Aspergillus: Allergic non-invasive fungal sinusitis. Magnetic resonance imaging revealed signal voids in the expanded ethmoid sinuses Courtesy of Prof. Valerie J Lund, MS, FRCS, FRCS (Ed), Royal National Throat, Nose and Ear Hospital, London, UK.
Orbital Aspergillosis: Management and Prognosis

Aspergillosis has a comparatively favorable prognosis in immunocompetent patients if treated appropriately and in a timely fashion. Management of orbital aspergillosis involves extensive debridement of the infected tissues, extending to the adjacent sinuses and skull base area, with intense intravenous liposomal amphotericin B followed by fluconazole or itraconazole. Recently, oral voriconazole, which is also highly active against Aspergillus spp., has gained favor in the management of invasive aspergillosis.

Invasive aspergillosis has a very poor prognosis, being fatal in approximately one-third of all cases, including immunocompetent patients, with mortality rates for intracerebral aspergillosis in debilitated patients lying between 66% and 100%. In the management of invasive aspergillosis, surgery is necessary.

Parasitic Disease

Parasitic orbital diseases, including Echinococcus, microfilaria, and cysticercosis infections, are rare in Europe and the United States, but commonly encountered in South America, Africa, and the Middle East.

Echinococcus Orbital Infection

Hydatid disease, caused by the parasite Echinococcus granulosus, occurs in agricultural regions of the Mediterranean, Middle East, South America, New Zealand, Australia, and Southeast Asia. Echinococcus parasites live in the intestines of dogs and sheep and shed their eggs within dog feces. These are then ingested by an intermediate host (such as a cow or sheep), and the eggs hatch in the animal’s gut. Hydatid cysts disseminate through the bloodstream to a wide variety of tissues and, when ingested by the definitive host (humans), progress to the final larval stage. Hepatic and pulmonary deposits are the most common clinical manifestations, and orbital hydatid disease occurs in fewer than 1% of cases, although in endemic areas it may account for up to a quarter of all cystic orbital lesions.

The clinical presentation of orbital hydatic disease is that of a gradually progressive, painless solitary intraconal lesion, with proptosis and motility restriction, in patients under 20 years of age. One study from Iran reported 28 cases, with the age at presentation ranging from 5 to 54 years (mean, 15 years), and with visual acuities ranging from 6/6 to no light perception. Although serological testing is unreliable because the parasite can remain encysted, ultrasonography identifies a well-circumscribed cystic structure, and CT imaging show a cyst with a contrast-enhancing rim. During surgery, excised ovoid lesions are found to be surrounded by an adventitial fibrous membrane in approximately half of all cases.

Orbital hydatid disease has traditionally been treated with surgical excision. However, since the introduction of albendazole in 1983, some authors have advocated for extended medical therapy alone, whereas others have favored its use in conjunction with surgery.

Microfilaria Infection

Dirofilaria is a parasitic worm that infests domestic and wild animals, but rarely, can be transmitted to humans by an insect vector (Culex and Aedes mosquitoes). Ophthalmic involvement includes subconjunctival, intraocular, or periorbital infestation, and can also involve the extraocular muscles, leading to pain, chemosis, and proptosis. The treatment is surgical excision.

Cysticercosis of the Orbit

Cysticercosis, caused by the parasite Taenia solium, is a potentially fatal infection, and is endemic to Latin America, sub-Saharan Africa, and parts of Asia. In human cysticercosis, T. solium eggs in raw pork hatch in the stomach and release larvae that disseminate through the bloodstream to all organs in the body, including the periorbital and eye. Management includes surgical removal of the cyst and medical therapy with cestocides (albendazole or praziquantel), alongside steroids used to reduce the inflammatory response around the dying cysticerci.

Ophthalmomyiasis

Myiasis is caused by infestation of human tissue by botfly larvae, typically the sheep botfly Oestrus ovis and the human botfly Diptera hominis. Specifically, it has been reported in the context of ulcerating periorbital cutaneous neoplasia. The eggs are deposited on the...
skin by a vector, such as a mosquito, where the larvae hatch before penetrating the skin. Ophthalmomyiasis occurs in 5% of all cases, with larval invasion of the periorbita, conjunctiva, or cornea, resulting in major tissue destruction.\textsuperscript{[88,89]} Symptoms include pain, itching, and a sensation of tissue movement because of the mobile larvae. The treatment is surgical excision, but, because of the numerous small spicules on the surface of the organism, this is not easily achieved [Figure 5]. Soaking in hydrogen peroxide or Dakin's solution is also advocated and has been found to be helpful. Severe, ulcerative orbital myiasis may require exenteration. However, in internal myiasis, larvae can be destroyed using laser photocoagulation or removed through pars plana vitrectomy.\textsuperscript{[90]}

**SUMMARY**

Although rare, fungal and parasitic organisms can be fatal. Therefore, clinicians should be vigilant and aware of the clinical signs, etiology, and management. Unusual infections of the orbit should be considered mainly in debilitated or immunocompromised patients. Management should be adapted to the organism, but generally it includes systemic antibiotics, debridement, and occasionally more extensive surgery. Taking meticulous history from the patient, and awareness of the disease improve the prognosis and increase the survival rate.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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There are no conflicts of interest.

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