Fungal Sinus Disease

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Introduction

Fungi are made up of several thousand species of eukaryotic spore-bearing organisms. More than 60,000 species of fungi are known. Fungi reproduce by both sexual and asexual means. Fungi are eukaryotic and are usually filamentous; they have no chlorophyll; cell walls are made of chitin. Two major groups of organisms make up fungi.

(a) Unicellular fungi are called yeasts.
(b) Filamentous fungi are called moulds

Yeast is unicellular and reproduces by budding; moulds coalesce as colonies of intertwined hyphae referred to as mycelia.

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Of the 60,000 fungal species, only about 300 have been documented as playing a definitive role in causing disease in humans. These fungal pathogens largely belong to three major groups. They are (1) Zygomycetes, (2) Aspergillus species and (3) various Dematiaceous genera.

Fungi are ubiquitous organisms and reside primarily in the entire respiratory tract. Microscopic colonisation by fungi of the nose and paranasal sinuses can be found in both the normal and in the diseased states.

Diagnosing Fungal (Mycotic) Infections

Confirmation and identification of mycotic infection may require a combination of diagnostic studies (Table 27.1). Fungi are difficult to culture, and growth is often negative. However, PCR (polymerase chain reaction) of the sinus mucus is much more likely to detect and identify a pathogenic fungus [1, 2].

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Table 27.1 Diagnostic methods for detecting and identifying fungi

Investigation	Comments
Microscopy of fresh clinical specimens	Potassium hydroxide (KOH) preparations or Calcofluor white stains help identify the presence of fungi
Histopathology	Tissue samples retrieved from the affected area Frozen section should be considered for necrotic material and tissue biopsies Evidence of fungal invasion confirms the presence of 'invasive fungal rhinosinusitis'
Culture	Fungal cultures take a considerable period of time A positive culture may be present when invasive fungal infection is absent Cultures will identify a specific fungus and guide antifungal medication
Serology	
Polymerase chain reaction tests	
Radiological imaging	

Mycotic Infection

Fungal infections can pose major medical challenges [3]. The incidence of mycotic infection and the number and diversity of pathogenic fungi have all increased exponentially in recent times.

Five categories of fungal entities are recognised:

- Saprophytic colonisation
- Fungal balls (mycetomas)
- Allergic fungal rhinosinusitis
- Chronic invasive (granulomatous and non-granulomatous disease)
- Acute invasive

True fungal infection is subdivided into noninvasive and invasive, and manifestations may overlap or progress from noninvasive to an invasive form. The latter is a particular risk with a decline in host immunity, and the latter should always be considered and assessed. Compromise of the immune system greatly increases the risk of fungal infection. Immune competent individuals were previously considered as having no risk of progressing to invasive disease, but this is no longer true. In 2020, significant numbers of immunocompetent COVID-19 patients developed serious fungal infection, often caused by *mucormycosis*, especially following the use of high-dose corticosteroids.

How Do Fungi Cause Disease?

To cause an infection, the fungus has to first gain access via a portal of entry, attach to cells and grow within the host. They must be able to replicate at 37 °C, obtain nutrients and evade natural defence mechanisms [4]. For dimorphic fungi, this also means transformation of an initial morphologic conversion to a tissue form of growth.

The outcome of inhaling fungal spores depends upon several factors:

- The number and size of inhaled spores
- The integrity of the nonspecific and specific host defences
- The virulence/pathobiological potential of the particular fungus

Pathogenesis of Inflammation from Fungal Disease

1. Some fungi are capable of colonising epithelial tissues surfaces without causing invasive manifestations. Fungal rhinosinusitis is often characterised by colonisation rather than invasion. Colonisation induces profound inflammatory and immune responses resulting in severe damage to the host.
2. Occasionally, fungi cause serious human disease by producing potent toxins and mutagens.
3. Less potent fungal irritants and enzymes also attack host cells leading to inflammation or immunopathology.
4. Fungal cell wall antigens can also stimulate an allergic response in the host [5].

The status of the host immunity will ultimately determine whether the individual at risk will develop non-invasive or invasive fungal rhinosinusitis, and conditions like diabetic ketoacidosis serve to promote the latter.

Prevention and Prophylaxis of Fungal Infection

Prevention of fungal sinusitis in the immunocompromised patient includes:

- Minimising exposure to the fungi most likely to cause rhinosinusitis
- Using prophylactic antifungal agents to diminish the risk of tissue invasion

Risk Factors

Patients with haematologic disease are at risk during the neutropenic phase. The duration of neutropenia is the most important risk factor in leukaemic patients, but this risk increases with corticosteroids, broad-spectrum antibiotics and the choice of chemotherapeutic agents.

Bone marrow transplant recipients are at greatest risk in the immediate post-transplant period before engraftment and in graft-versus-host disease (GVHD). Chronic GVHD is associated with increased risk of invasive aspergillosis, especially with corticosteroid use [6, 37].

Prevention

The Environment

Fungi are ubiquitous, but exposure levels may increase in certain situations such as building work on old properties.

Hospital outbreaks are associated with direct contamination of the ventilation system, as may occur with demolition or constructive projects in or near to the hospital [7].

Hospital ventilation systems ducts should be cleaned regularly to prevent transmission of filamentous fungi, especially in units caring for immunosuppressed patients. High-efficiency particulate air (HEPA) filtration is recommended, but laminar airflow is not.

Prophylactic Antifungal Medications

Prophylaxis should be limited to patients likely to develop infection and should be given only during period of maximum risk.

The prophylactic drug should target the most likely fungal organism. As *Aspergillosis* species is the most common pathogen, medication should be directed at this pathogen [8]. Patients most at risk are those with haematologic malignancies and prolonged neutropenia and those who undergo bone marrow transplantation. The use of fluconazole to prevent invasive candidiasis in bone marrow transplant recipients has been a hugely successful advance.

Patients undergoing intense chemotherapy or bone marrow transplantation who have suffered a previous attack of aspergillosis are particularly at risk of infection, and whilst secondary prophylaxis is recommended, a third will develop a relapse of aspergillosis [9].

With regard to rhinosinusitis and immunotherapy, it is important to identify, diagnose and treat any sinus pathology before commencing immunosuppressant treatment. Sinus disease should be excluded or identified by radiological imaging scans. Rhinosinusitis following immunosuppressive therapy is more likely to occur with long-term antibiotic use, indwelling catheters, nasal intubation, systemic steroids and metabolic abnormalities [10].

Fungal Balls (Mycetomas)

Fungal balls, previously known as aspergillomas, are composed of matted fungal hyphae, typically within a single sinus.

Pathogenesis

A fungal ball is a non-invasive extra-mucosal condition that is typically unilateral and most often found in the maxillary sinus, followed by the sphenoid sinus. They are more common in older women but not described in children [11].

The histology characteristically shows a non-granulomatous inflammatory mucosal reaction with a tangled mat of fungal hyphae within the debris, most often caused by an overgrowth of *Aspergillus* spp.

This fungal overgrowth begins with persistent germinating fungal spores within the nasal cavity and paranasal sinuses. Aetiological factors include dental paste, amalgam and the presence of ferritin and zinc within the sinus lumen.

Fungal balls can form a community with bacteria to form bacterial or mixed balls; double balls describe a combination of a fungal ball and a bacterial ball coexisting within the same sinus [12]. Mixed balls are more likely in chronic rhinosinusitis and immunocompromised patients. Persistence of a fungal ball, despite adequate surgery, can occur secondary to a biofilm [13].

Patients are generally immune competent, but should they become immunocompromised, the condition can become invasive [14].

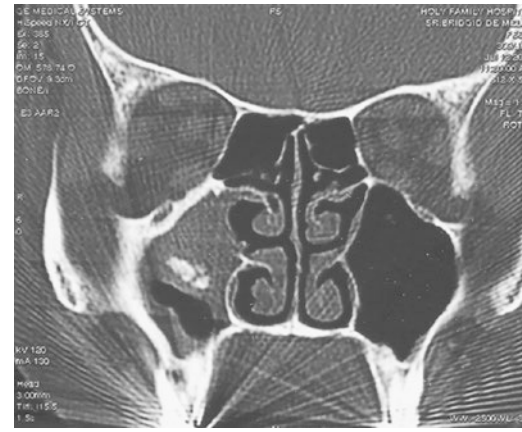

Fig. 27.1 Coronal view of a CT scan showing the typical appearance of a fungal ball in the right maxillary sinus as a hyperintense mass

Clinical Features

Symptoms normally include nasal obstruction, purulent nasal discharge, dysosmia and facial pain, similar to bacterial rhinosinusitis. Bilateral fungal balls have been described but present with symptoms such as foul odour and severe mucopurulent anterior and post-nasal discharge. Inflammatory polyps arise from the ipsilateral affected side of the nose in 10% of patients. A fungal ball may be associated with a mucocele, foreign body or an antrochoanal polyp.

Fungal balls within the sphenoid sinus can induce local inflammatory effects that cause non-specific headaches and occasionally ipsilateral visual symptoms.

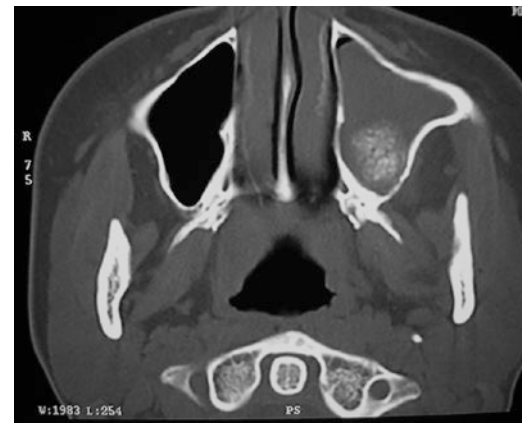

Fig. 27.2 Axial section of a CT scan showing a fungal mass in the maxillary sinus

Radiological Imaging

A CT sinus scan typically shows a heterogenous opacity: radiological features include central radiodense areas, sclerosis of the lateral sinus wall, bone erosion of the inner sinus wall and an irregular surface (Figs. 27.1 and 27.2) [15].

A sinus mycetoma ('fungus ball') may appear on CT as a mass within the sinus, with accompanying features such as erosion and calcification of the sinus [1]. On MRI, hypointense signal may be obtained from the fungus ball on T1- and T2-weighted scans. This is due to the relatively low free water content of the mycetoma.

In invasive disease, specific radiological signs may be seen. In the acute phase, it may be difficult to appreciate signs on CT scanning. If seen, non-contrast CT changes may include hypoattenuation of the mucosa and fat stranding beyond the sinuses. These features are not diagnostically specific, and CT changes should be correlated with the clinical picture. CT scanning is useful for assessing bony involvement. If localised bone destruction has occurred, we may see evidence of intracranial and intraorbital spread.

However, evidence of disease spread beyond the mucosa may be more easily appreciated on

MRI; thus, this is the modality of choice to assess invasion. Fat stranding and soft tissue involvement may be better visualised. Common locations to find fat stranding (on both CT and MRI) include intraorbital, masticator space and pterygopalatine fossa. MRI scanning can also help to identify important complications of invasive disease, such as meningitis, intracranial abscesses and cavernous sinus thrombosis.

Chronic invasive disease may demonstrate iso- or hyperdensity in the sinus spaces on CT, when compared to muscle tissue. Hyperdensity is not usually seen in the acute phase. T1- and T2-weighted MRI imaging may show low signal intensity.

Management

The definitive treatment of a fungal ball is surgical removal and clearance of the fungal debris from the sinus lumen (Fig. 27.3). Endoscopic surgery is usually effective, even if bacterial balls coexist, and is often combined with saline irrigation [16]. Recurrence is rare.

Should a patient be asymptomatic, the need for surgery could be questioned. However, surgery will confirm the diagnosis and prevent later problems should bacterial infection supervene. It may also prevent aggravation of asthma.

Surgery is indicated in symptomatic patients or those with immune suppression where a risk of invasive fungal disease exists.

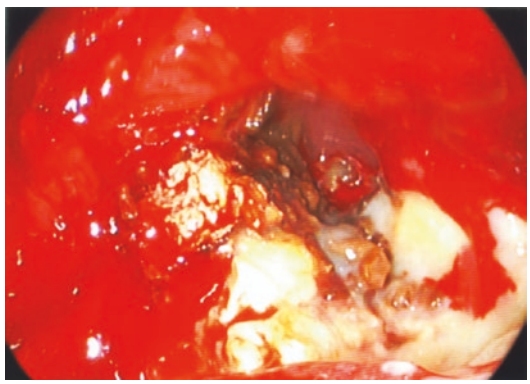

Fig. 27.3 Intraoperative appearance of the whitish mass of the fungal ball being evacuated from the maxillary sinus

Allergic Fungal Rhinosinusitis (AFRS) or Eosinophilic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) was introduced in 1989 to describe a constellation of unusual findings in a unique group of patients suffering from chronic rhinosinusitis [17]. Fungal species of the dematiaceous species are the most common cause of AFRS.

The prevalence of AFRS is approximately between 5 and 10%, especially in younger age groups from 23 to 42 years. Paediatric patients present in a similar way as adults with AFRS. Patients with AFRS are, by definition, atopic; 27% show sensitivity to aspirin; about a third to half of patients have asthma [18, 19]. The condition is much more likely to be seen in hot humid environments and is unusual in cooler temperate climates.

Pathogenesis

AFRS is believed to have an aetiology, similar to that of allergic bronchopulmonary aspergillosis (ABPA).

AFRS is initiated when an atopic individual is exposed to an antigenic stimulus by inhaled fungi. The immunological response induces an intense eosinophilic inflammatory reaction that causes gross mucosal oedema, stasis of secretions and inflammatory exudates, obstructing sinus ostia, creating an ideal environment for fungi to proliferate. Antigenic exposure is thus increased, and the cycle becomes self-perpetuating.

The immunology is very similar to that of ABPA.

- A type 1 (IgE) and type III (IgG-antigen immune complexes) Gell and Coombs reaction takes place [20, 38].
- The Th2 CD4+ subpopulation of T cells, which are prominent in atopic IgE-mediated disease, cause escalation of inflammation.
- Interleukins 4, 5, 10 and 13 are released by the T cells: IL-10 suppresses the alternative Th1 response; IL-4 and IL-13 increase class switching of B cells to produce IgE molecules;

IL-3 and IL-5 enhance eosinophil maturation and activation.

A characteristic of the condition is allergic or eosinophilic mucin that propagates the allergic process. Secondary bacterial infection may occur, but fungi do not invade the underlying mucosa. Charcot Leyden crystals and fungal hyphae within a background of eosinophilic mucus are typical of AFRS.

Aspergillosis also impairs the hosts mucosal defences by suppressing the macrophage and T-cell response.

Clinical Features

Most patients with AFRS are young, atopic and immunocompetent [21]. AFRS is a subset of chronic rhinosinusitis with nasal polyposis in which all affected patients have nasal polyps, and these are typically extensive. Thick inspissated almost solidified eosinophilic mucus is characteristic of the condition. The condition can be exacerbated by septal deviation and turbinate hypertrophy. Unilateral disease is common and has been described in almost half of AFRS patients (now classified as a phenotype of primary localised chronic rhinosinusitis).

The ideal diagnostic criteria for AFRS are as follows:

1. Excessive eosinophilic mucin containing non-invasive fungal hyphae
2. Nasal polyposis
3. Characteristic CT scan radiographic findings
4. Positive fungal stain or culture
5. Type 1 hypersensitivity

Other typical characteristics of AFRS include the presence of asthma, unilateral disease, bone erosion shown on the CT scan, positive fungal culture, Charcot Leyden crystals and serum eosinophilia. Whilst the diagnostic criteria listed above seem clear, in practice, things may be not so simple. Patients often demonstrate all of the clinical characteristics, including the cheesy concretions that suggest fungal disease, but fungi are not always identified on staining or culture. This may be reflective of sampling and laboratory techniques but does cause a diagnostic dilemma and sometimes a pragmatic approach is required. Also, not all patients demonstrate allergy to fungi, but the term 'Allergic' FRS is so well established that it has been retained (EPOS2020).

Salient diagnostic investigations include:

Blood tests:

- Eosinophil count (eosinophilia 500+ cells per microliter; normal 100 - 500 cells/mcl)
- Total serum IgE (normal range 150 - 1000UI/L but commonly accepted normal 150 - 300UI/L)
- Antigen-specific IgE for fungal and other inhalant allergens
- Fungal antigen-specific IgG
- Precipitating antibodies for Aspergillosis (IgG precipitins)

Skin prick:

- Assessment of a range of inhalational allergens including fungal allergens

Histology:

- Microscopic evaluation of the mucin evacuated during surgery

Culture:

- Fungal culture of the mucus/debris evacuated during surgery

Radiological Imaging

The gradual accumulation of allergic fungal mucin gives AFRS a characteristic pattern on the CT sinus scan. As the mucus accumulates, the involved paranasal sinus begins to resemble a mucocele. The central high attenuation can at times be described as 'starry sky', 'ground glass' or a 'serpiginous' pattern. Sinus expansion and bone erosion are common features.

Management

The treatment of AFRS is thorough endoscopic clearance of polyps and eosinophilic mucin, combined with intensive long-term medication. The principle of surgery in AFRS is to provide sinus ventilation and drainage. However, surgery will not completely eradicate disease, and multiple operations may be necessary. This has subsequently led to variations in opinion as to how radical surgery should be.

Whilst some encouraging results have been described with the use of topical antifungal therapy, their use is inconclusive.

Core Message
The goals of surgery are:

- *To remove all mucin and fungal debris from within the sinuses*
- *To create permanent drainage and ventilation of affected sinuses*
- *To preserve the integrity of the underlying mucosa*
- *To provide access to facilitate removal of debris and mucin from previously inaccessible areas within the nose and sinuses*

Chronic Invasive Fungal Rhinosinusitis

Chronic invasive fungal rhinosinusitis typically occurs in healthy immunocompetent individuals. Fungi reside in all sections of the respiratory tract [22]. Some authors [23] have further divided the chronic form into granulomatous and non-granulomatous forms.

Pathogenesis

Whilst there is general agreement that Aspergillus is often a secondary invader of a diseased sinus, it is not clear why certain immunocompetent individuals develop invasive disease. Some speculate that a hot dry climate in individuals with nasal obstruction predisposes to Aspergillus infections. Others believe that anaerobic conditions in the sinus, caused by repeated inflammation, predispose the patient to invasive fungal disease.

The condition can be granulomatous or non-granulomatous. The formation of a granuloma requires an indigestible organism and cell-mediated immunity to be directed towards the inciting agent.

Granulomatous chronic invasive fungal rhinosinusitis: This has been described as granulomas composed of eosinophilic material surrounded by fungus, giant cells, variable lymphocytes and plasma cells [24].

Non-granulomatous chronic invasive fungal rhinosinusitis: This is characterised by tissue necrosis, dense fungal hyphae and scanty inflammatory infiltrate. The fungi in this form may breach mucosal barriers to invade blood vessels or just cause arteritis without vascular invasion.

Ultimately both granulomatous and non-granulomatous forms can result in tissue necrosis.

A new classification, based on mucosal invasion in the absence of angioinvasion, has implications on the use of adjuvant antifungal therapy [25]. Histology of the sinonasal mass typically shows periarterial invasion, without direct involvement of fungal elements or no true vascular invasion. Three histological variants are described:

- Proliferative (granulomatous pseudotubercles in a fibrous stroma)
- Exudative necrotising (with prominent foci of necrosis)
- Mixed

Patients suffering from chronic invasive rhinosinusitis are usually immunocompetent. Extensive investigation to uncover any hidden immunological abnormality has proved negative, and no specific immunological defects have been detected. However, patients with the granulomatous type of disease have been shown to have a cutaneous type 4 hypersensitivity (delayed skin reaction) to aspergillus antigen that is not demonstrated in those with non-granulomatous disease [24].

Clinical Features

Patients typically present with a history of chronic rhinosinusitis symptoms, respiratory tract allergies or nasal polyposis. Symptoms may take months even years to present.

Nasal examination reveals severe nasal congestion, polypoid mucosa, a soft tissue mass that is usually covered with debris or thick inspissated nasal secretions.

Radiological Imaging

An early CT sinus scan is recommended in the initial stages of the disease. Fungal colonisation induces focal or diffuse areas of hyper-attenuation within a sinus. Characteristic features of the invasive process include bone erosion or expansion.

MR imaging is useful to determine if dural involvement or invasion has taken place. Differentiation between a malignant neoplasm and chronic fungal rhinosinusitis may be difficult and should be confirmed by biopsy and histopathology.

Management

The current recommendation is that surgery to remove all diseases where feasible is indicated for both granulomatous and non-granulomatous invasive fungal disease. Surgery should be followed by prolonged courses of amphotericin B and itraconazole.

Whilst the granulomatous form responds well to surgery, it has been suggested that the non-granulomatous form responds best to an aggressive surgical approach [26, 27].

Core Message

There is no general agreement on the extent of surgery necessary to control, arrest or eradicate chronic invasive rhinosinusitis. Neither is it clear if the granulomatous form be treated differently from the non-granulomatous form.

Treatment and outcomes depend on the correct identification of the fungus as well as the specific treatment measures administered.

Invasive Fungal Rhinosinusitis in the Acquired Immunodeficiency Syndrome (AIDS)

The increasing prevalence of AIDS has left patients suffering from this problem at great risk of suffering from fungal infections. Since these patients are immunocompromised, the infections that they suffer are usually serious and have poor outcomes.

Aspergillosis is the most common pathogen in AIDS patients. It usually causes arterial invasion, thrombosis and subsequent necrosis of tissue. *Aspergillus fumigatus* is the most common pathogen isolate in the AIDS population.

Infection by HIV causes selective depletion of CD4 (T helper) lymphocytes. Although impaired cellular immunity predisposes to fungal and intracellular bacterial infections, phagocytic polymorphonuclear cells and macrophages are the primary defences against fungal infections, killing the mycelial and conidial forms of the fungus. However, AIDS patients demonstrate neutrophil and macrophage dysfunction.

Fungal rhinosinusitis has been found to be associated with advanced AIDS and low CD4 cell counts. Neutropenia is the single greatest factor predisposing to the development of invasive fungal sinusitis in patients suffering from AIDS [28].

Core Message

In immunocompromised patients suffering from AIDS and invasive aspergillosis infection, the treatment outcomes improve once the infection has been identified and effective treatment has commenced.

Acute Invasive Fungal Rhinosinusitis

Acute invasive fungal rhinosinusitis is a term used when vascular invasion is the predominant histopathological feature, and the duration of the disease is less than 4 weeks [29]. Patients present with acute invasive rhinosinusitis and are frequently found to be immunologically compromised. A new phenomenon seen during the COVID-19 pandemic was a significant rapid increase of mucormycosis in India, caused probably by the temperate climate, over-the-counter systemic steroids, diabetes mellitus and other immunosuppressants.

Aspergillosis

Aspergillosis refers to several forms of disease caused by dissemination of airborne fungal spores in the genus *Aspergillus* spp.

Pathogenesis

Aspergillosis spores enter the body primarily through inhalation but can also lodge in the eye and ear. Immune suppression is crucial in the susceptibility of this disease, and the increase in organ transplantation has greatly increased the number of patients vulnerable to fungal infections. Transplant recipients, particularly those receiving bone marrow and heart transplants, are highly susceptible to infection by aspergillosis.

Clinical Features

The condition lacks distinctive symptoms and is probably underdiagnosed and under-reported. It primarily affects the lungs but can lead to disease in the nose, paranasal sinuses, eyes and ears. The severity of illness is variable, but it can be significant and lead to death.

Radiological Imaging

Affected patients will need the usual combination of CT scans and MRI scans.

CT scanning is the imaging modality of choice. Typically, radiodensities with calcification in it are very suggestive of aspergillosis [30]. Bony erosions are also seen. Frequency sites involved are the maxillary sinus, nasal cavity, ethmoid sinuses and last the orbit and cavernous sinuses. Cone bean CT scans used by dentists have been found to be useful in the diagnosis of asymptomatic aspergillosis infections that are discovered as incidental findings [30, 31].

Management

Treatment of aspergillosis will depend upon the form of aspergillosis. In patients with a mycetoma, amphotericin B is the first line of treatment, and surgery is likely to be indicated.

Serum galactomannan measurements facilitate early diagnosis and also helps discriminate various fungal species, with levels being high in aspergillosis but not in mucormycosis [32].

The prognosis will depend on the underlying medical condition: if the problem is primarily an allergic response, then the patient should respond to systemic steroids, but the prognosis of invasive aspergillosis is quite poor.

Mortality rates range from 50 to 95%, with the higher mortality risk affecting patients with bone marrow transplants those with AIDS.

Mucormycosis

Mucormycosis is a term used to refer to any fungal infections of the order Mucorales which belong to the class of Zygomycetes. *Rhizopus oryzae* is the predominant pathogen and accounts for 60% of all forms of mucormycosis. It accounts for 90% of rhinocerebral mucormycosis.

Mucormycosis rarely affects a healthy individual but is likely to affect diabetics or immunocompromised patients [33].

Pathogenesis

All fungi of the order Mucorales reproduce sexually as well as asexually. Members of the family Mucoraceae have characterised sporangia which envelops numerous asexual spores.

Mucormycosis may have an acute fulminant course or a slower indolent invasive course. When immunocompromised is not easily reversible, then the course of the disease is aggressive and rapid.

Diabetics presenting with ketoacidosis are disproportionately affected [34]. Rhizopus organisms have an active ketone reductase system and thrive in high glucose acidotic conditions. Diabetics also have decreased phagocytic activity because of an impaired glutathione pathway. Normal serum inhibits the growth of *Rhizopus*, whereas diabetic ketoacidosis stimulates growth [35].

Patients on dialysis treated with deferoxamine B(DFO), an iron and aluminium chelator, are more susceptible to mucormycosis.

Other risk factors are prolonged neutropenia, long-term systemic steroid therapy, protein calorie malnutrition, bone marrow transplantation, immunodeficiency, leukaemia and intravenous drug users.

The relative infrequency of mucormycosis in AIDS reflects the ability of neutrophils to prevent growth of the fungus.

Histological Investigations

Blankophor and Calcofluor white are fluorescent whiteners that bind to chitin and cellulose and fluoresce when exposed to ultraviolet light.

A diagnosis of mucormycosis can be made on histological examination of specimens from a diseased patient but can be difficult and challenging. Histopathology demonstrates that the fungus has a distinct predilection for vascular invasion and predominantly arterial invasion.

Broadband ribbon like hyphae 10–20 microns branched haphazardly along with the absence of septations. Mucor stains easily with haematoxylin and eosin stains. To confirm the presence of a fungal infection, nonpigmented hyphae showing tissue invasion must be demonstrated. This can be seen on tissue sections stained with haematoxylin-eosin (HE), periodic acid Schiff (PAS) or Grocott-Gomori methenamine-silver (GMS) stains. The historically described 90° branching angle of Mucorales in tissue versus the 45° branching angle of septate moulds can at times be difficult to identify because of tissue processing during staining.

Clinical Features

The leading symptom is fever. This is quickly followed by ulceration in the nose followed by necrosis, periorbital, facial swelling or decreased vision (Figs. 27.4 and 27.5). Ultimately, approximately 80% develop a necrotic lesion on the nasal mucosa. Facial numbness is also present in some patients. The significance of anaesthesia of the affected facial areas is an early sign of invasive mucormycosis. Cutaneous and soft tissue involvement by mucormycosis is a common manifestation of the disease in immunocompetent patients.

Headache, fever, proptosis and blackening of tissues in and around the nose are very typical of Mucor infections.

In addition to the clinical features, the diagnosis of Mucor is dependent on radiological imaging, mycological investigations and biopsies for histology.

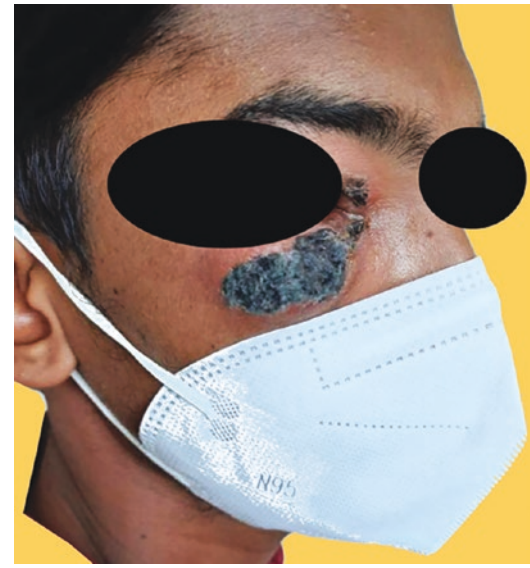

Fig. 27.4 Mucor involving the skin of the cheek and nasal cavity and also extending into the eye. The patient is not obviously obtunded. The patient had COVID 19 and was treated with high doses of steroids for a prolonged period of time. Surgical debridement along with antifungal medication was the treatment modality given

Fig. 27.5 A patient suffering from extensive mucormycosis. The patient suffered from COVID-19 and was treated with high doses of steroids. The patient succumbed to the disease

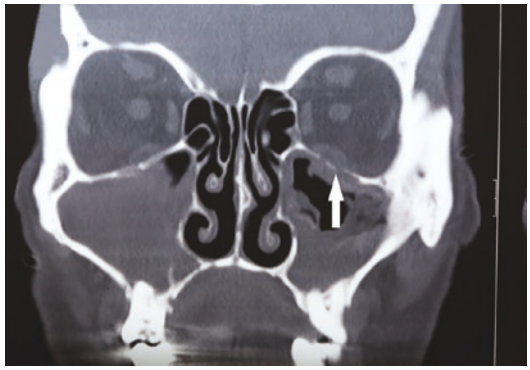

Fig. 27.6 CT scan of a patient suffering from mucormycosis. The white arrow points to the erosion of the orbital floor by the fungus. Of note is the normal looking nasal cavity even though both maxillary sinuses are involved by mucor

Radiological Imaging

CT scanning is imperative though MRI is much more sensitive (Fig. 27.6).

Management

Surgery alone is not curative, and a combined approach is necessary, including:

- Reversal of immunosuppression
- Systemic amphotericin B, isavuconazole, posaconazole as salvage or second-line treatment
- Repeated aggressive surgical debridement until infection and tissue destruction resolves

Hyperbaric oxygen: This has also been reported to be a useful adjunct and reverses ischaemic acidotic conditions that cause fungal infections to perpetuate. Hyperbaric oxygen is usually given daily for 1 hour at 2 atmospheres and may require up to 30 sessions. Hyperbaric oxygen limits the area of deformity by decreasing the required area of debridement without affecting mortality.

Amphotericin B is fungicidal and the drug of choice but also very nephrotoxic. However, liposomal amphotericin is not nephrotoxic and also well tolerated.

Recently, isavuconazole has been used as first-line medication with good results and posaconazole as a second-line treatment for salvage [36].

Mortality in diabetic patients is dependent on diabetic control; survival ranges from 60 to 90% but decreases to 20% unless impaired immune competence is addressed.

Core Message

The mainstay of therapy is:

- *Reversal of Immunocompromisation*
- *Systemic high dose of amphotericin B with isavuconazole using posaconazole for second-line salvage treatment.*
- *Surgical debridement/nasal toilet of nonviable tissue. This may need to be performed several times.*

Key Learning Points

- Fungi are ubiquitous microorganisms, exposure cannot be avoided, and spores are easily inhaled.
- Host exposure is critical if the immune response is compromised.
- Full assessment requires radiological imaging by CT and MRI scans.
- Invasive fungal rhinosinusitis is typically caused by aspergillosis or mucormycosis.
- The treatment for invasive fungal rhinosinusitis is a combination of repeated surgical debridement and antifungal medication.
- Repeated endoscopic clearance of necrotic tissue and fungal debris is effective.
- Amphotericin B is a nephrotoxic fungicidal, but liposomal amphotericin is safe and not nephrotoxic.
- Isavuconazole and posaconazole are new antifungal azoles.

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