Special Article - Fungal Sinusitis

Paranasal Invasive Fungal Sinusitis and its Central Nervous System Complications: Current Understanding and their Management

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Abstract

Paranasal fungal sinusitis, a relatively less common and frequently misdiagnosed medical entity, is occurring in about 5-50 % cases especially of chronic unremitting paranasal sinusitis. It could be symptomatic or asymptomatic as well as acute or chronic. The diagnosis of invasive or non-invasive paranasal fungal sinusitis is primarily clinical, but imaging studies, histopathology and cultures can be helpful. Modern nasal endoscopy is the choice of procedure which is routinely used for the diagnostic and therapeutic purposes. In cases of fungal sinusitis, there are many variations in their clinical manifestations, progression, ultimate prognosis and resultant complications despite currently available modern management.

Common complications of the paranasal fungal sinusitis are related to local growth characteristics of the fungi and their further spread in the local nasal tissues, oro-pharynx, respiratory passages, orbital cavity and intracranial spaces. Obviously, the fungal invasion through the cranium leads to orbital and intracranial complications of paranasal invasive fungal sinusitis. All these complications need to be recognized as joint medical and surgical emergencies. These complications are although infrequent but most feared ones as these cases are associated with high morbidity and mortality necessitating greater awareness, early recognition and timely diagnosis, attention to details of the co-morbid factors and immediate recourse to management strategies simultaneously with combination of medical therapies & aggressive surgical means/interventions.

The paramount importance of these aforementioned actions cannot be over emphasized in improving the morbidities and mortalities associated with some of the cases of the intracranial and intra-orbital complications: cranial osteomyelitis, orbital apex syndrome, superior orbital fissure syndrome, cavernous sinus thrombosis with ocular nerve palsies, intracranial granulomas, meningitis, meningo-encephalitis, brain abscesses, ischemic and hemorrhagic strokes, and cerebral fungal aneurysm, etc. The newer antifungal drugs besides amphotericin-B such as agents Liposomal amphotericin-B, fluconazole, fluocytosisn, Echinocandins, have significantly improved the clinical results by lowering the hepato-renal and hematological side effects in comparison with the Amphotericin-B along with their better efficacy.

Worst prognosis occurs in cases of vascular invasion of fungal infections causing hemorrhagic or ischemic strokes with cerebral infarction. However, non-invasive over invasive fungal sinusitis, immune competent patients over immune compromised patients and meningitis (due to Cryptococcus or Candida over Aspergillum or Mucor) over other intracranial complications favor relatively better prognosis. In immune-compromised patients, the prognosis is extremely guarded with mortality figures of approximately 85 to 100%.

Keywords: Central nervous system; Paranasal sinuses; Fungal sinusitis; Non-invasive; Invasive; Intracranial; Intra-orbital; Clinical syndromes; Meningitis; Hydrocephalus; Brain abscess; Granulomas; Strokes; New antifungal drugs; Current understanding; Management strategies

Introduction

Sinusitis is basically characterized by an inflammation of the mucosal linings of the paranasal and/ or mastoid air sinuses [1-6]. Para-nasal sinusitis is most commonly caused by non infective agents such as allergens, chemicals & particulate matters, and among the infective micro-organisms, commonly caused by viruses & bacteria. Fungal sinusitis, a relatively uncommon and frequently misdiagnosed medical entity, is occurring in about 5-50 % cases of chronic paranasal sinusitis. The clinical presentation could be symptomatic or asymptomatic (Figure 1). The diagnosis of sinusitis is primarily clinical, but imaging studies and cultures can be helpful as exemplified by the clinical disorder of fungal sinusitis. Nowadays, with modern radio-imaging studies, fungal sinusitis is found to be much more common than previously thought. One of the most significant advances is the development of modern nasal endoscopy which is routinely used to assess the sinuses involved, to obtain secretions for cultures and to take biopsies for histopathology as well as to do an accurate assessment of any local rhino-sinus pathology with a high degree of certainty. In cases of fungal sinusitis, there are many variations in their clinical manifestations, progression and resultant complications along with unpredictable clinical outcome and therefore, their prognosis remain uncertain despite currently available modern management.

Common complications of the fungal sinusitis are related to local growth characteristics of the fungi and their further spread in the local nasal tissues and respiratory passages such as intractable chronic sinusitis, pharyngitis, laryngitis, lung infections etc. Invasion through the cranium leads to orbital and intracranial complications of fungal sinusitis. Although, the intracranial fungal lesions are infrequent; but these are associated with high morbidity and mortality [4-6].

The cranium protects important intra-orbital and intra-cranial structures. Until unless significantly breached, the cranial base remains a firm barrier for the direct fungal spread from the paranasal sinuses into the orbits and the cranial cavity (Figure 2). In less than 5% of cases of chronic fungal sinusitis, the disease spreads to the intra-orbital or intracranial compartment. Direct intracranial spread due to proximity of sinuses and indirect via blood vessels in cases of fungal sinusitis is a serious clinical concern with many challenges in its management [6].

The following intracranial complications of a fungal sinusitis are highly morbid and or life threatening irrespective of the patient

Figure 1: A known case of non-invasive fungal sinusitis with recurrent rhinal inflammation with interval quiescent phases.

Figure 2: T2 weighted MRI scan showing chronic fungal pan-paranasal sinusitis with invasion of the orbit (lamina papyracea) and middle cranial fossa (left sphenoidal wall).

whether he is immune competent or immune compromised: cranial osteomyelitis, orbital apex syndrome, superior orbital fissure syndrome, cavernous sinus thrombosis with ocular nerve palsies, intracranial granulomas, meningitis, meningo-encephalitis, brain abscesses, ischemic and hemorrhagic strokes, and cerebral fungal aneurysms, etc [4,6-11].

Therefore, early detection and management of the fungal sinusitis is of paramount importance to prevent such complications and reduce the incidence of the aforementioned risks. Liberal use of neuro-imaging studies such as CT scanning, MRI scanning, MR angiography, etc should be made. An early recognition and an appropriate medical and surgical management strategies are therefore of paramount importance in improving the overall prognosis in paranasal and CNS fungal infections. Attention to details is needed with higher degree of suspicion in cases of chronic intractable or refractory paranasal sinusitis. Once diagnosed it should be treated on an urgent basis with aggressive surgery with or without anti fungal medical therapy as needed to prevent fatality [4-7]. The clinical disorder of fungal sinusitis, per se, portends a bad prognosis due to invariably delayed diagnosis, disastrous intracranial (whether direct or indirect) extensions and higher rate of mortality.

Worst prognosis occurs in cases of vascular invasion of fungal infections causing hemorrhagic or ischemic strokes with cerebral infarction. However, non-invasive over invasive fungal sinusitis, immune competent over immune compromised patients and meningitis (due to Cryptococcus or Candida over Aspergillum or Mucor) over other intracranial complications favor relatively better prognosis [6].

Historial Features & General Characteristics of Fungi

Historically, Hippocrates is credited with the first description of candidiasis in his book-"epidemics", in which he described white patches in the oral cavity of a debilitated patient [4-20]. The fungal etiology of these thrushes was established in 1840s by Berg and Bennett. Zenkar described the first case of intracerebral candidiasis that had died in 1861. In 1792 in his book, Micheli (a priest and botanist) described Aspergillus to refer to the nine species that microscopically resembled to aspergillum, a perforated globe frequently used to sprinkle holy water during religious ceremonies. However, it was Oppe (1897) who reported the first case of rhino-orbito-cerebral aspergillosis. First case of human zygomycetes infection was described by Kurchenmeister in

Figure 3: Asymptomatic patient of invasive fungal sinusitis with oropharyngeal white patches: colonization with Candida Albicans).

Figure 4: Severe maxillary sinusitis caused by Aspergillus fungi isolated from the secretions localized to the confines of the maxillary sinus cavity.

Figure 5: The contrast CT scan demonstrating a sphenoidal fungal mass with invasion of the skull base, pituitary fossa, cavernous sinus, middle cranial fossa, sub-temporal region, etc.

1855 that isolated nonseptate hyphae from a cancerous lung. In 1943, Gregory described in detail three cases of rhinocerebral zygomycosis. Coccidioidomycosis was first reported by Alejandro Posadas and Robert Wernicke in 1892 and in 1905 Ophuls described first case of coccidioidal meningitis. Blastomycosis by Gilchrist (1894), Histoplasmosis by Darling (1906), and coccidioidomycosis (South American Blastomycosis) by Adolfo Lutz in 1908 in Brazil were well described. Cryptococcus was reported initially by Buses in 1894 and later by Fuglemen in 1901.Smith and Sano were first to report a case of Candida Meningitis in 1933. Gonyea reported three patients with blastomycosis meningitis in 1978.

In general, fungi are cited to be ubiquitously abundant in the environment and some forms have a more restricted geographical distribution than others. More than 300 thousand fungal species are recognized by now and about 3-4 hundred species are found to be pathogenic to humans. Only less than 4 dozen species are implicated in causation of the CNS fungal infections [21-31]. Although many normal individuals are colonized by fungi such as candida (asymptomatic patient with oropharyngeal colonised candida), but their healthy immune system prevents subsequent infection (Figure 3).

Majority of fungi have low pathogenicity and therefore, they rarely infect normal subjects. However, immune-compromised patients, such as with sepsis, diabetes mellitus, prolonged ventilation, oncological therapies, organ transplants, extensive use of antibiotics, HIV, etc are having increasing incidences of opportunistic paranasal and CNS fungal infections. Fungal sinusitis is the inflammation of the sinus mucosa generally caused by certain types of fungi which are commonly soiling the paranasal sinuses such as Aspergillus, Bipolaris, Rhizopus, Candida, Cryptococcus, etc.

True pathogenic fungi (having a restricted geographic distribution, mostly in USA) are Blastomycetes, Coccidioides, Paracoccidioides, Histoplasma, Sporothrix etc. They produce clinical lesions in normal individuals and then provide long term immunity to the patients recovered from the active infections. Whereas the opportunistic fungi (having ubiquitous distribution) are Aspergillus Fumigatus, Candida albicans, Cryptococcus neoformans, Rhizopus arrhizus etc .These fungi usually infect immune compromised subjects and provide no long term immunity to them and therefore, clinical relapse is not uncommon in such cases (Figure 4).

Usually, the inhaled aerosolized fungi initiate a primary fungal infection in the paranasal sinuses and the lungs which is usually self-limiting but may spread to other organs especially in immune compromised subjects. Direct contiguous spread to the CNS occurs from the paranasal sinuses, orbits, petro-mastoid region and retro-pharyngeal area in some patients. Invasive fungal sinusitis (80 % of overall sinusitis related CNS cases) is caused mainly by Aspergillus species (commonest), Mucor (next common), Rhizopus, Cladosporium, Candida, and Cryptococcus. The non-invasive fungal sinusitis is usually caused by the pigmented fungi such as demateacious molds including Curvularia, Bipolaris, Alternaria, Fusarium, Aspergillus, etc in about 20% of the patients presenting with CNS fungal infections or complications.

The fungal sinusitis spread to the central nervous system 21-31 by many ways such as direct extension (Figure 5) through the involvement of the cranium, arterio-venous channels, along the cranial nerves via perineural invasion, through the pores in the cribriform plate of the ethmoid and following exposure of the brain tissues at surgery or trauma. Majority of cases are due to direct extension and next common mode is due to vascular spread. Fronto-ethmoidal fungal sinusitis leads to invasion of the thin cribriform plate and perineural spread via the olfactory nerves to reach anterior cranial fossa and through the thin membrana papyracea to reach orbital cavities. Maxillary sinusitis leads to intraorbital, subtemporal fossa, retroantral area, pterygopalatine area, superior and inferior orbital fissures, cavernous sinuses, carotid vessels as well as the middle cranial fossa; and sphenoidal fungal sinusitis may easily reach and invade central skull base structures such as sella turcica, cavernous venous sinuses, carotid arteries, clival invasion, meninges and basal cisterns, basilar artery, and posterior fossa structures. These extensions present with protean clinical manifestations.

Whatever the mode of transmission, the fungi once they reach their target tissues, they cause inflammation, invasion and tissue

necrosis to satisfy their biological needs. Many fungi have various enzymes (proteolytic, lipolytic and saccrolytic enzymes) to digest the living or dead tissues.

In the cranium, initially it causes osteitis followed by erosive osteomyelitis, and then the extension in at least one of the cranial fosse with extradural abscess or granulomas, meningitis, cerebritis, cerebral abscess, granuloma, and angio-invasion resulting in vasculitis leading to thrombotic occlusion and or aneurysmal dilation with cerebral hemorrhage, etc [4,6,13,18]. In cases of direct vascular invasion (usually of the proximal vessels), the outer vascular layer, lamina externa, is invaded first and then the lamina media. Then ultimately the invasion of internal elastic lamina and intramural spread leads to the formation of thrombosis, infarction, aneurysmal dilatations and cerebral hemorrhage [6].

In immune compromised patients, from invasive paranasal fungal sinusitis, pulmonary fungal infection, infected artificial heart valves, etc, the fungal invasion of large proximal cerebral vessels occurs from within the vessel via the fungal emboli. In these cases, the fungi are engulfed by the endothelial cell of the internal lining of the vascular lumen, and these proliferate within these cells to destroy the internal elastic lamina before reaching muscle layers of lamina media and thereby causing the pathological states of arteritis and phlebitis with resultant highly fatal clinical states of vascular thrombosis, cerebral infarction, intracranial aneurysms and cerebral hemorrhages.

The Clinical Spectrum of Paranasal Fungal Sinusitis

In general, sinusitis is mainly the inflammation of the paranasal and mastoid air sinuses which present with variety of symptoms such as headaches, chronic pains or discomfort within the sinuses as well as tender spots overlying the sinuses or juxta-sinus tissues (such as teeth, gums, ears etc), swelling / puffiness of face and orbits , stuffiness of the nasal passages, post nasal drip, cloudy discolored nasal or postnasal drainage, sore throat, cough and fever, recurrent upper respiratory infection and later, lower respiratory infection in increasing pattern of severity. Tenderness over the infected sinus is possible to elicit over the anterior paranasal sinuses, but the usual presenting symptom of posterior paranasal sinusitis is the occurrence of bi-temporal or vertex headaches [32-44].

Fungi are plant-like organisms devoid of chlorophyll and therefore, to exist, acquire food from other organic sources; mainly the dead matters but rarely proliferate in living organism by breaking down their complex organic matter and cause fungal infections which can only be eradicated with a planned management strategy. Fungi do not need light for living; they can reside in a damp and dark environment.

The rhino-sinuses being moist and dark cavities are naturally a good opportunity for the invading fungi responsible for fungal sinusitis. Fungal sinusitis is caused when inhaled aerosolized fungi get deposited in the nasal passageways and paranasal sinuses, and are causing irritation and inflammation. As mentioned before, the moist secluded environment of the paranasal sinuses is ideal for fungi.

Paranasal fungal sinusitis is relatively uncommon among other types of infective sinusitis. The fungi such as Aspergillus, Mucor, Candida, Histoplasma and Coccidioides are main causative agents.
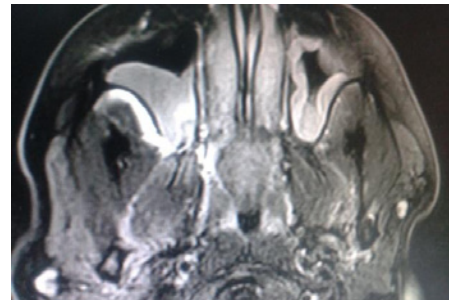
Figure 6: T2 weighted MRI scan showing extensive chronic fungal paranasal sinusitis.

Aspergillosis in the maxillary sinuses is the most common fungal lesion in the immune suppressed patients. The fungal sinusitis usually present with the symptoms of recurrent nasal obstruction & nasal discharge; unremitting bitemporal or frontal or vertex headaches; fever; frequent nausea & vomiting; anosmia; epistaxis; periorbital pain, facial pains & swelling, diplopia, visual disturbance seizures, and weakness of limbs, altered sensorium progressing to coma and death in the worse scenario.

The physical signs usually depend upon the location of the intracranial or intra-orbital areas involved like speech disturbances, focal neurological deficits in intracranial extensions where as the ophthalmoplegia, chemosis, proptosis, ocular lateral/medial rectus palsy, and visual disturbances in intra-orbital or cavernous sinus involvement. Neuro-imaging studies, such as CT head and the MRI brain scans, are mainstay of the diagnostic investigations (Figure 6).

Recognition of fungal sinusitis requires a high index of suspicion especially if the sinusitis is not responding to the antibacterial medications. The final diagnosis of fungal sinusitis is usually made by antrostomy via middle turbinate and biopsy or culture. The Sabouraud media is routinely used for the fungal culture. Histo-pathological examination is routinely performed on the soft tissues and the bony material obtained from the diagnostic nasal endoscopic biopsy or open paranasal sinus surgery. The fungi could be detected only on special stains such as methamine silver for Mucor, Rhizopus, & Absidia. The Aspergillus has uniform septate hyphae branching at 45 degrees; whereas, the Mucor shows nonseptate, nonuniform branching at 90 degrees.

Classification of the fungal sinusitis

The paranasal sinusitis can be classified in many ways. In general, depending on the temporal pattern and the severity, the Sinusitis may be classified as fulminant, acute, sub-acute, and chronic sinus infections [32-52]. It can also be classified as noninfectious sinusitis due to allergens, chemicals, particulate matters and infected sinusitis due to bacterial, viral, protozoal and fungal infections.

Most importantly, depending upon the histo-pathological evidence of fungal invasion (such as the presence of fungal hyphae within the tissues, reactive granulomatous reaction, tissue necrosis, etc) of the local tissues and their confines, the fungal sinusitis is mainly categorized into two main groups-: 1. Non-invasive and 2.Invasive.

I. Non-invasive extra-mucosal conditions:

i. Allergic fungal sinusitis (most common),

ii. Fungus ball/sinus granuloma (rare);

II. Invasive mucosal conditions:

i. Acute fulminant fungal sinusitis (common)

ii. Chronic indolent fungal sinusitis (less common)

iii. Chronic Granulomatous fungal sinusitis (rare)

In fungal sinusitis, there is a continuum of the spectrum of the clinico-pathological conditions ranging from allergic responses to tissue invasion with major implications on the basis of the severity of invasion and extent of the tissue destruction.

I. Non-invasive extra-mucosal fungal sinusitis

Noninvasive fungal sinusitis is defined by the absence of fungal hyphae within the live sinus mucosa, bony walls & its associated vascular structures. The fungi are either detected in the sinus secretions or are contained within the sinus sac or are present in the cavity of the fungus ball occupying the sinus.

i. Allergic Fungal Sinusitis (AFS): AFS is the most common type of fungal sinusitis. It is reported in about 10% surgical cases of chronic hypertrophic sinus disease and about 50% of rhino-sinusitis cases in some parts of northern India. It is common in warm humid climates such as in India and southern parts of USA. Recurrent mild episodic allergic fungal rhino-sinusitis in the perfectly normal individuals is now believed to be a short lived allergic reaction to environmental fungi that is finely dispersed into the air. These cases are usually treated with symptomatic treatment for a long period of time without having a proper diagnosis. Moreover, these patients usually have a history of allergic rhinitis, and this disorder progresses imperceptibly in the long run to establish as chronic Allergic Fungal Sinusitis (AFS) if the environmental conditions remain unresolved. Allergic Fungal Sinusitis (AFS) has many other names such as chronic eosinophilic fungal rhino-sinusitis, EFRS (Eosinophilic Fungal Rhino-Sinusitis) or EMRS (eosinophilic mucinous rhino-sinusitis). Allergic Fungal Sinusitis (AFS) is commonly caused by hyaline molds such as Aspergillus, Fusarium, etc, and dematiaceous fungi such as alternaria, bipolaris, curvularia, etc.

It usually occurs in immune competent individuals in their second and third decades of life with significant hypersensitivity to the fungal antigens and these cases are having a past history of chronic bacterial and polypoid sinusitis. Nearly about 70% cases have history of asthma as well. The duration of symptoms prior to the diagnosis of allergic fungal rhino-sinusitis is usually between 1-3 years.

The clinical presentation is mainly with the symptoms such as nasal obstruction with nasal discharge, recurrent headaches and visual disturbances in many patients. Plain X-Ray studies show sinus opacification and soft tissue masses in paranasal sinuses. The CT and MRI scans show largely a homogeneous opacification of sinuses with expansion and in some cases, bony erosion. The CT scans demonstrates hyper-attenuating allergic mucin within the lumen of the paranasal sinus.

The consistency of mucin is like peanut butter or a rubber cement called "allergic mucin" which typically contains a few hyphae, no invasion, and no predisposing systemic disease. Charcot-Leyden crystals (breakdown products of eosinophils) are often found in the
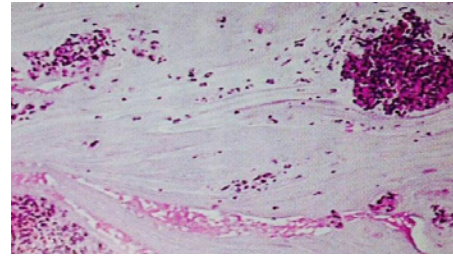
Figure 7: Fungal Allergic Mucin showing necrotic eosinophils and Charcot-Leyden crystals (H&E stain).

Figure 8: Allergic Mucin containing fragmented septate fungal hyphae (GMS stain).

allergic mucin (Figure 7).

There are variations in sinus secretion which may usually have a characteristic golden-yellow color but in some cases it may have a dark green or black material. These secretions contain allergic mucin with degranulated eosinophils, scanty fungal hyphae and no tissue invasion. Patients often have received multiple treatments (including steroids) for chronic rhino-sinusitis before a confirmed diagnosis of AFS establishes.

Interestingly, a Mayo clinic study [35] found fungal growth in washings from the sinuses in 96% of patients with chronic sinusitis, but similar findings were noted in normal controls as well. However, chronic fungal sinusitis had activated eosinophiles in the sinus secretions, but activated eosinophiles were absent in normal subjects. As a result of their activation, the eosinophiles in AFRS released a product called MBP (Major Basic Protein) into the mucus which usually attracts, attacks and kills the fungus and this MBP-fungal antigen complex is very irritating and injurious to the lining of the sinuses and thereby, predisposing the secondary bacterial proliferation. Waxman et al. demonstrated elevated IgE in about 60% of AFRS cases. The MBP can be tested in the nasal mucus (Sinutest, Accentia) but it is not generally available at present.

Microscopic examination (Figures 7 & 8) of the biopsy tissues with secretions obtained from the paranasal sinuses usually show pale eosiniphilic mucoid material with eosinophils, sloughed epithelial cells, multilayered cellular debris and charcot Leydon crystals with scattered fungal hyphae in mucin. Mainly, there is no tissue invasion noted.

Plain X-Rays usually show opacification of multiple paranasal sinuses. This is confirmed with CT scanning along with findings of pressure expansion of the involved sinuses at times. The CT scans typically show areas of hyper attenuation in the sinuses due to the presence of allergic (highly proteineous) mucin. There is 'double

density' appearance when viewed on both bone and soft tissue windows pictures of the CT Scanning. Areas of mottling with the areas of sclerosis present in the sinus walls in chronic cases. T1 weighted MRI scanning show slightly hypointense to hyperintense inflamed sinus mucosa which enhances further on contrast administration but the sinus contents do not enhance and thereby differentiating from the neoplastic lesions. On T2weighted images, the inflamed mucosa is distinctly hyperintense. Highly proteineous allergic mucus appears as hyperintense material on T1weighted images in cases of AFS which becomes little hypointense on T2 weighted images.

These cases of AFS are usually treated with symptomatic treatment for a long period without a proper diagnosis but once the diagnosis is established, the surgery remains a primary treatment to provide a good drainage and aeration of the pathological sinuses and is followed by long-term medical management including broad spectrum antifungal medications. Endoscopic sinus surgery achieves diagnostic biopsy and mechanical cleansing & aeration of the sinuses. For the satisfactory clinical outcome, the medical treatment includes anti-fungal drugs, anti-bacterial antibiotics for superadded bacterial infection and rarely, corticosteroids (systemic and topical) on case to case basis.

ii. Fungus ball infection: Fungus ball infection is also called "Mycetoma Fungal Sinusitis". These infections mainly occur in pre-existing aerated cavities such as para-nasal sinuses (usually maxillary or sphenoid sinus) or post tubercular pseudo-cysts in the lungs. These patients usually maintain an effective immune system, but may have experienced trauma or injury to the affected sinuses. In this condition, an isolated paranasal sinus is completely filled with a ball of fungal debris, most frequently in the maxillary sinuses. Generally in this condition, the fungi do not cause a significant inflammatory response, but sinus discomfort occurs recurrently.

Fungus ball are more common in the middle or old age patients. Clinical symptoms may include fullness, pressure and discharge in the rhino-sinus region. Some patients have long standing headaches, foul smelling breath and no allergic or atopic symptoms. Sinus is filled with thick pus or a clay-like substance.

Plain Radio-imaging usually shows fungus ball in the sinuses as a soft tissue mass and opacification of the involved sinus. It is typically hypointense on both T1and T2 weighted MR images due to the presence of high levels of calcium with paramagnetic trace metal elements such as iron, magnesium and manganese as well as there is usual vascular signal voids on the T2 weighted images. The fungus ball may vary in size from a few mms to a size which completely occupies the sinus. Obviously on the CT scanning, the presence of high contents of metal elements in the fungus ball with dense matted fungal hyphae results in a hyper attenuation sinus lesion with punctate calcification. It may have a greenish-black appearance.

The histopathology usually shows a fungus ball composed mainly of dense fungal hyphae either as a tangled mass of dead hyphae or a friable material containing innumerable fungal hyphae arranged in concentric growth layers Figure 9). Rarely, the live hyphae may be present in it. There is some inflammatory response in the mucosa but no actual invasion. It usually remains confined to the cavity of origin and only, in extremely rare occasions, the invasion of the adjacent
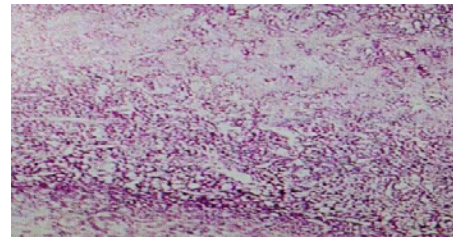
Figure 9: Paranasal Fungus ball with aggregated innumerable fungal hyphae (H&E Stain).

tissues may occur which may result in erosion and bleeding with a fatal outcome.

The complete excision of the fungus ball is the treatment of choice. The surgery is needed for exenterating the sinuses for a total removal of all fungal elements via simple scraping of the infected sinus. An anti-fungal therapy is generally not prescribed if the sinus exenteration process is complete and satisfactory but may be needed on the case to case basis. The overall prognosis is usually good.

II. Invasive mucosal fungal infections

The virulent fungi can invade paranasal sinuses even in the immune-competent hosts; whereas, the opportunist fungi do so only in the immune-compromised host to cross beyond the paranasal sinuses into the orbits and intracranial cavity with resultant more loss of functions, morbidities and mortality. Invasive fungal sinusitis is defined by the presence of fungal hyphae within the mucosa, sub-mucosa, bone, or blood vessels of the paranasal sinuses. Their characteristic clinical presentation categories them in three types: - acute invasive fungal sinusitis, chronic invasive fungal sinusitis, and chronic granulomatous invasive fungal sinusitis.

Obviously, the acute invasive fungal sinusitis occurring in immune compromised individuals is more serious. Fungi usually feed on dead organic matter, but weakened immune defenses can allow fungi to begin thriving on and consuming live tissues. As the fungi reproduce, they spread rapidly into the local paranasal sinus tissues, blood vessels, orbits and intracranial structures with devastating results. Invasive fungal infection may behave much like a malignant neoplasm, with destruction of soft tissues and bone. Therefore, acute invasive fungal sinusitis carries a high mortality rate. The recommended therapies for all cases of invasive fungal sinusitis are an aggressive radical wide surgical excision of the invaded tissues and an intravenous broad spectrum anti-fungal therapy.

i. Acute fulminant fungal sinusitis: As stated earlier, although rare in normal individuals, it usually occurs in patients with a compromised immune system either due to immune-deficiency disorder (sepsis, diabetes mellitus, prolonged ventilation, extensive use of antibiotics, HIV, etc) or due to the use of the immune-suppressive agents (cancer, oncological therapies, organ transplants, etc). This invasive fungal disease rapidly leads to fulminant progression, within hours to days, in destruction of the paranasal sinuses by invading the mucosa, sub-mucosa, blood vessels, and bony walls of the nasal cavity and paranasal sinuses and spreading in the orbits and intracranial spaces. Angioinvasion and hematogenous dissemination are frequent with high morbidity and mortality. Fungi belonging to Zygomycetes

directly invades vascular channels and causes thrombosis, ischemia, aneurysm, hemorrhage & infarction with 40-50 % mortality rate in normal subjects and an approximately 90-95% mortality rate in immune compromised patients.

Aspergillosis and mucormycosis are main causative fungal infection in these cases. Aspergillosis results in about 80% of cases of AFS in patients with hematological malignancy with neutropenia (systemic chemotherapy, systemic steroid therapy, bone marrow transplantation, or immunosuppressive therapy for organ transplantation; and patients with acquired immune deficiency syndrome). Mucormycosis / zygomycosis (fungi belonging to the order Zygomycetes, such as Rhizopus, Rhizomucor, Absidia, and Mucor,) is responsible for about 80% of cases of acute fulminant fungal sinusitis in patients with diabetic keto-acidosis with highest morbidity and mortality same as in aspergillosis.

a. Clinical features: The group of patients with neutropenia is having fulminant progression within hours show painless sero-sanguineous nasal discharge with obvious sinusitis associated with a necrotic ulcer on the nasal septum. Persistent neutropenia and rapid orbital and intracranial spread lead to higher fatalities. The other group of patients (with diabetes mellitus and keto-acidosis) present with fever, nasal congestion-epistaxis-sero-sanguineous discharge, facial pains and numbness in the areas overlying the paranasal sinuses for few days followed by spread in the nearby areas of orbits, cranium and maxillofacial region. The orbital invasion leads to proptosis, visual disturbances and impaired ocular motility; and whereas the intracranial spread causes headaches, disturbances of higher mental functions (somnolence, lethargy, confusion, disorientation, memory loss, loss of speech), epileptic seizures, focal neurological deficits, and a progressively deepening coma. The spread to the maxillo-facial region lead to localized facial swelling and localized pains.

b. The age is no bar in these cases: The age ranges from second decade through to the sixth decades in these cases. Initially, the patients may develop a focal area of necrotic tissue in the infected area (i.e., dead tissue due to invasion by the fungus) within the paranasal sinuses, and later, within a short period of few hours to couple of days, it rapidly progresses through the cranial base to involve the eye and the brain tissues. In these cases, higher virulence of fungi leads to a large number of fungal hyphae causing bony destruction, tissue necrosis and angio-invasion. Rapidity of spread leaves no time for the generation of tissue reaction or the formation of granulomatous changes (Figure 10).

The CT imaging usually reveals mucosal thickening along the walls, soft tissue mass in the lumen and significant destruction of the bony confines of the paranasal sinus with intracranial and intra-orbital extensions of the fungal infection. The fungi may directly invade arterial and venous systems even with intact bony walls to reach intracranial cavity: cavernous sinus thrombosis and even carotid artery invasion, occlusion, or pseudo-aneurysm with resulting fatal cerebral infarct and hemorrhage. Obviously, MR imaging delineates intracranial and intra-orbital extensions better than the CT scanning.

Emergent surgery achieves tissues for biopsy to confirm the diagnosis, mechanical cleansing of sinuses to remove infected material, and removal of all necrotic tissues to get to normal tissues for
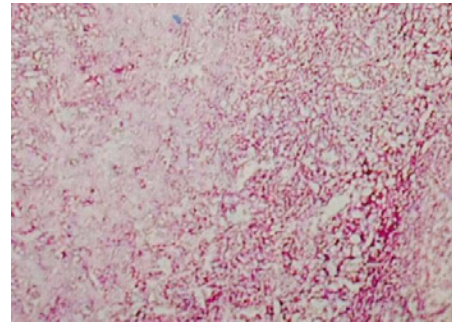

Figure 10: Acute fungal sinusitis with extensive tissue destruction (H&E stain).

healing, drainage of the toxic materials to improve clinical state of the patient and to start antifungal drugs with correction of predisposing conditions to give a rare chance of survival. The best indicator for survival is a recovering neutropenia, whereas intracranial extension predicts higher morbidity and mortality. These fungi can easily invade any living tissue of these immune compromised patients, like knife in a cheese or melting them as ice, as if no real resistant or a competent barrier exists to prevent their disastrous invasion. Prognosis is extremely poor as the mortality reaches more than 90-95% cases. Acute fulminant fungal sinusitis is the most lethal form of fungal sinusitis.

ii. Chronic indolent fungal sinusitis (less common): Chronic Indolent fungal Sinusitis is an invasive form of fungal sinusitis occurring mainly in immune-competent individuals. Aspergillus, Mucor, Bipolaris and Candida are common fungi to cause this disorder. It is uncommon in the USA, but commonly found in the Sudan and northern India. The insidious progression of the fungal disease takes a long chronic course from months to years in which the fungi gradually invade mucous membrane, submucosa, blood vessels, and bony walls of the paranasal sinuses. It clinically presents with chronic headache, anosmia, progressive facial swelling and diplopia with visual impairment in appreciable number of cases. Other symptoms may include pain or tenderness overlying the paranasal sinuses, episodic sero-sanguineous nasal discharge, occasional epistaxis, chronic nasal polyposis, mild visual disturbances and recurrent unexplained fever.

The CT imaging studies show appreciable hypo-attenuated thickening of mucosa and hyper-attenuating soft tissue mass in the paranasal sinuses which is better delineated on the MRI scans as T2 weighted images show hyperintense to isointense mucosa and hypointense core which does not enhance on intravenous contrast administration in T1 weighted images. In invasive maxillary fungal sinusitis cases, the usual T2 weighted hyperintensity of the normal periantral fatty tissue is changed to markedly low T2-weighted intensity due to the fungal infiltration. Undoubtedly, the MRI scans present better definitions of the intracranial and intra-orbital extensions.

Microscopically, chronic indolent fungal sinusitis is characterized by a granulomatous inflammatory infiltrate (nodular shaped inflammatory lesions) of the sinus mucosa and its wall (Figure 11). Typically, Langhans'type giant cells contain fungal hyphae and are
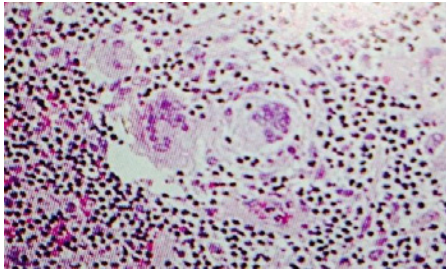
**Figure 11:** Granulomatous reaction & Giant cells in chronic indolent sinusitis (H&E stain).

surrounded by epitheloid histiocytes, plasma cells and eosinophils. Although not extensive, the focal angio-invasion and tissue necrosis are seen in many cases.

Obviously, any condition which results in a decreased immune system in these patients can place them at increased risks for further progression and complications of this invasive fungal disorder. Once recognized, aggressive surgical excision of the fungal material and intravenous anti-fungal therapy form the mainstay of management of this condition to prevent further complications. Once become active, the chronic indolent fungal sinusitis results in significant morbidity and may even cause fatality in some cases.

iii. Chronic granulomatous fungal sinusitis (CGFS): CGFS commonly presents with progressively increasing chronic headaches, seizure disorders, decreased mental faculties, appearance of focal neurologic deficits and rarely, progressively increasing raised intracranial pressure.

It is usually caused by Aspergillus flavum in immune-competent persons. However, Mucor, Bipolaris and Candida are other common fungi to cause this disorder. There is formation of non-caseating granulomas in the paranasal sinus and juxta-sinus tissues. It follows a chronic persistent and recurrent episodic flare up courses over months to years with eventual extension beyond the walls of the paranasal sinuses (usually in the maxillary sinus) with orbital and intracranial extensions. However, many authors consider it as an advanced stage of chronic invasive fungal sinusitis and not as a distinct clinical entity (Figure 12).

However, its hallmarks are chronic inflammatory changes with granulomatous tissue reaction in the sinus mucosa, its bony walls and juxta-sinus orbital and cranial cavities. Orbital involvement will result in proptosis, impaired ocular motility and visual impairment (orbital apex syndrome) which worsens on steroid uses. Extra-antral
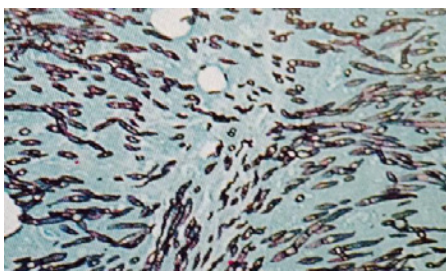
Figure 12: Tissue and vascular invasion by innumerous fungal hyphae in granulomatous sinusitis (GMS Stain).

extension from maxillary sinus will lead to soft tissue swellings, loss of fat pads in pterygopalatine fossa and infratemporal fossa with cranial neuropathy, and palatal erosions. Intracranial extension is highly morbid condition. Invasion of the fungal infection from paranasal sinusitis via cranium to the meninges leads initially to pachy-meningitis and lepto-meningitis which is seen on imaging studies as subtle or an obvious reactive enhancement. Chronic progressive fungal infections result in the formation of adjacent cerebritis, cerebral abscess, granulomas and vascular lesions.

The CT imaging studies show areas of meningeal enhancement with significant thickening of sinus mucosa and soft tissues within the paranasal sinus as well as in ipsilateral nasal cavity. On the bone window settings, mottled areas of low attenuation (lucencies) of irregular bone destruction may be seen in the walls of the paranasal sinuses. There may also be sclerotic changes in the bony walls of the affected sinuses representing chronic sinus disease. Hyper-attenuating soft-tissue collection in paranasal sinuses is well visualized on the plain CT scanning. There could be expansion of sinuses and thinning erosion or remodeling of the bones with well delineated trans-cranial invasions and intracranial/intraorbital extensions.

MRI scans show intracranial granulomas as hypointense mass lesions on T1- and T2-weighted images due to the presence of high concentration of various metals such as iron, magnesium, and manganese concentrated by the fungal organisms with minimal enhancement on contrast administration. More specific but infrequent changes at the site of cranial erosion: Retro-antral fat-pad inflammation and orbital or intracranial mass lesions, are late features.

Therapy needs to be as aggressive as possible for acute invasive fungal sinusitis due to the high mortality and morbidity. Mainstay management comprises of extensive surgical debridement of affected tissues and systemic antifungal therapy along with supportive measures.

Neurological Manifestations of the Invasive Paranasal Fungal Sinusitis

Based on the aforementioned facts, the clinical presentations of the CNS fungal infections, either alone or in combinations, are as follows: Meningitis; encephalitis; raised intracranial pressure(raised ICP); mass effect producing parenchymal space occupying lesions (cerebral cysts, abscesses, granulomas etc), orbito-rhino-cerebral syndromes; acute cerebro-vascular events such as ischemic or hemorrhagic strokes producing vascular syndromes and spinal fungal infections presenting with myelopathic symptomatologies. However, the most common presentations among these are rhino-orbito-cerebral syndromes, basal meningitis, space occupying lesions (cerebral abscesses and granulomas) and hydrocephalus [53-66].

Among the plethora of syndromes, the rhino-orbito--cerebral form is the most common presenting syndrome with fungi such as Aspergillus, Zygomycetes (Mucor), etc. Because of the contiguous spread of the infection from the adjacent paranasal sinuses and orbit, skull-base syndromes are often the presenting clinical syndromes in patients with rhino-sino-cranial aspergillosis. Subacute meningitis is usually due to pseudomycetes such as Candida and Cryptococcus, and the chronic meningitis in patients with HIV infection is more
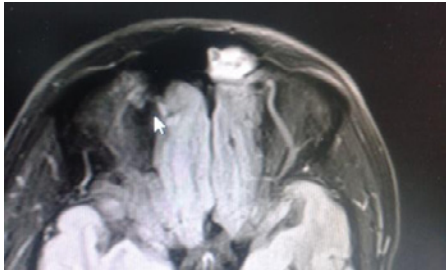
Figure 13: MRI scan is showing left frontal sinusitis in a patient with pan-paranasal fungal sinusitis with loss of smell and frontal signs.

likely to be due to cryptococcal infection.

Rhino-orbito-cavernous sinus syndromes

Long standing intractable fungal paranasal sinusitis due to invasive fungi i.e., Aspergillus, Cladosporium, Zygomycetes (Mucor) as well as fungus like bacteria such as Actinomycetes and Nocardia etc are mainly responsible. Diabetic ketoacidosis is the most common predisposing factor apart from others as mentioned before (Figure 13).

According to the involvement of the anatomical structures (paranasal sinuses, orbits, optic nerves, cranial bone penetration with involvement of intracranial space and the brain parenchyma) in the skull base region, many types and combinations of clinical syndromes are named: sinocranial(commonest), sino-orbital, sino-orbito-cranial, orbito-cranial, cavernous sinus, orbital apex, purely orbital syndromes and more extensive orbito-rhino-cerebral syndromes with associated specific and non-specific symptoms and signs. Some patients present purely with cranial mono- or poly-neuropathy. Each patient must be clinico-radiologically assessed according to his symptomatology to define the anatomical extent of the fungal involvement.

In majority of cases, recurrent nasal discharge, nasal blockage and periorbital pains are the initial presenting features. The appearance of the symptoms such as recurrent headaches, proptosis, impaired ocular movements, progressive visual loss, sensory impairment in ophthalmic (frequently) and maxillary(infrequently) divisions of the trigeminal nerve, chemosis progressing to ophthalmoplegia, blindness and periorbital-facial swelling unilaterally(commonly) or bilaterally(less commonly). Further progression beyond the orbits and the cavernous sinuses to the brain is far more dangerous and is manifested by the symptoms such as unremitting bifrontal or vertex headaches, confusion, irritability, seizures, speech disturbances, focal cranial and limb deficits, deteriorating level of consciousness and then coma with fatalities in many cases. Therefore, the recognition of the clinical condition in the early phases of invasion and progression is of paramount importance.

A. Orbital syndrome: The first indication is inflammatory edema of the eyelids which progresses to cellulitis, proptosis, chemosis and ophthalmoplegia with or without meningism (Figure 14).

There are five types of orbital involvement:

1) Inflammatory lid edema only

2) Diffuse orbital cellulitis with proptosis but no abscess

Figure 14: The CT scan of the orbit showing proptosis with orbital apex syndrome in a case of right paranasal ethmoidal sinusitis and complete invasion of the lamina papyracea.
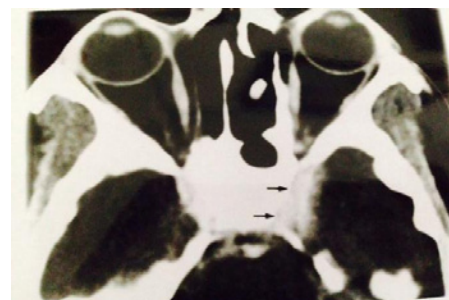
Figure 15: The CT scan showing sphenoidal sinusitis with cavernous sinus involvement.

3) Sub-periosteal abscess beneath the lamina papyracea

4) Orbital abscess with proptosis

5) Cavernous sinus thrombosis with bilateral proptosis and ophthalmoplegia

B. Cavernous sinus thrombosis: Cavernous sinus, one on either side of the sella turcica, gets hematogenous fungal invasion from the sphenoid sinus, mid facial structures, and ophthalmic veins. This results in sinus thrombosis, carotid aneurysms and vascular thrombotic occlusions which are potentially fatal complications needing urgent treatment measures (Figure 15).

Most cases of cavernous sinus thrombosis are caused by the bacterial infections of the middle one third of the face as the ophthalmic veins are valve less and lead directly to the cavernous sinus. As compared to the bacterial infections, the paranasal fungal sinusitis is encountered less frequently in cases of cavernous sinus thrombosis. The retrograde involvement of the other eye may occur via the cavernous sinus infection due obviously to the lack of valves in the superior and inferior ophthalmic veins.

The patient suddenly presents with chemosis, proptosis, loss of feelings in upper half of the face, double vision, inability to move the eyeball in some or all directions and blindness in some cases. Severe frontal headaches, fever, and progressive unilateral or bilateral orbital findings are common. Initially, the eye becomes proptotic and chemotic with subsequent inability to move the eye ball.

Neurological findings include palsies of cranial nerves (3, 4, V1, V2 and 6) which are located either in the lateral-inferior wall of the cavernous sinus or within its cavity (Figure 16). In some cases, the

Figure 16: MRI scan of the brain showing pan paranasal sinusitis with bilateral skull base involvement bilateral cavernous sinuses and middle cranial fossa extensions and left CP angle granulomas with multiple cranial involvements. Internal carotid and basilar arteries are normal.

optic nerve involvement will result in blindness.

Although the diagnosis is primarily clinical, CT scans show a filling defect of the involved sinus with a dilated ophthalmic vein.

Treatment includes intravenous broad spectrum antifungal medications, anti-bacterial antibiotics, surgical drainage of the affected sinuses and supportive measures. Infusion of heparin, although controversial, is sometimes performed.

Control of diabetes, radical surgical procedures to the orbit and paranasal sinuses, neurosurgical intervention for intracranial infection and aggressive antifungal drug therapy including irrigation of aerated paranasal sinuses with antifungal agents are needed. Excision of necrotic and infected tissues as well as the drainage of paranasal sinuses is needed in these patients. Mortality rates are 30%, but less than half of the survivors are neurologically intact.

Cranial nerve palsies

Around the paranasal air sinuses, there are many skull base foramina and fissures through which the cranial nerves, venous channels and the arteries traverse to connect the extra-cranial and intracranial spaces. From the infected paranasal sinuses, the fungi can take these avenues to enter the skull base and intracranial compartment. Whilst doing so, within these channels, the fungi affect, infect, invade, infiltrate and may destroy these important structures and result in various cranial nerve palsies, venous channel thrombosis to spread of venous fungal infections, arterial thrombosis and aneurysm formations. Anosmia, visual loss, ocular palsies, trigeminal neuralgia, and even lower cranial palsies can occur [67-71] (Figure 17).

Meningeal syndromes

Meningitis, meningo- encephalitis and hydrocephalus: Chronic fungal meningitis is common, whereas subacute meningitis relatively less common, and the acute fungal meningitis distinctively rare except in ICU patients or prolonged ventilatory patients with severely immuno-compromised states. Most of the pseudomycetes (yeasts) are capable of producing meningitis or meningo-encephalitis via hematogenous spread causing vasculitis and meningeal inflammation [72-79] (Figure 18 & 19).
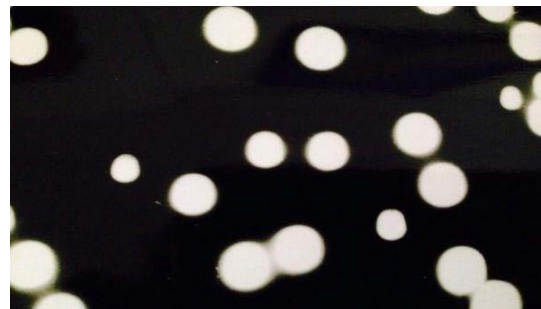
Initial clinical features of fungal meningitis and meningo-encephalitis are usually the features of meningism such as cervico-

Figure 17: MRI Scan showing the fungal invasion of the paranasal sinuses as well as destruction of the sphenoidal sinus and clivus.

Figure 18: Symptomatic patient with candida meningitis with Oral Thrush.

Figure 19: Cryptococcus seen in India Ink prepararion.

occpital pains, neck stiffness, fever and later nausea, vomiting, visual impairment, subtle papilledema as well as personality changes, and then progressing to severe neck rigidity, obvious papilledema, seizures, deterioration in sensorium, cranial nerve palsies and hydrocephalus with high morbidities and mortality until unless timely interventions and management instituted. In many patients, there are no focal or generalized physical signs. High degree of clinical suspicion detects primary fungal infection in the paranasal sinuses and oral cavity in significant number of cases and that leads to better prognosis in such cases.

Fungal meningitis ranges from the relatively common cryptococcal meningitis to the rare meningitis due to large pseudomycetes (diamorphic) or filamentous (septate and non-septate) fungi. Therefore, the fungal meningitis more frequently occurs with Cryptococcus, Coccidioides, Blastomyces, Paracoccidioides, Sporotrichum, Histoplasma and Candida as compared to filamentous fungi such as Aspergillus, Phaeohyphomycetes and Zygomycetes.

CNS Cryptococcal infection (European Blastomycosis) usually
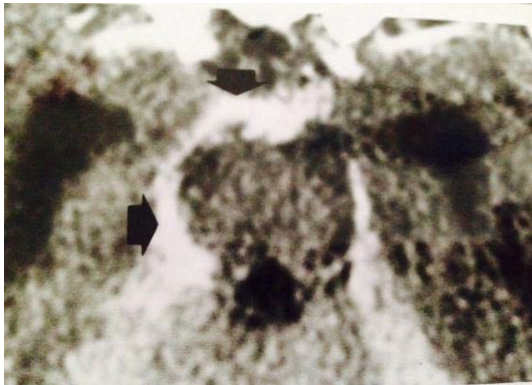
Figure 20: T1 weighted MRI scan with contrast showing the lighting up of the peri-mesencephalic granulation tissues in chronic meningitis.

Figure 21: Flair MRI scan showing the periventricular hyperintensity in the right atrium and corpus callosum in a case of treated fungal meningitis and ventriculitis with residual changes in the right frontal horn.

Figure 22: The CT scan of the head showing left parieto-occipital aspergillus abscess with no firm capsule.

present with typical clinical features of meningitis (subacute or chronic) or meningo-encephalitis. Acute fatal meningitis is rare in cryptococcosis; but the periods of remissions and relapses are well known. Cryoptcoccosis is one of the most common CNS fungal infections in immune-compromised patients. Nearly one tenth of the patients with HIV develop crytococcosis and in significant number of patients, cryptococcosis manifest as an initial presentation of HIV infection. Coccidioides is probably the most virulent of the fungi causing human fungal infections.
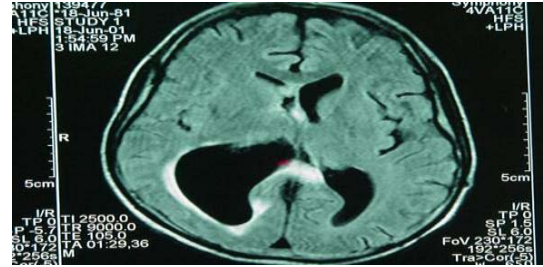
Meningeal inflammation due to fungal infection results in accumulation of exudates, opacification of leptomeninges and obliteration of sulci with caseous granulomatous nodules at the base of the brain and in the cervical region. Extensive fibrosis causes obstructive hydrocephalus (Figure 20) and invasion of blood vessels leads to multiple aneurysms. Unusually large granulomatous lesion and frank abscesses may occur in the brain and spinal cord.

In autopsy studies, the most common cerebral mycosis is caused by candidiasis. Candida albicans originally infects the oral cavity (Figure 18) and oesophagus usually following prolonged antibiotic treatment, then invades submucosal blood vessels and finally disseminates hematogenously to the CNS. Candida also reach CNS via colonization of the ventricular drains, shunt tubing and central venous lines. Therefore, Candidal meningitis can occur spontaneously as complications of disseminated candidiasis or as a complication of an infected wound or ventriculostomy via direct inoculation of the organism into the CNS (Figure 21).
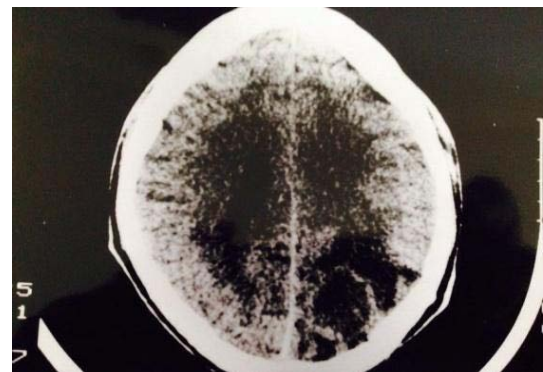
Usually chronic but infrequently subacute, basal fungal meningitis causes obliteration of intracranial subarachnoid spaces and results in increased intracranial pressure with or without hydrocephalus. All the other major fungi (i.e., Histoplasma, Phaeohyphomycetes, and Aspergillus) can also produce life threatening meningitis and therefore high index of suspicion, prompt diagnosis and vigorous therapies are required to reduce morbidities and mortality.

Intracranial fungal space occupying lesions

Intracranial granulomas, abscesses and cysts, especially in the intraparenchymal locations, form the bulk of the intracranial fungal Space Occupying Lesions (SOLs). Clinically, fungal granulomas are more frequently diagnosed as compared to fungal abscesses and in many cases, a mixed picture is seen. Intraparenchymal cysts occur commonly in basal ganglia in cryptococcal infection as compared to other mycosis.

CNS fungal abscesses: Candidiasis, aspergillosis, cryptococcosis, cladosporiosis, mucormycosis etc commonly produce CNS fungal abscesses [80-89] (Figure 22). Fungi disseminating hematogenously from an extracranial site cause multiple areas of infection within the brain. Initially, meningoencephalitis occurs with vasculitis-thrombosis of the small cortical or subcortical vessels and later hemorrhagic cerebral infarction develops and then an abscess forms. Abscess forming organisms may progress in a fulminant fashion leading rapidly to death. Extremely preterm neonates and patients with definitive immunological deficiency syndromes/states are at high risk of developing these complications with high morbidities and mortality.

Unfortunately in many cases, the diagnosis of these lesions is revealed only at autopsy. There could be an extradural abscess due to direct focal bony invasion- erosion-spread from invasive fungal sinusitis. The patients with brain abscess per se present with persistent fever, severe unremitting headaches, vomits, seizures, focal neurological deficits and then progressive deterioration in the sensorium with high morbidities and mortality.

CNS fungal granulomas: The fungal granulomas are commonly produced by aspergillosis, histoplasmosis, blastomycosis, para coccidioidomycosis, cladosporiasis, mucormycosis, cryptococcosis, etc. These are relatively less common as compared to the other intracranial fungal lesions and mainly behave as space occupying
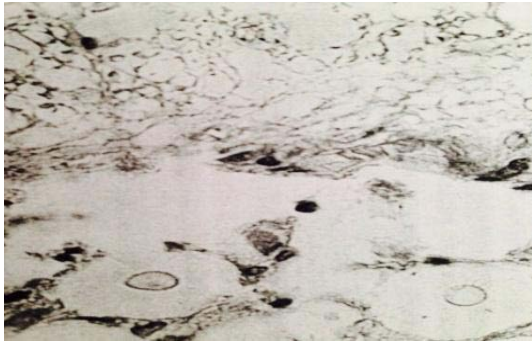
Figure 23: Cerebral cryptococcoma with a distinct reactive tissue capsule but scanty inflammatory cells (H&E stain).

Figure 24: Cerebral Aspergilloma with multiple branching septate hyphae (Grocott with H&E stain).

Figure 25: The CT scan showing right basal ganglionic infarct in cerebral mucormycosis.

Figure 26: Cerebral angiography showing fungal aneurysm of the peripheral sylvian branch of the MCA.

masses. The age is no bar for them as they have been documented from infancy to the old ages. The mode of transmission is either due to direct cranial invasion and intracranial extensions in the skull base regions of frontal, temporal and sellar regions or more commonly due to hematogenous spread in the parenchymal locations. Aspergillosis and mucormycosis of the paranasal sinuses infect the subjacent meninges and brain parenchyma to produce frontal and temporal granulomas whereas hematogenous spread of other fungi from elsewhere produce parieto-occipital granulomas in general [90-97].

Interestingly, these skull base fungal granulomas are more common in immune-competent patients (*Aspergillus flavus* more commonly the culprit) and intra-parenchymal lesions in immune-compromised cases (*Aspergillus Fumigatus, Mucor, Cryptococcus, Candida albicans*, etc) as seen in (Figures 23,24).

Clinical symptomatology depends on fungal infection at the primary location, the site of brain lesion as well as associated meningitis, edema and mass effect, etc. The rhino-sinal symptoms include recurrent intermittent nasal obstruction, anosmia, discharge, epistaxis, puffiness of the face, tenderness over lying sinuses, recurrent headaches, etc. The features of raised intracranial pressure may also be present such as morning headaches, vomiting, blurring of vision, visual obscurations and papilledema. The focal symptoms of the intracranial mass producing granulomas comprise such as speech disturbances, focal cranial or limb deficits, as well as cranial nerve deficits (first to sixth cranial nerves).

Fungal granulomas may resemble tuberculomas except that they have a more fibrous consistency. Intraparenchymal cerebral cysts in the basal ganglia sometimes develop in patients with cryptococcosis.
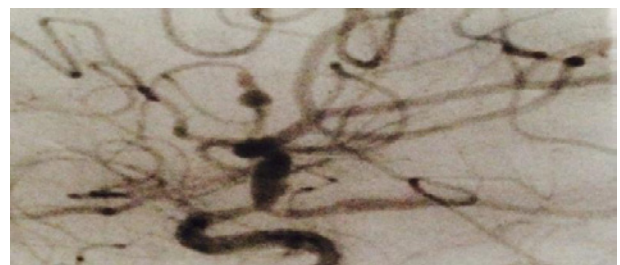
Small fungal SOLs are managed with antifungal medications and supportive care whereas significantly large lesions may also need conventional, stereotactic or ultrasound guided surgical interventions.

Acute fungal cerebro-vascular disorders

In CNS fungal infections, acute cerebro-vascular events take the form of either ischemic (commonly) or hemorrhagic (uncommonly) strokes. Aspergillosis, Zygomycosis, Candidiasis, Coccidioidomycosis, Histoplasmosis, Cryptococcosis, Penicilliosis, etc are all well known fungal infections rarely presenting with acute cerebro-vascular events [98-108].

Gradual contiguous involvement of the skull base structures in cases of prolonged paranasal fungal sinusitis (commonly aspergillosis, zygomycosis, cladosporiosis, etc) leads to angio-invasion which in turn results in fungal vasculitis and thereafter, the thrombotic occlusions occur in the major branches of the cerebral vasculature at the skull base: internal carotid arteries and or vertebro-basilar system. The hyphae invade the vessel walls causing cerebral arterial thrombosis, cerebral infarction (Figure 25) and cerebritis. The evolving hemorrhagic infarcts may convert into septic infarcts. In cases of major cerebral fungal arteritis in which the direct surgery is inappropriate, reliance has to be placed on the antifungal antibiotics and supportive therapy.

Ischemic cerebral strokes also result due to cardiac-emboli in patients with fungal endocarditis. Organisms frequently involved in fungal endocarditis are Candida, Aspergillus, etc. However, Candida is the most common causative organism of fungal endocarditis in, both, immuno-competent and immuno-compromised patients. Rarely, disseminated fungal cardiac emboli lodging in the peripheral cerebral vasculature leads to intracranial fungal mycotic aneurysms,

solitary or multiple, which may present with extremely rare and usually fatal complications of subarachnoid hemorrhage/intracerebral hemorrhage with and without cerebral infarctions (Figure 26).

Intracranial fungal mycotic aneurysms in the proximal cerebral vasculature (internal carotid vessels and vertebro-basilar branches) usually result from the fungal angio-invasion in cases of long standing fungal sinusitis (aspergillosis, zygomycosis, coccidioidomycosis etc).

Apart from antifungal drug therapy and supportive treatment, if a peripheral cerebral aneurysm is recognized, it should be excised whenever possible. However, a direct surgical treatment is usually not possible in proximal cerebral fungal aneurysms except rarely endovascular therapy, surgical trapping or peripheral ligations. In general, the outlook is extremely poor for these patients with CNS fungal infections presenting with acute strokes.

Management of the Invasive Fungal Sinusitis and Sino-Orbito-Cerebral Complications

Over the decades, for the invasive fungal infections, the broad spectrum antifungal drug named amphotericin-B remained the first choice of medical management.. However, in the last two decades, more elaborate use of intensive care units for serious medical disorders, transplant procedures, use of immunosuppressive therapies as well as pandemic spread of HIV etc have certainly increased the incidence of systemic fungal infections especially life threatening or lethal CNS fungal infections. In many such cases, the use of Amphotericin B was not effective. Fortunately, during the same period, many useful antifungal drugs were simultaneously discovered and introduced in the clinical practices. Initially, the lipid based formulations of the Amphotericin B, then the new triazoles and most recently, echinocandins. These medications are frequently used in combinations for effective management in seriously ill patients with invasive fungal infections. Now evidence based data are gathering together in favor of their important roles in the management of invasive fungal infections. But still there are many unanswered questions and controversies relating to their use [6].

Unquestionably, CNS fungal infections pose serious challenges in their management with controversies surrounding their medical and surgical therapies:

Surgical management of fungal infections

The principles of surgical management in CNS fungal infections focus on the following aspects

High index of clinical suspicion on the invasive fungal paranasal sinusitis in chronic cases, prompt endoscopic tissue biopsy, proper fungal culture and careful histopathological studies to diagnose the problem early, prompt aggressive surgery depending upon the cranial and intracranial areas involved, antifungal drug therapy as well as a good control of underlying systemic and metabolic problems (such as diabetes mellitus, immune-suppression, etc) [109-115].

a. The surgical procedures for the diagnostic purposes: Obviously in known cases of invasive paranasal fungal sinusitis, currently the ENT surgeons more frequently perform endoscopic biopsy than the open ones. The paranasal sinuses are well cleared of the involved mucosal-bony tissues as well as the accumulated infected debris in the sinus cavities. In the intracranial compartment, image guided biopsies are taken with the help of stereotaxis or Brain lab. These pathological tissues are then sent in toto for the histopathology examination and microbiological fungal cultures. These investigative procedures will help to identify the extent of sinus tissue invasion by the fungi, the nature of the intracranial lesions as well as the type of fungi involved.

b. The surgical procedures for the established invasive fungal sinusitis with intracranial extensions:

i. Extradural fungal infection: Purely extradural fungal infection occurs commonly in non-invasive fungal sinusitis such as allergic fungal sinusitis or a fungal ball due to pressure expansion with bone erosion and in invasive fungal sinusitis such as chronic indolent fungal sinusitis and in chronic granulomatous fungal sinusitis due to direct fungal invasion of the mucosal lining & bony architecture of the paranasal sinuses. The dura mater (meaning tough mother) is a strong resistant layer of internal lining tissue for the cranium and an effective external protective covering for the brain and its vasculature for any direct invasion from the infected paranasal sinuses. Such extradural infections may be dealt with during the extensive endoscopic or open surgical sinus clearance / exenteration surgery. Meatotomies and turbinectomies are done to excise the fungal infected areas. All the infected mucosa, bony linings of the sinuses and the extradural infected materials such as granulomas, abscess, inflammatory tissues are removed by curettage with blunt curettes whilst protecting the dura to prevent the CSF leak. High magnification, good illumination, low suction with saline irrigation, adequate exposure and marsupilization of the sinuses with post operative mild negative suction drainage of the operative cavities favor a good prognosis. Appearance of CSF leak is the single most important factor of negative prognostic value in cases of the extradual fungal lesions as its occurrence portends a relatively poor outcome with increased morbidity and mortality.

ii. Intradural fungal infections: Transcranial surgical options are less controversial in cases of focal or localized superficial cortico-subcotical fungal lesions (such as abscesses and granulomas) in the non-eloquent areas of the brain as these lesions are treated with craniotomy and microsurgical total excision of the cerebral fungal lesion with a safe margin. Whereas invasive multifocal cortico-subcortical lesions, deep cerebral and or brain stem lesions, and the focal cerebral lesions rapidly spreading to involve larger parts of the brain as well as major vascular invasions are usually not surgically amenable or curable; however, palliative benefits comes from the minimal invasive diagnostic and or therapeutic stereotactic or image guided surgery. Reliance has to be placed heavily on the antifungal drug therapy along with further appropriate surgical options where indicated.

Frontal and ethmoidal invasive fungal sinusitis usually results in osteomyelitis of the frontal-ethmoid bones with involvement of the dural lining of the anterior cranial fosse and then the frontal lobes. Usually all parts of the osteomyelitic cranial bone is well excised including the air sinuses. In such cases, a team approach is needed for the excision of the rhino-sino-orbital fungal lesions and bi-frontal craniotomy with a safe though wider surgical excision of the infected cranio-cerebral tissues with a great care especially of the eloquent areas such as Broca's area. A watertight dural repair should be performed which will pose a challenge in itself but with the

availability of the tissue glues it is much better nowadays. Craniofacial team (Neurosurgeon, ENT surgeon, Plastic surgeon, etc) works better in such cases with better understanding, approach and outcome. Hydrocephalus is best treated with ventriculo-peritoneal shunt.

Invasive fungal infections in the maxillary, posterior ethmoidal and sphenoid air sinuses may spread to the middle cranial fossa, cavernous sinuses and then involving the temporal lobes, and pituitary fossa, whereas the invasive fungal infections of the mastoid air sinuses spread to the sub-temporal fossa, middle cranial fossa and posterior fossa with involvement of the temporo-parieto-occipital cerebral regions. The transcranial and skull base approaches are used for such cases with higher morbidities and mortality. In these areas, wherever it is possible to excise the fungal mass lesion or simply fungus load it is done widely such as in temporal and posterior fossae; but in many areas it is not feasible such as cavernous sinuses, posterior fossa, retro-clival areas and the cerebral arterial system except limited surgical role and a major reliance on the medical therapy is placed.

iii. The post operative care: Post operatively, ENT surgeon periodically checks the sinuses using routine endoscopy to make sure a fungus free sino-nasal mucosa, Neurosurgeon evaluates clinically for the status of the neurological manifestations, Neuroradiologist performs neuro-imaging studies to make sure that there is no recurrence of the fungal infection and the patient keep his eyes on his health and is diligently doing dilute amphotericin-B nasal washes to keep the paranasal air sinuses moist and clean.

Anti-fungal medicational therapy

The newer antifungal medications are proving to be safer with their greater efficacy and lesser toxicity than the Amphotericin-B especially in immune-compromised patients having invasive fungal sinusitis with intra-orbital and intracranial complications. In comparative studies of the single versus combination therapy, the current evidence is favoring the latter. Evidence based studies (using new drugs, singly or in combination) are accumulating and are assuming greater roles in the management of these serious infections [116-127].

Currently following classes of natural and synthetic antifungal drugs are commonly used:

1. Polyenes: Amphotericin B Deoxycholate Complex

(Fungizone-registered, Bristol-Myers Squibb), Nystatin

Lipid formulations of Amphotericin B:

a) AmBisome,

b) Amphocil (Amphotericin B colloidal dispersion

{cholesteryl sulfate}, ABCD)

c) Abelcet (Amphotericin B lipid complex, ABLC)

2. Pyrimidines: 5- fluorocytosine (flucytosine)

3. Triazole drugs: Fluconazole, Itraconazole, Posaconazole, Voriconazole

4. Echinocandins: Caspofungin, Anidulafungin, Micafungin

5. Miscellaneous: Imidazoles (Clotrimazole, Ketoconazole etc),

Oral polyenes (Amphotericin, Nystatin)

Griseofulvin etc for dermal, oropharyngeal, esophageal, intestinal and vaginal infections. Terbinafine is effective for nail and ring worm infections.

Amphotericin is the broad spectrum antifungal drug active against most fungi: moulds and yeasts. Being a Polyene drug, it is usually not absorbed through the gastrointestinal tract and is mainly given intravenously after a test dose (intravenous infusion of 1 mg over 30 minutes) before the first therapeutic dose (at least 30 minutes of observation period) to prevent anaphylactic reaction. In the blood circulation, it is highly protein bound with less penetration in the tissues and body fluids hence behaves like a highly toxic substance with profound nephrotoxicity. It combines with the ergosterol in fungal Cell membrane and manifests its antifungal properties. The maximum dose is 2-4 gm/day.

Lipid formulations of Amphotericin are less protein bound with more tissue penetration and are less toxic with lesser infusion related as well as renal side effects. However their clinical indications as well as efficacies are nearly same as Amphotericin and are 8-10 times more costly. In patients with pre-existing renal dysfunctions, obviously, lipid formulations are preferably advised but same is not justified in patients with normal renal functions. For life threatening invasive fungal infections (aspergillosis, zygomycosis, etc), lipid formulations are initially advised.

Amphotericin-B and its Lipid formulations are indicated for systemic candidiasis, cryptococcosis and the endemic mycoses (blastomycosis, histoplasmosis, coccidioidomycosi and paracoccidioidomycosis. In these infections, Amphotericin-B and triazole antifungals such as Voriconazole, Fluconazole, and Posaconazole, are advised either singly or in combinations. Amphotericin can also be used topically or instilled in the operative cavity in the paranasal sinuses.

Flucytosine (5-fluorocytosine) is the only commonly used drug (usually in combination with Amphotericin-B) among the pyrimidine class of antifungal drugs especially in infections such as invasive candidiasis, cryptococcosis, aspergillosis etc with significant bone marrow toxicity, hepatotoxicity and drug resistance.

Triazoles also act by blocking ergosterol. In that respect, Voriconazole is very much like amphotericin-B but with less toxic effects. Apart from Voriconazole, fluconazole or itraconazole may be used 400 mg twice daily.

Among the azole group of antifungal medications, imidazoles (miconazole, ketoconazole) are commonly used for localized surface infections and triazoles (itraconazole-{for dermatophytes only}, fluconazole, voriconazole, posaconazole) are used for invasive life threatening fungal infections because of their ease of administration(oral preparations), high bioavailability, water solubility, low protein binding and a good body fluid distribution, relatively low toxicity and long half life. A good CSF penetration is usually achieved. Triazoles have a relatively broad spectrum of activity against common fungal pathogens e.g., *Aspergillus, Blastomyces, Candida, Cryptococcus, Coccidioides, Paracoccidioides, Histoplasma* etc. However, their limitations lie in the interactions with co-administered drugs, development of the resistance of fungal organisms (*Candida*) especially with fluconazole and hepatotoxicity.

Most recently introduced antifungal drugs are Echinocandins (Caspofungin, Anidulafungin, Micafungin) which are showing promising results in combination antifungal therapy in the serious opportunistic invasive fungal infections (cadidiasis and aspergillosis{caspofungin only}). The prototype is Capsofungin, which acts on the cell membrane. The recombinant interferon gamma (IFN) can also be used, to improve antifungal properties of polymorphs and helper T cells. GMCSF 200 microgram thrice weekly can be used.

There is high risk of fungal infections in immunocompromised patients i.e., long term care in ICUs (intensive care units), HIV, renal transplant with immuno-suppressants etc.

Prophylactic antifungal drug therapy using oral azoles (fluconazole, itraconazole, ketoconazole) is given in such cases. Fluconazole is the drug of choice for long term use.

If fungal infection is confirmed then the Amphotericin is used initially on empirical basis.

Once the type of the opportunistic fungal infection is established then the more specific antifungal drugs are given: Candidiasis (Triazoles, Echinocandins), Crptococcosis (Amphotericin and Flucytosine in synergistic combination), Aspergillosis (Amphotericin, Voriconazole, Posaconazole, Caspofungin), Mucormycosis (Amphotericin) etc.

Caspofungin is licensed for the empirical treatment of systemic fungal infections (Candidiasis, Aspergillosis, etc) with neutropenia. Fluconazole is often used in prevention of the relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy.

Fungal invasive complications like cavernous sinus thrombosis and meningitis respond very well to intravenous antibiotics like cephalosporins and amikacin, in addition to the antifungal drug treatment.

There are many questions and controversies ranging from the choice of antifungal medications in CNS mycoses to calculation of their doses, and the route of administration as well as effective therapeutic combinations. Only further research and evidence based data will help resolve these questions and many more controversies in the management of the CNS fungal infections in future.

Conclusions

Fortunately fungal sinusitis is less common and its CNS complications are rare as compared to bacterial and viral infections; however, recently there is an increase in such infections following relative increase in immune-compromised patient population due to apparent reasons.

The CNS fungal infections present with various clinical syndromes which may be specific for certain fungi: Meningitis , encephalitis, hydrocephalus/ raised intracranial pressure; mass effect producing space occupying lesions (cerebral cysts, abscesses, granulomas etc); orbito-rhino-cerebral syndromes; acute cerebro-vascular events

and spinal fungal infections. The common presentations among these are basal meningitis and or hydrocephalus, space occupying lesions (cerebral abscesses and granulomas) and stroke syndromes.

Clinical picture may mimic tubercular meningitis and need careful evaluation.

The CNS mycosis carries higher risks of morbidities and mortality as compared to other infective processes and therefore promptly requires precise timely diagnosis and appropriate medical and or surgical management strategies to optimize the outcomes. With the routine use of nasal endoscopy and emergence of newer less toxic antifungal drugs, the management of the fungal sinusitis and its intracranial extensions has improved, leading to less morbidity and mortality. Rigid nasal endoscopy and biopsy of suspicious areas in the nasal cavity and in the paranasal sinuses are advocated for early diagnosis. Reversal of underlying causes of immune-suppression as well as administration of systemic broad spectrum antifungal medications such as amphotericin B or its lipid formulations with or without azoles and echinocandins should be instituted with supportive medical and surgical therapies. Prompt diagnosis and initiation of appropriate management strategies are essential to avoid a protracted or fatal outcome.

The morbidity and mortality rates are high in immune compromised patients in the range of 80-95% and in the immune competent patients in the range of 50%– 80%, but active surveillance of the at-risk population, reversal of underlying neutropenia and other causes of immunosuppression, reversal of diabetic ketoacidosis, prompt aggressive surgical debridement, and systemic antifungal chemotherapy can decrease the mortality rate to 20% at lease in immune competent patients.

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