Review Article

Fungal infections of the orbit

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Fungal infections of the orbit can lead to grave complications. Although the primary site of inoculation of the infective organism is frequently the sinuses, the patients can initially present to the ophthalmologist with ocular signs and symptoms. Due to its varied and nonspecific clinical features, especially in the early stages, patients are frequently misdiagnosed and even treated with steroids which worsen the situation leading to dire consequences. Ophthalmologists should be familiar with the clinical spectrum of disease and the variable presentation of this infection, as early diagnosis and rapid institution of appropriate therapy are crucial elements in the management of this invasive sino-orbital infection. In this review, relevant clinical, microbiological, and imaging findings are discussed along with the current consensus on local and systemic management. We review the recent literature and provide a comprehensive analysis. In the immunocompromised, as well as in healthy patients, a high index of suspicion must be maintained as delay in diagnosis of fungal pathology may lead to disfiguring morbidity or even mortality. Obtaining adequate diagnostic material for pathological and microbiological examination is critical. Newer methods of therapy, particularly oral voriconazole and topical amphotericin B, may be beneficial in selected patients.

Key words: Amphotericin B, aspergillosis, fungal, mucormycosis, orbital infection, voriconazole, zygomycosis

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Fungi are ubiquitous eukaryotic organisms found in dead, decaying vegetative matter, soil, and air. Genetic studies have surprisingly revealed them to be more closely related to animals than plants. Several fungi can cause devastating infections in humans, including in the orbits. The taxonomy of the kingdom of fungi is vast, complicated, and confusing. For our convenience, we will concentrate on the organisms commonly causing orbital infections. Orbital fungal infections are not only vision-threatening but are also associated with high mortality. It thus becomes imperative to diagnose fungal disease at the earliest and initiate appropriate therapy. This review aims to provide a comprehensive insight of common orbital fungal infections, and their clinical features and management. We performed a search of relevant literature in English from 1990 to 2015 using PubMed (MedLine), Cochrane, and Google Scholar with multiple combinations of search terms including orbital infection, fungal, aspergillosis, mucormycosis, zygomycosis, amphotericin B, and voriconazole. All relevant articles after 1990 were reviewed.

The most common orbital fungal infections are mucormycosis and aspergillosis. Mucormycosis is caused by fungus in the order Mucorales, of which Rhizopus species is the most common. Aspergillosis is caused by fungus in the order Eurotiales and genus *Aspergillus*.[1] There are several differences in the pathogenesis, clinical presentation, risk factors, and management of these fungal infections. In both forms, initial site of involvement is usually the paranasal sinuses with secondary involvement of the orbit.

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Mucormycosis

Rhino-orbital-cerebral zygomycosis (ROCZ), or Rhino-orbital-cerebral mucormycosis (ROCM), zygomycosis, phycomycosis, or orhyphomycosis is most commonly caused by *Rhizopus oryzae* (90%).[1,2] Other common species of the order mucorales-causing infections include *Absidia corymbifera*, *Mucor ramosissimus*, *Rhizomucor pusillus*, and *Apophysomyces elegans*.[2] It is a nonseptate filamentous fungus and is generally found in soil, decaying fruit and vegetables, animal feces, and old bread.[1]

Pathogenesis

Zygomycetes is an opportunistic pathogen and needs breakdown of our immunity system to cause infection. Primary orbital infections are extremely rare. The most common modes of infection are by invasion from the adjacent paranasal sinuses or direct traumatic inoculation into the orbit.[1] Rarely they can reach the orbit via hematogenous spread. They can also reach the orbit from respiratory tract where they get inoculated by inhalation in cases of immunocompromised hosts.[1] Chahal *et al*. have recently reported a case of orbital spread from contiguous cutaneous mucormycosis in a poorly controlled diabetic patient.[3]

ROCZ occurs almost exclusively in the immunocompromised host.[2] Approximately 60–80% of cases occur in diabetic

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patients with ketoacidosis.[4,5] Other risk factors include neutropenia, desferrioxamine therapy, patients with iron overload (hemodialysis, hemochromatosis), intravenous drug abuse, chemotherapy, hematologic malignancy, bone marrow transplant, solid organ transplant, and use of steroids or immunosuppressives.[1,6-9] In several epidemiologic studies, hematological malignances have been found to be a major etiological risk factor for mucormycosis, ranging from 17% to 77%.[5,10,11] Neutrophils form the primary defense mechanism against fungal infections. Neutropenia, thus, is attributed as a major risk factor for mucormycosis. Notably, among immunocompromised conditions, HIV infection has not been found to be a major independent risk factor. The probable explanation lies in the fact that HIV infects lymphocytes, and that neutrophils are spared with neutropenia being uncommon in HIV-infected patients.[12] Most mucormycosis cases in HIV are associated with intravenous drug use, neutropenia, or concomitant diabetes. All fungi of zygomycota class require iron for growth and virulence; therefore, patients with iron overload are at increased risk.[13,14] These fungi can also utilize the iron-desferrioxamine complex for their growth, making chelating therapy an independent risk factor. Deferoxamine has also been shown to promote mucormycosis independent of iron overload.[15] The acidotic environment of diabetic ketoacidosis promotes both phagocytic dysfunction and decrease in the iron-binding capacity of the blood, thereby providing additional iron to the fungus.[13] Periorbital burns may lead to ROCZ due to the breakdown in the mucocutaneous barrier and administration of broad-spectrum antibiotics. The risk for infection is high when traumatic inoculation with spores in wounds contaminated with water, soil, and debris acts as entry point for fungal invasion.[2]

Increased incidence of invasive fungal infections, especially mucormycosis, has been reported after natural disasters (tsunami, earthquake, tornado, and floods).[16,17] Increase in environmental concentration and displacement from their natural habitats with subsequent contact with injured persons is postulated to be the cause for fungal infections. The increase in morbidity and mortality is compounded by the characteristic features of postimpact phase of these disasters, e.g., population displacement, inadequate sanitation, and hygiene leading to immunocompromise.[16,17]

Clinical Features

Early sign and symptoms of ROCZ include fever, sinusitis, nasal discharge, epistaxis, orbital and periorbital pain, nasal mucosal ulceration, crusting, and necrosis.[18] A black eschar over skin, nasal mucosa, or palate is characteristic of mucormycosis but is a late and inconsistent finding. This is caused by thrombosis of vessels and the resulting tissue necrosis [Fig. 1]. Decreased vision, proptosis, periorbital edema, and complete external ophthalmoplegia are the most common ophthalmic features. Other ophthalmic signs and symptoms include ptosis, chemosis, congestion, internal ophthalmoplegia, and corneal anesthesia[19] [Fig. 2]. Sudden blindness can occur due to central retinal artery occlusion, thrombosis of posterior ciliary arteries, infarction of the intraorbital part of optic nerve, or direct fungal invasion of the intracranial part of the optic nerve or optic chiasm.[20] ROCZ can also present less commonly as a painless orbital apex syndrome without any signs of orbital cellulitis.[21,22] From the orbit, the infection can spread to brain through cribriform plate and orbital apex. Invasion of the cavernous sinus and cavernous part of carotid artery can lead to carotid occlusion, cerebral infarction, intracranial aneurysm/hemorrhage, fungal meningitis, mycotic abscess, and, eventually, death.[23,24] Changes in mental status due to either central nervous system (CNS) invasion or ketoacidosis consist of somnolence, coma, disorientation and emotional lability, hemiparesis, and hemiplegia.[18,25]

Features associated with a poorer prognosis include periorbital necrosis, cavernous sinus thrombosis, and hemiplegia.[18] Periorbital mucormycosis may be very invasive locally, involving not only the cutaneous and subcutaneous tissues but also the fat, muscle, and fascial layers beneath [Fig. 3]. Necrotizing fasciitis secondary to cutaneous zygomycosis may lead to significant morbidity and mortality.

Investigations

A high index of suspicion is necessary to diagnose ROCZ. Nasal and oral mucosa should be thoroughly examined in a suspected case and specimens should be sent for microbiological evaluation. Potassium hydroxide (KOH) mounts show nonseptate-branched fungal hyphae arranged at right angles.[20]

Although the zygomycetes may be demonstrated on either Papanicolaou or Gram's stain, these are not generally the stains of choice. Calcofluor white, Gomori's methenamine silver (GMS), hematoxylin and eosin (H and E), and periodic acid–Schiff stains also provide reliable information on the presence and morphology of the fungus[1,13,18] [Fig. 4]. Care should be taken to obtain an adequate amount of tissue for biopsy, and even then, it may have to be repeated in case of negative or inconclusive reporting. A part of the biopsied tissue should also be sent for culture. Any part of involved excised tissue, including necrotic mucosa or surgically debrided tissue, is suitable for culture. Sabouraud's agar without cycloheximide is used for culture. It should however be borne in mind that positive cultures alone are not diagnostic as mucorales are a very common laboratory contaminant and can also be grown from uninfected mucosal surfaces. Histopathology shows thrombozing arteritis with vessel walls invaded with fungal hyphae. Veins are relatively spared.[14] Extensive areas of necrosis with accompanying hemorrhage, abscess formation with central tissue necrosis, acute inflammatory exudates, and peripheral tissue invasion by hyphal elements may be seen. Often, the hyphae are not well preserved and become crinkled or gnarled demonstrating a "crinkled cellophane" appearance, which should not be confused with septations.[3]

Alternate techniques for diagnosing the causative agent present in the tissue sample include immunohistochemistry, *in situ* hybridization, and polymerase chain reaction (PCR) for fungal DNA.

Apart from the diagnosis of fungal infection, PCR has an important role in the identification of the exact species involved in the infection, as this can be difficult on routine culture and microscopy.[26] According to Hata *et al*., the clinical sensitivity and specificity of real-time PCR assay from culture isolates were 100% and 92%, respectively, for zygomycetes. Sensitivity and specificity from fresh tissue samples were both 100%. The advantage of PCR lies in the speed. The histopathology examination report of biopsy specimens takes a minimum of

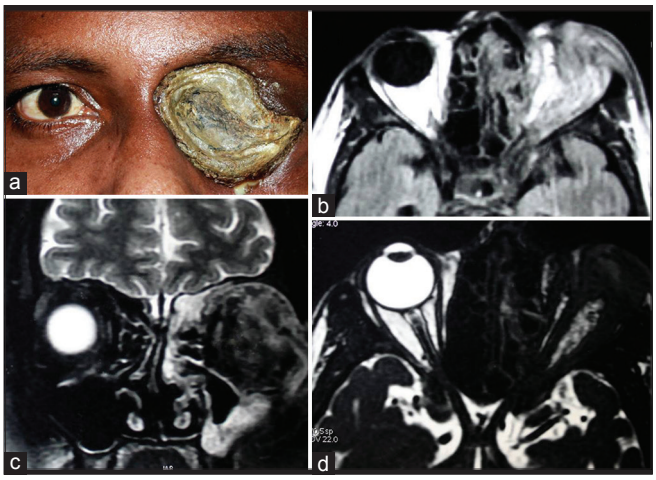

Figure 1: (a) Clinical photograph of patient showing eschar involving left periocular skin. Eyelids and ocular structures cannot be differentiated, (b) T1-weighted axial magnetic resonance image scan through the mid-orbit level. Left globe is not visualized. There is an ill-defined isointense mass in the left orbit. Extension is seen through the superior orbital fissure and into the cavernous sinus, (c) T2-weighted coronal section through the orbit and maxillary sinus. There is mucosal thickening and opacification of the maxillary sinus. Diffuse hypo- to iso-intense mass filling up the extraconal and intraconal space. Globe is not identifiable, (d) T2-weighted axial scan through the orbit. Extraocular muscles are enlarged. Ill-defined mass infiltrating orbital structures and fat, showing mixed intensity signal in intraconal and extraconal space

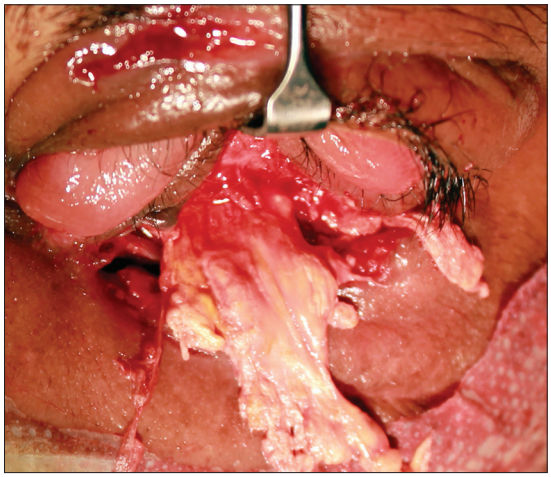

Figure 3: Intraoperative photograph of periorbital mucormycosis following road traffic accident with soil contamination of wound, showing invasion and necrosis of subcutaneous tissues, orbital fat, and fascial layers

4–5 days whereas combination of automated DNA extraction with real-time PCR takes 2–4 h.[27]

Imaging

Computerized tomography (CT) or magnetic resonance imaging (MRI) scans are useful rather for preoperative planning than for diagnosis as the imaging findings may be subtle and nonspecific. CT scan will demonstrate sinusitis, mucosal thickening, bone necrosis with involvement of pterygoid and infratemporal fossa, and thrombosis of superior ophthalmic vein. Intracerebral fungi appear as hypodense

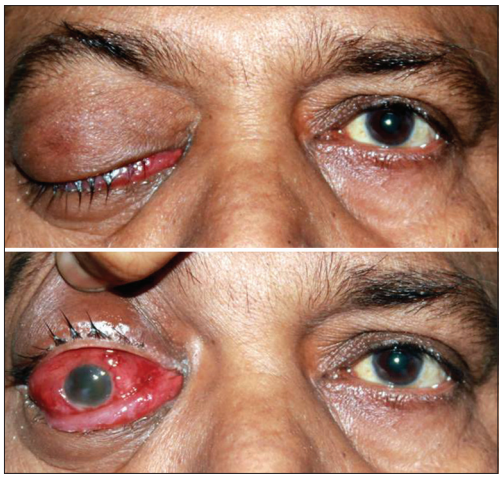

Figure 2 : Patient with fungal orbital cellulitis and orbital apex syndrome presenting with complete ptosis, proptosis, total ophthalmoplegia, chemosis, and congestion

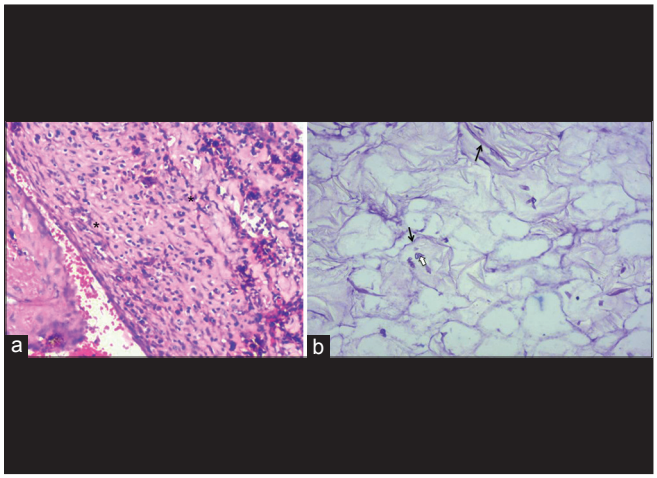

Figure 4: Microphotograph of specimen of tissue infected by mucor. (a) H and E staining: Areas suspicious of fungal hyphae (asterisk), (b) periodic acid–Schiff stain: Nonseptate fungal hyphae with wide angle branching (black arrows) and end-on view (white block arrow) of hyphae

masses with peripheral enhancement (ring abscess).[18] MRI appearance ranges from T2 hyperintensity to marked hypointensity in all sequences, often with obliteration of fat planes [Fig. 1b-d].

The fludeoxyglucose positron emission tomography (PET)/CT scan is emerging as a useful tool for detecting ROCZ and to evaluate response to treatment. However, the cost of serial PET/CTs may prove prohibitive with regard to patient care.[28,29]

Management

ROCZ is a dangerous infection with more than 50% mortality rate.[30] It should be treated as an emergency without any delay in initiation of therapy. ROCZ should be managed by a multipronged, multispecialty approach. Involvement of an infectious disease specialist is mandatory in the management of the patient. Correct treatment of mucormycosis entails early diagnosis, reversal of the predisposing factors, wide local

debridement of the necrotic tissues, establishment of adequate sinus drainage, and systemic antifungals.[18,19,31]

Antifungals

Several antifungal agents can be used in the setting of orbital fungal infections. Most of them exert action by inhibiting the synthesis or by affecting the integrity of ergosterol, the major sterol that forms fungal cell wall membranes.[32] Based on the mechanism of action, they are classified as polyenes, azoles, allylamines, pyrimidines, and echinocandins. Most commonly used antifungal agents for invasive infections include, among polyenes, amphotericin B and its derivatives; among the azoles, ketoconazole, clotrimazole (imidazoles), fluconazole voriconazole, and posaconazole (triazoles). The turn of the century saw the advent of the new class of antifungals called echinocandins. Caspofungin belongs to this new group and has shown potent activity against *Candida* and *Aspergillus*.[33]

Intravenous amphotericin B

The dosage of amphotericin B is slowly increased from 0.7 to 1 mg/kg intravenous to a cumulative dose of 2–4 g over a period of weeks to months, after giving an initial test dose of 1 mg.[34] Most common side effects of amphotericin B include fever, chills, headache, myalgia, anorexia, malaise, anemia, hypokalemia, and vomiting. Nephrotoxicity is the major dose-limiting side effect.[35,36] The blood urea nitrogen and creatinine can be allowed to rise to 50 mg/dl and 3.0 mg/dl, respectively. If the limit is exceeded, the dose is given on alternate days.[18] If the levels remain elevated beyond 50 mg/dl and 3.0 mg/dl, the dose and frequency of the drug must be further reduced. It is always better to involve an infectious disease specialist in the care of the patient.

Liposomal amphotericin B

Lipid formulations of amphotericin B (amphotericin B lipid complex and liposomal amphotericin B) are newer preparations of amphotericin B with fewer side effects and are reportedly more effective against ROCM.[37] They are now the first drug of choice for treatment of ROCM. Liposomal encapsulation of amphotericin B appears to enhance its delivery to fungi, infected organs, and phagocytes, thus accounting for its increased efficacy. Conversely, the renal delivery is decreased.[18,35] A reasonable dose for liposomal amphotericin B would be 5 mg/kg/day, up to a maximum of 10 mg/kg/day for CNS infections. Combined complete and partial response rates are 32–100%, and overall mortality ranges from 5% to 61%.[7]

Surgery and local debridement

Wide local excision of the necrotic orbital tissues and sinuses should be carried out to decrease the fungal burden. Infected tissue typically bleeds less because of the ischemia caused by mucor arteritis and thrombophlebitis. Hence, debridement of tissues until bleeding occurs is a good indicator of the extent of surgical resection needed.[19] Repeated surgical debridement is necessary in many cases. Further serial imaging studies are needed to document the further extension of infection after the initial procedure and a need for a second surgical procedure. Many authors agree that in the presence of active fungal infections, exenteration may be life-saving.[18] Exenteration should be carried in the presence of an actively inflamed orbit with a blind eye or advanced involvement of the orbit.[18,38,39] Exenteration may be helpful even after intracranial spread by decreasing the fungal load.[40] Frozen section-guided surgical debridement may also obviate radical exenteration.[41]

Topical amphotericin B

Irrigation and packing of the involved orbit and paranasal sinuses with amphotericin B (1 mg/ml) can achieve excellent results by increasing the delivery of the drug to the infected site.[34,36] Twice daily, intraconal injection of amphotericin B (1 mg/ml) for 9 days was successfully used along with intravenous amphotericin B in one patient of ROCM and diabetic ketoacidosis and exenteration was avoided.[42] Many authors have described methods of intraorbital infusion of amphotericin B (concentration 0.25–1.25 mg/ml; volume 1–15 ml; frequency 1–4 times daily; duration 5 days to 4 weeks) along with intravenous amphotericin B, and exenteration was avoided in most of these cases.[13,34,36,43] In an attempt to increase the effectiveness of local drug delivery, Kahana and Lucarelli described the use of radiopaque silicone catheter that allows the surgeon to radiologically confirm ideal catheter placement for intraorbital drug delivery.[44]

Hyperbaric oxygen

The role of hyperbaric oxygen in the management of mucormycosis is not clearly defined. The proposed mechanism of action is multifactorial. It acts by increasing oxygenation and thereby decreasing acidosis and increasing the phagocytic activity. Hyperbaric oxygen is also believed to augment the action of amphotericin B.[45] Some studies have shown promising results after treatment with hyperbaric oxygen in ROCM with cerebral extension.[46] The treatment regimen includes hyperbaric oxygen every 12 h with 2 h of 100% oxygen at 2 atmospheres absolute for 3 days, then daily treatments of 2 h duration, with the total number of treatments dependent on patient response.[34,45] However, it is expensive, cumbersome, and not readily available.

Newer modalities

Posaconazole is an oral antifungal agent. It can be used in combination with liposomal amphotericin B in patients with refractory mycosis. It is also a good alternative for patients who are intolerant to amphotericin B. Posaconazole is effective as an oral step-down therapy in patients with good response to amphotericin B. However, primary therapy with posaconazole is not recommended.[6,47]

Caspofungin is an echinocandin which has shown efficacy against *R. oryzae*.[48] It has shown increased survival in patients of ROCM when given in combination therapy with polyenes.[30,48] Multiple immune augmentation strategies have been proposed for mucormycosis, such as granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage (GM)-CSF, and interferon-γ.[18,35,49]

Prevention

Preventive measures can be targeted to the population at risk, for example, transplant recipients, patients with hematologic malignancy.[2] Although drugs such as fluconazole and posaconazole have been used for prophylaxis against fungal infections in solid organ/hematopoietic stem cell transplant patients, there is no standardization in this regard.[50] Since the prevalence of infection is low even in the population at risk, the

routine use of prophylactic antifungals is not warranted in all such patients. There is a risk of emergence of resistant species and possibility of drug toxicity with prolonged use of antifungal drugs.[51] Simple preventive measures such as modification and control of environment should be undertaken. These include high-efficiency particulate arrestance filter (HEPA filter) treatment of the air supply, maintenance of positive pressure in the wards, banning of flowers and live plants in the wards, and compulsory protective masks.[2] Fungal infections are an often-overlooked clinical and public health issue, and increased awareness by health-care providers and community members regarding disaster-associated fungal infections is required.

Aspergillosis

Aspergillosis is an uncommon infection of the orbit that can affect both immunocompromised and healthy immunocompetent hosts.[19,52] *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus niger* account for most cases of human *Aspergillus* infection. Similar to mucormycosis, the most common mode of orbital infection is from the adjacent sinuses.[53] *A. fumigatus* and *A. flavus* are the most common fungal contaminants of the sinuses.[54] *A. fumigatus* is the most common species affecting immunocompromised patients while *A. flavus* is common in immunocompetent.[55] Noninvasive aspergillosis (allergic fungal sinusitis and sinus mycetoma) rarely involves the orbit. Since they can be precursors of invasive fungal infection of the orbit, they are briefly discussed.

Risk Factors

Total neutrophil count of < 1000/mm^3, T-cell defects (e.g., AIDS), defective phagocytosis, hematologic malignancy, steroids and other immunosuppressive agents, diabetes mellitus, prosthetic devices, trauma, excessive environmental exposure (e.g., nearby demolition or restoration of buildings, yardwork, and compost heaps), residence in endemic area (e.g., Sudan), and advanced age are some of the risk factors for orbital aspergillosis.[54,56] Burn patients and those with occlusive dressings are at risk because of the predilection of this fungus to warm and humid environment and loss of tissue integrity.[13] Smoking-contaminated marijuana increases the risk for development of sino-orbital aspergillosis, particularly in immunocompromised patients.[1,4]

Clinical Features

Noninvasive aspergillosis

Immunocompetent patients may harbor either fungal balls (sinus mycetoma) or present with allergic sinusitis with signs and symptoms of allergic rhinitis, chronic sinusitis, and nasal obstruction. Orbital involvement is rare in noninvasive aspergillosis. Proptosis, secondary to expansion of the sinus cavities, may be seen.[2]

Invasive aspergillosis

By definition, tissue invasion by fungal elements is seen in invasive sino-orbital aspergillosis. Although invasive aspergillosis chiefly occurs in immunocompromised hosts, a great degree of suspicion should also exist in case of healthy patients as recent reports suggest that it is not so infrequent after all.[57]

Clinical features of orbital aspergillosis are highly variable leading to misdiagnosis and inappropriate management. The initial diagnosis in these cases has been reported as bacterial orbital cellulitis, idiopathic orbital inflammatory disease, temporal arteritis, sino-orbital malignancies, and even rhabdomyosarcoma.[57] Fungal etiology must be ruled out before initiating steroid therapy in any patient presenting with painful proptosis. Patients presenting with severe and persistent headache or retrobulbar pain may be harboring invasive aspergillosis of the sphenoid sinus and may be misdiagnosed as temporal arteritis and treated with steroids.[58]

Invasive sino-orbital aspergillosis in an immunocompromised host without AIDS presents with acute proptosis with severe pain and visual loss. There may be very minimal clinical signs of orbital inflammation.[59] Patients with AIDS, on the other hand, typically present with headache, periorbital pain, gradual proptosis, and limitation of ocular movements over a period of weeks to months. They usually do not experience visual loss.[4] Areas of black eschar which may otherwise indicate a mucor infection may represent *Aspergillus* in the late stage.[53]

Bilateral orbital involvement may be seen even in immunocompetent patients.[57] Although concurrent sinus involvement is characteristic (rhinorrhea, epistaxis, epiphora, and nasal stuffiness), patients' symptoms may not always implicate sinus involvement, thereby adding to the dilemma.

Investigations

Anterior rhinoscopy, examination of the hard palate and gingiva, and palpation over the sinuses may demonstrate paranasal sinus disease in patients with otherwise unexplained orbital processes.[53]

Imaging

CT scans show heterogeneous soft tissue masses with calcification and bony erosion [Fig. 5a]. This heterogeneous image may be due to the presence of iron, calcium, or manganese in the fungal concretions.[19] MRI shows contrast-enhancing masses that are hypointense both on T1- and T2-weighted images. In contrast, neoplasms and bacterial infections show hyperintensity on T2-weighted images.[19] MRI gives better details in areas such as posterior orbit, optic nerve, and cavernous sinus. MRI also detects enhancement of optic nerve and cerebral dura adjacent to involved paranasal sinuses, frequently seen with aspergillosis[60] [Fig. 6a and b]. However, CT is the preferred initial imaging of choice because of its ability to image bone and also to differentiate tissues (air, mycetoma, and hemorrhage), which otherwise give almost similar low intensities on T1- and T2-weighted MRI images.[61]

Fine needle aspiration biopsy may help in the diagnosis of orbital aspergillosis, especially if the patient is too debilitated to undergo surgery.[53] Lesions extending up to superior orbital fissure and cavernous sinus can be biopsied under CT guidance, with the help of a neurosurgeon. In general, classical biopsy techniques are preferred because of their ability to provide large amount of samples under controlled conditions[53] [Fig. 5b]. Specimen should be then sent for direct microscopic examination under KOH and calcofluor white. Typical *Aspergillus* hyphae are septate with uniform width and dichotomous branching approximately at 45°[62] [Fig. 7]. The fungi can also be identified on H and E and GMS stains. False negative results from biopsy specimens have been reported; several authors have emphasized on repeat biopsy after a

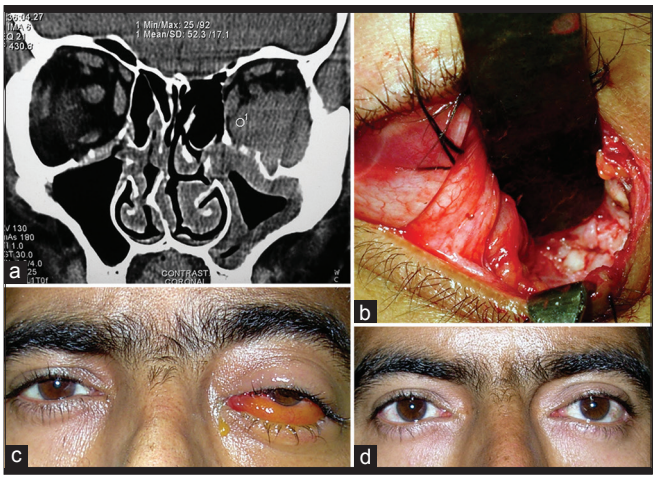

Figure 5: (a) Coronal computerized tomography scan of patient showing soft tissue in the left orbit occupying both extra- and intra-conal space. The inferior and lateral recti are not identified separately. Erosion of posterolateral wall of maxillary sinus with diffuse mucosal thickening seen, (b) incisional biopsy through transconjunctival approach: Intraoperative photograph showing typical grayish-white firm avascular mass filling the orbit, (c) patient at presentation with proptosis, congestion, and chemosis, (d) patient after completion of 12 weeks of voriconazole and resolution of symptoms

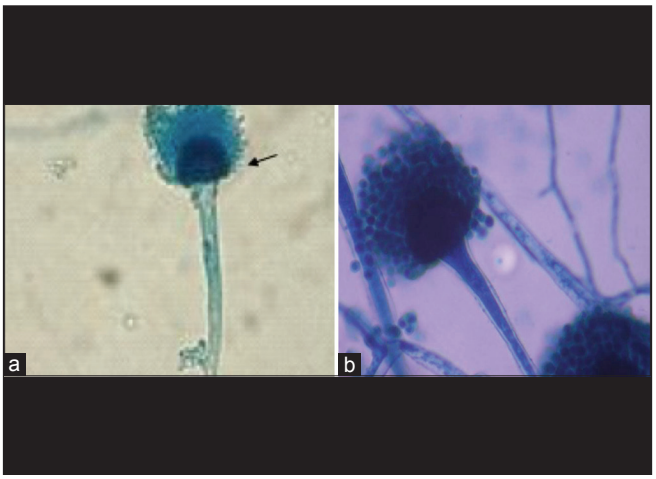

Figure 7: Aspergillus hyphae showing septae with uniform width and dichotomous branching at 45°. (a) Lactophenol cotton blue-stained mount of *Aspergillus fumigatus*, (b) lactophenol cotton blue slide mount of *Aspergillus flavus*

negative result, in cases with strong clinical suspicion.[1,63] *Aspergillus* is routinely grown on Sabouraud's dextrose agar. *A. fumigatus* colonies are gray-green, *A. flavus* are yellow-green, and *A. niger* are black[53] [Fig. 8]. Newer serological techniques such as estimation of serum galactomannan (GM) and beta-D-glucan (BG) have found a new place in the diagnosis of invasive aspergillosis.[64,65] BG is found in the cell wall of many fungi, with the exception of *Zygomycetes* and *Cryptococcus*. However, GM is found in the cell wall of *Aspergillus* spp. The revised guidelines by the European Organization for the Research and Treatment of Cancer/Mycoses Study Group include serum GM as one of the diagnostic criteria for invasive Aspergillosis.[66] The sensitivity and specificity of serum GM is estimated to be 79–94% and 81–86%, respectively.[64] Although

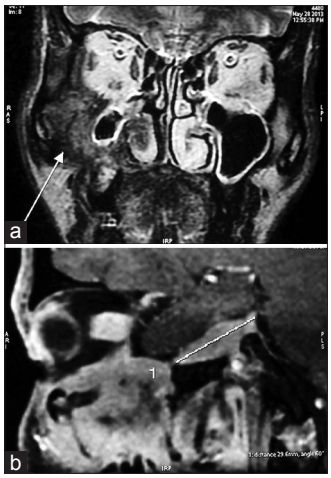

Figure 6: (a) Coronal and (b) sagittal magnetic resonance imaging showing an ill-defined hypointense enhancing lesion in the right maxillary sinus (white arrow) causing erosion and extending into right pterygopalatine fossa (line)

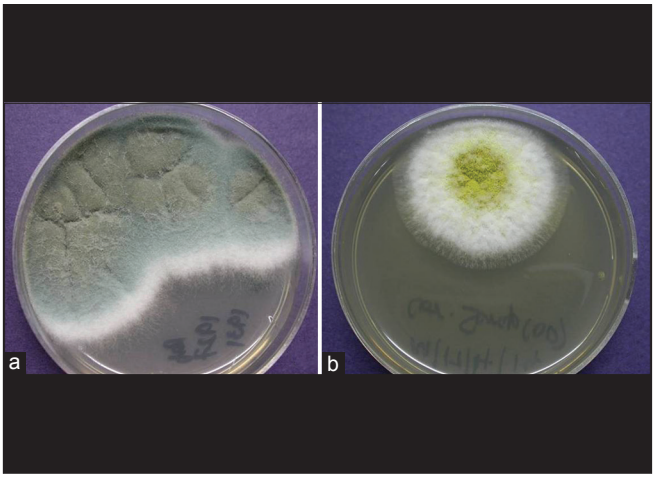

Figure 8: Aspergillus colonies grown on Sabouraud's dextrose agar. (a) Gray-green *Aspergillus fumigatus* colonies, (b) colonies of *Aspergillus flavus* are yellow-green

PCR for *Aspergillus* antigens has been available for more than 20 years now, its clinical utility has been limited due to lack of standardized techniques.[64,66] Nonetheless, further development in PCR techniques provides hope for achieving a rapid, highly specific, and sensitive diagnostic test with precise identification of species.[64,65]

Management

Allergic sinusitis with or without orbital involvement

Patients are usually immunocompetent. Management includes surgical debridement of the involved sinuses followed by systemic and topical corticosteroids. Systemic antifungals are usually not needed.[67,68]

Fungal ball or aspergilloma

This condition is also seen in immunocompetent individuals. Management is surgical debridement of the involved sinus with aeration of the involved sinus. Systemic and local antifungals are not needed as the condition does not lead to orbital invasion.[68]

Invasive sino-orbital aspergillosis in immunocompetent individuals

Incisional biopsy with microbiological and histopathologic examination of specimens is paramount for diagnosis. Fungal culture and microbiological analysis will aid in the identification of species.[57] Currently, there are no universal guidelines for the treatment of invasive aspergillosis. Conventional therapy suggests use of systemic amphotericin B followed by oral azoles.[57,69] Oral itraconazole can be instituted after completion of parenteral amphotericin B or can be considered as an alternative therapy in patients who cannot tolerate amphotericin B.[46,62,70] Oral voriconazole is equally effective. In fact, in a recently randomized trial by Herbrecht *et al*.,[71] the authors concluded that primary therapy with voriconazole led to better response and improved survival with fewer side effects than conventional use of initial treatment with amphotericin B. The authors recommend intravenous voriconazole 6 mg/kg body weight twice on day 1, followed by 4 mg/kg for 1 week, and then switching over to oral voriconazole 200 mg twice daily for 12 weeks.

There is no consensus regarding surgical debridement or exenteration in cases of invasive sino-orbital aspergillosis. Some authors recommend exenteration in all patients with retrobulbar or apical involvement[63] while others recommend less aggressive debridement.[72] While debridement definitely helps in reducing the fungal load and improving delivery of and response to antifungal therapy, not all patients require surgical treatment. Conservative prolonged medical therapy alone has been reported to have achieved high cure rates without recurrence[57,62] [Fig. 5c and d].

Invasive sino-orbital aspergillosis in immunosuppressed individuals

Reversal of immunosuppression is the primary therapy in such cases. Treatment is otherwise similar to as in immunocompetent patients. Exenteration may be needed in advanced cases.[53] Prognosis is poor if immunosuppression cannot be reversed. Adjuvant local irrigation of amphotericin B with indwelling catheters is recommended to improve survival.[1,73] There has been one report of good response to intralesional amphotericin B used in isolation, without limited debridement or exenteration.[74]

Other fungal species which may rarely cause orbital infections are *Candida*, Scedosporium, entomophthoramycosis, blastomycosis, and histoplasmosis.[19,75-79]

Conclusion

Fungal infections of the orbit, though rare, are a cause of significant morbidity and mortality, especially in immunocompromised and debilitated individuals. An ophthalmologist should have a high index of suspicion of fungal infection as delay in diagnosis and improper management is the cause for increased morbidity and mortality. In both immunocompromised and immunocompetent patients with orbital pathology, fungal infection should be considered when the presenting features are unusual or patient is not responding to standard therapy. Newer techniques in detection, safer modalities of antifungal treatment have brought in a paradigm shift in management from aggressive surgery and exenteration to sight and globe-conserving measures. In addition, preclinical research in immunomodulation therapies for fungal infections has shown promising results, further escalating hope for a definitive cure.

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Conflicts of interest

There are no conflicts of interest.

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