Clinico-Radiological Manifestations of Invasive and Non-Invasive Fungal Infections in Sinuses and Respiratory Tract

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Abstract

Introduction : Fungal sinusitis was once considered a rare disorder but is now reported with increasing frequency throughout the world. Fungal chest infection is relatively considered common. The classification of fungal sinusitis has evolved in the past two decades, and this entity is now thought to comprise five subtypes. Acute invasive fungal sinusitis, chronic invasive fungal sinusitis and chronic granulomatous invasive fungal sinusitis made the invasive group, whereas non-invasive fungal infection is composed of allergic fungal sinusitis and fungus ball (fungal mycetoma). **Objective :** The five subtypes of sinusitis described above are distinct entities with different clinical and radiologic features. The treatment strategies for the subtypes are also different, as are their prognosis. We aim to clearly delineate the radiologic features of culturally proven fungal cases so as to direct the clinician towards expeditious diagnosis and necessary treatment. **Methodology :** 40 culturally positive patients with the spectrums of different manifestations were studied and recorded. They were followed up for one month. **Conclusion :** An understanding of the different types of fungal sinusitis and knowledge of their particular radiologic features allowed the radiologist to play a crucial role in alerting the clinician to use appropriate diagnostic techniques for confirmation. Prompt diagnosis and initiation of appropriate therapy avoided a protracted or fatal outcome.

Key Words : Fungal sinusitis, Fungal ball (mycetoma), CECT

Introduction :

Of more than 400,000 known fungal species, approximately 400 are human pathogens, only 50 of which cause systemic or central nervous system infection. Many of these fungi are ubiquitous in our environment. Although many people are colonized by fungi, an intact immune system prevents subsequent infection. [1] Although several fungi have been implicated to cause sinus infection, Aspergillus, Bipolaris, and Rhizopus are the more commonly implicated organisms causing fungal sinusitis. Fungal sinusitis is a relatively common, often misdiagnosed disease process involving the paranasal sinuses. It is a serious condition, as certain forms of fungal sinusitis are associated with a high rate of mortality. Successful treatment requires a prompt diagnosis and frequently relies on radiologic imaging, specifically computed tomography (CT) and magnetic resonance (MR) imaging.

Under the most recent and widely accepted classification fungal sinusitis is broadly categorized as either invasive or non-invasive. Invasive fungal sinusitis is defined by the presence of fungal hyphae within the mucosa, submucosa, bone, or blood vessels of the paranasal sinuses. Invasive fungal sinusitis is subdivided into acute invasive fungal sinusitis, chronic invasive fungal sinusitis, and chronic granulomatous invasive fungal sinusitis. Conversely, non-invasive fungal sinusitis is defined by the absence of hyphae within the mucosal and other tissues of the paranasal sinuses. Non-invasive fungal manifestations are allergic fungal sinusitis and fungus ball (fungal mycetoma). [2]

To distinguish between the invasive and non-invasive forms, adequate quantities of sinus contents and biopsy specimens of diseased and healthy mucosa and bone adjacent to areas of frank necrosis must be obtained for pathologic analysis. [2] Fungi do not stain well with routine stains, and special silver-impregnated fungal stains and fungal cultures are required for accurate diagnosis of the fungal sinusitis and sub classification. Fungal cultures are difficult and frequently no fungal growth is achieved despite their identification by staining the surgical specimen, and identification of the actual fungal organism is not always possible. A preoperative suggestion of fungal sinusitis is often helpful by prompting the surgeon to obtain appropriate samples during surgery and alerting the pathologist prior to histopathological processing for proper identification of allergic mucin, and would also prompt the use of special stains and cultures for the detection of the fungal elements.

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Methodology

Current study was prospective type cross-sectional study with purposive sampling. The study was conducted at Department of Radiology; one of the tertiary care hospital attached with medical college at Gujarat region of India. The study duration was July 2012 to April 2014. All patients referred from ENT Department with related clinical features or provisionally diagnosed by clinicians were asked to participate in the study. 40 patients (28 males and 12 females) gave their consent for the same. Patients had a mean age of 35 years (17 to 60 years) and were residents of Gujarat.

CT analysis was done using 16 slice Siemens CT Machine. Thin slice sections of paranasal sinuses with contrast administration was implicated. After obtaining the scout projection, the area of scanning was defined to include the region from roof of frontal sinus up to the hard palate. Axial sections were performed with the patient in supine position and the plane of data acquisition parallel to hard palate. The sections were taken with slice thickness of 5 mm and table feed of 7 mm i.e. a pitch of 1.4. Images were reconstructed at 4 mm intervals i.e. with an image overlap of 1 mm. Scanning

parameters included 105 mA, 130 kV and tube rotation time of 1.5 seconds. Coronal sections were performed with the patients in prone position with extended neck and the plane perpendicular to axial plane. The scanning parameters were the same as in axial plane. Extended cephalic / caudal sections were done in a few patients to see extension of the disease process.

The images thus generated were photographed at appropriate window widths and window level to depict the bony abnormalities as well as soft tissue pathologies.

The authors evaluated the images for characteristics of opacity produced by the diseased tissue, sinuses involved, expansion of sinuses, areas of bone erosion and extra-sinus extension. The patients were operated within one month of doing the scans and had histologically confirmed fungal sinusitis.

Inclusion criteria Clinically and culturally diagnosed proven cases of fungal sinusitis or pulmonary aspergilloma.

Exclusion criteria Patients who had previous episodes of adverse reactions to contrast or proven cases of malignancy were excluded.

Permission for the study was granted by the ethics committee of the institute.

All patients were informed about the procedure beforehand and a written consent was also obtained. A detailed history was elicited to determine the clinical correlation accurately. All the patients studied were clinically stable. There was no side effect noted during the follow-up. After one month, the necessary surgical procedure (debridement/extirpation) was performed and biopsy was obtained to confirm the diagnosis.

Results :

Fungal sinusitis is an important clinical problem with diverse manifestations. It should be considered in all immunocompromised patients and in all patients with chronic sinusitis. It can be noninvasive or invasive with five major subtypes.

In general men outnumbered the women in the study. (Table 1)

Table 1: Predilection of one or both sides of paranasal sinuses/hemithoraces

Diagnosis	Unilateral Involvement		Bilateral Involvement		Total
	Males	Females	Males	Females	
Acute FS	51%	43%	5%	1%	100%
Chronic FS	45%	24%	21%	10%	100%
Allergic FS	9%	1%	78%	12%	100%
Fungal ball	42%	26%	19%	13%	100%

We found that acute invasive fungal sinusitis affects immunocompromised patients and patients with poorly controlled diabetes (70%). Orbital and intracranial invasion is common (50%), and mortality tends to be high unless the condition is detected early and treated aggressively. Imaging features are often subtle in the initial stages, and radiologists need to be alert while evaluating the sinuses in this group of patients for early signs of arterial (60%) and bony (80%) invasion. Figure 1: MSCT scan for PNS in a 60 year old diabetic patient with bilateral loss of vision. (A) Non-contrast Axial plane (B) Coronal reformatted image (C) Non-contrast enhanced Axial plane (D, E) CECT Axial sections (F) Sagittal reformatted image demonstrate pansinusitis with erosion of posterolateral wall of left maxillary sinus and medial wall of left ethmoid sinus. There is noted well defined inhomogeneously enhancing soft tissue lesion in intraconal compartment of both orbits. It was histopathologically proven acute fungal sinusitis with orbital extension.

Figure 1: MSCT scan for PNS in a 60 year old diabetic patient with bilateral loss of vision, a proven case of acute fungal sinusitis with orbital extension.

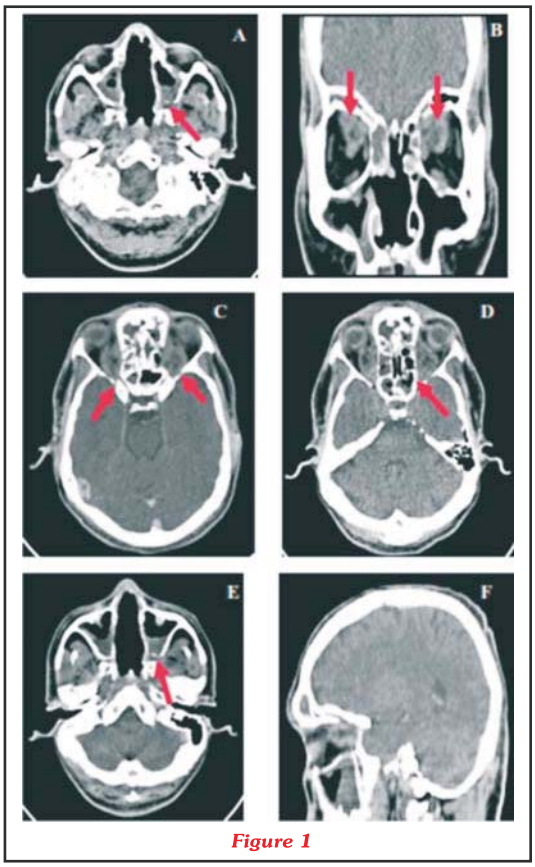


Figure 1

Chronic invasive fungal sinusitis and chronic granulomatous invasive fungal sinusitis are characterized by a prolonged clinical course with slow disease progression. Imaging manifestations may mimic aggressive neoplastic lesions (40%). Features of chronic sinus disease are seen in addition to invasive disease in the orbits and cranium. *Figure 2:* MSCT for PNS in a 50 year old male with history of tuberculosis 5 years back. AKT completed. Complaint of breathlessness with hemoptysis was there. (A) Non-contrast Axial plane (B) CECT Axial section (C) Coronal reformatted image (D) Bone

window MPR (E) Bone window Axial plane (F) CECT Axial section Delayed image reveals expansile soft tissue density lesion with few hyperdense areas within it noted in left nasal cavity, left frontal, ethmoid, maxillary and sphenoid sinuses. On post contrast study, minimal post contrast enhancement is noted. Posteriorly and inferiorly, extension up to posterior nares and medially thinning of septum with deviation towards the right was seen. Medially the lesion causes thinning of septum and compresses and deviates the nasal septum towards right side. There is erosion of the medial wall of left maxillary sinus by the lesion.

Figure 2: **MSCT for PNS in a 50 year old male, histopathologically positive for chronic fungal sinusitis.**

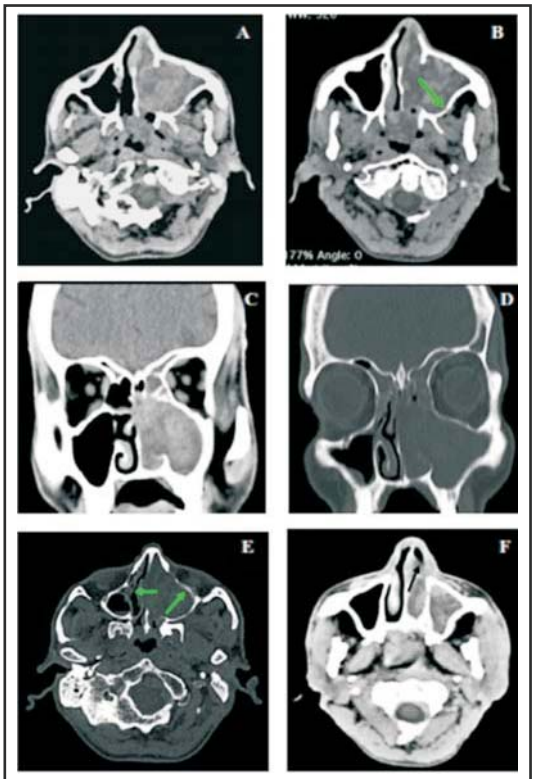


Figure 2

As per Lund Mackay system of scoring, if the number of sinus[2] sides were counted and multiplied by the score of individual unit (0-2), then the anterior osteomeatal unit was found to be maximally involved in 30/40 (75%) and sphenoids least involved in 3/40 (8%). (Table 2)

Table 2: Lund Mackay system of scoring guidelines

Variable	Score	Percentage
Maxillary antra	14	25%
Osteomeatal complex	30	70%
Anterior ethmoids	36	75%
Posterior ethmoids	12	55%
Frontal sinuses	5	15%
Sphenoid sinuses	3	8%

Allergic fungal sinusitis tends to be a disease of young atopic individuals. There is usually pan-sinus disease with expansion and smooth thinning of the affected sinuses. The sinus contents tend to be hyperattenuating. There is thin peripheral enhancement with no enhancement noted in the central sinus contents. Surgical extirpation and antiallergic medications are the mainstay of therapy without the need for toxic systemic or local antifungal therapy. Figure 3: MSCT non-contrast PNS in a 20 year old male patient with chronic sinusitis and headache for over a year. (A, B) Axial section (B, C) Bone windows MPR

Sagittal and Coronal images respectively demonstrate bilateral pansinusitis with near opacification and polypoidal mucosal thickening of left side. Hyperdense areas of allergic mucin noted within the soft tissue opacity. Sinuses appear expanded but bony erosion is absent. It was pathologically proven and clinical case of allergic fungal sinusitis with characteristic features on CT scan.

Figure 3: **MSCT non-contrast PNS in a 20 year old male. (Pathologically proven case of allergic fungal sinusitis)**

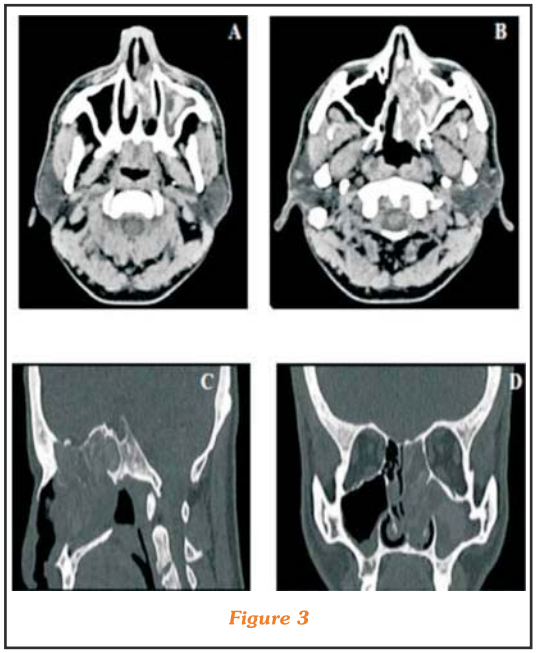


Figure 3

Fungus ball (mycetoma) Aspergillomas occurs in patients with normal immunity but structurally abnormal lungs (82%), with pre-existing cavities. Air-crescent sign is noted in 95% cases. Figure 4: HRCT thorax in a 40 year old patient with complaints of cough and whitish expectoration for 1 month (A) Coronal reformatted image (B) Scanogram (C) Axial section reveal Multiple fibrotic strands and cavities are seen in both upper lobes (Right more than Left 65%). One of the cavities in right upper lobe shows hyperdense lesion (average attenuation 79HU) suggestive of fungal ball Air crescent sign. Emphysematous bullae in right lower lobe. The same was culturally positive for fungal etiology.

Figure 4: **HRCT thorax delineating air crescent sign in fungal ball.**

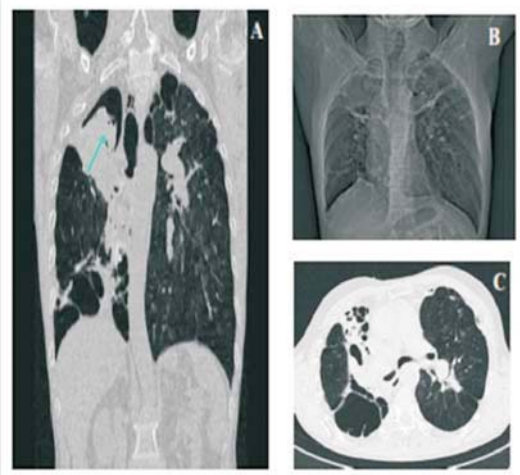
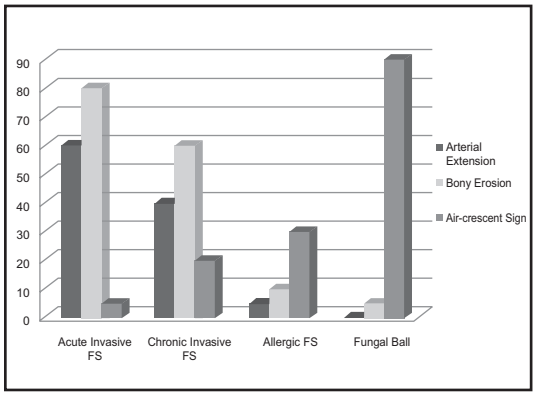


Figure 4

Demographics will therefore match those of the underlying condition, such as:

1. Pulmonary Tuberculosis most common, accounting for 25-80% of cases depending on the prevalence of TB in the population [3]
2. Pulmonary sarcoidosis
3. Bronchiectasis from any cause
4. Other pulmonary cavities__ Bronchogeneic cyst, pulmonary sequestration, Pneumatocoeles

Graph 1: **Characteristics of all fungal manifestations imaged on MSCT.**



Discussion

❖ Acute Fungal Sinusitis :

Acute invasive fungal sinusitis is a rapidly progressing lethal infection seen predominantly in immunocompromised patients and patients with poorly controlled diabetes and rarely in healthy individuals. It is the most lethal form of fungal sinusitis, with a reported mortality of 50% 80%. [3] It is also thought that the nasal cavity is the primary site of infection, with the middle turbinate accounting for two-thirds of positive biopsy results. [4] Two distinct patient populations were seen as reported by Waitzmann AA. [3] One group is patients with diabetes (80%), especially those with diabetic ketoacidosis. The other group is immunocompromised patients with severe neutropenia (fulminant invasive sinusitis or neutropenic sinusitis). We had majorly diabetic patients (95%) of group 1.

Clinical Features:

Invasive fungal sinusitis is clinically characterized by a painless, necrotic nasal septal ulcer (eschar), sinusitis (40%), and rapid orbital and intracranial spread leading to death (90%). There is fulminant progression over a few days to several weeks in which fungal organisms invade the mucosa, submucosa, blood vessels, and bony walls of the nasal cavity and paranasal sinuses. Angioinvasion and hematogenous dissemination are frequent (44%). Similar incidence has been reported by Gillespie MB et al [4] (51%). Symptoms include fever, facial pain or numbness, nasal congestion, serosanguineous nasal discharge, and epistaxis. Intraorbital, intracranial, and maxillofacial extension is common with resulting proptosis, visual disturbances, headache, mental status changes, seizures, neurologic deficits, coma, and maxillofacial soft-tissue swelling. Intracranial spread of infection predicts higher mortality and morbidity, with up to 73% of patients dying. Patients who do not recover from their neutropenia seem to have a poor prognosis irrespective of the adjunctive therapeutic measures. [5]

Imaging Features:

Noncontrast CT demonstrates hypoattenuating mucosal thickening or an area of soft-tissue attenuation within the lumen of the involved paranasal sinus and nasal cavity (88%). There is a predilection for unilateral involvement of the ethmoid and sphenoid sinuses as reported by Parikh SL et al. [5] Aggressive bone destruction of the sinus walls occurs rapidly with intracranial and intraorbital extension of the inflammation. Bone erosion and mucosal thickening may sometimes be very subtle and nonsignificant also reported by Parikh SL [5]. As per Silvermann et al. [6], these fungi tend to extend along the vessels, and extension beyond the sinuses may occur with intact bony walls. Intracranial extension of disease from the sphenoid sinus leads to cavernous sinus thrombosis and even carotid artery invasion (13%), occlusion, or pseudoaneurysm (4%) with resulting fatal cerebral infarct and hemorrhage (28%). Leptomeningeal enhancement (15%) may be seen with intracranial invasion and is subtle in the initial stages and must be diligently sought for. With progressive infection, adjacent cerebritis, granulomas, and cerebral abscess formation may be encountered (12%) as compared to 10% reported by Silvermann et al. [6]

Severe unilateral nasal cavity soft-tissue thickening is the most consistent, though nonspecific, early CT finding. [7] More extensive changes such as retroantral fat pad inflammation, bone erosion, and orbital or intracranial invasion are more specific but late, infrequent features.

❖ Chronic Invasive Fungal Sinusitis:

Clinical Features:

In 1972, 37 cases had been reported with immunocompetence.[6] Our study showed that 90% individuals are usually immunocompetent, but those with diabetes or a low level of immunocompromise are susceptible. Similar studies by Del Guadio et al [7] have reported a high incidence (83%). Patients have a history of chronic rhinosinusitis. Symptoms may include paranasal sinus pain, serosanguineous nasal discharge, epistaxis, nasal polyposis and fever. The disease is usually persistent and recurrent.

Maxillofacial soft-tissue swelling develops with destruction of the bony sinus walls. Invasion of the maxillary floor leads to palatal erosions. Orbital invasion leads to orbital apex syndrome with proptosis; third, fourth, and sixth cranial neuropathy and diminished vision. Patients may present with a clinical syndrome mimicking orbital pseudotumor and progress rapidly if steroid therapy is instituted. The cribriform plate may be eroded with resulting chronic headache, seizures, decreased mental status or focal neurologic deficits. [8]

Imaging Features:

Sarti EJ et al [9] proposed that stenosis of the osteomeatal complex, from either the anatomical configuration or hypertrophied mucosa, can cause obstruction and stagnation of secretions that may become infected or perpetuate infection. The incidence in our study is 70% as compared to 98.5% by Sarti EJ et al, [9] but DeShazo [10] reported an almost similar incidence of 68% [10]. A hyperattenuating soft-tissue collection is seen at noncontrast CT within one or more of the paranasal sinuses. It may be mass-like and mimic a malignancy with destruction of the sinus walls and extension beyond the sinus confines. Mottled lucencies or irregular bone destruction may be seen in the paranasal sinuses. There may also be sclerotic changes in the bony walls of the affected sinuses representing chronic sinus disease.

Infiltration of the periantral soft tissues about the maxillary sinus is an indicator of invasive disease. Invasion of adjacent structures such as the orbit, cavernous sinus, and anterior cranial fossa may lead to epidural abscess, parenchymal cerebritis or abscess, meningitis, cavernous sinus thrombosis, osteomyelitis, mycotic aneurysm, stroke, and haematogenous dissemination. Differentiation from malignant neoplasm may not be possible based on imaging. [8, 9]

❖ Allergic Fungal Sinusitis:

This is the most common form of fungal sinusitis. It is particularly common in warm, humid climates of India. [10] Incidence may have geographic variation, and it has been reported to 51% of patients in northern India with chronic rhinosinusitis. [11] The underlying cause is thought to be a hypersensitivity reaction to certain inhaled fungal organisms resulting in a chronic non-infectious, inflammatory process. Immunoglobulin E mediated type I immediate hypersensitivity and type III delayed hypersensitivity are thought to be involved. [12] Histological analysis reveals eosinophils and eosinophil degradation products known as Charcot-Leyden crystals. [13]

Clinical Features :

Allergic fungal sinusitis tends to be a disease of younger individuals, usually in their third decade (50%), [13] Mukherjee [14] reported 15% and it was less than that reported by Sarvanan K [12] (45.9%). Typically, afflicted individuals are immunocompetent. There is a frequent associated history of atopy including allergic rhinitis and asthma. Patients usually experience chronic headaches, nasal congestion, and chronic sinusitis for several years. There is often a history of sinus surgery.

Imaging Features:

Stamberger et al [14] proposed the Kuhn and Swain criteria may not be met in 40% patients, as opposed to his study ours showed that 93% met the criteria. So have the studies shown by DeShazo et al [13] (88%) and Mukherjee et al [15] (90%). There is usually involvement of multiple sinuses if not pansinusitis and rhinitis. Disease tends to be bilateral, and there is a frequent nasal component. The majority of the sinuses show near-complete opacification and are expanded. Noncontrast CT demonstrates hyperattenuating allergic mucin within the lumen of the paranasal sinuses. [15]

There is no enhancement in the centre or in majority of the sinus contents, which distinguishes this condition from neoplastic entities. Although the condition is not considered invasive, if left untreated, the involved sinuses expand and there is smooth bone erosion with subsequent intracranial or intraorbital extension and resulting cranial or orbital symptoms.

❖ Fungal Ball (Aspergilloma):

Also known as mycetoma, fungus ball is a common manifestation of chest fungal infection. The most widely accepted pathogenesis theorizes a deficient mucociliary clearance mechanism in which fungal organisms deposited in the paranasal sinuses are inadequately cleared. Organisms germinate, replicate, and incite an inflammatory response within the paranasal sinus. The fungus ball represents a tangled collection of fungal hyphae

in the absence of allergic mucin. There is no fungal invasion of the sinus mucosa, blood vessels, or bone, although chronic nongranulomatous inflammation may be observed in the mucosa. [16]

Clinical Features:

Fungal mycetoma tends to occur in older individuals with an apparent female predilection (72%). Similar findings have been put forth by Manning SC et al. (69%). [16] Afflicted individuals are usually immunocompetent. Patients are either asymptomatic or have minimal symptoms due to chronic pressure sensation. Other symptoms may include nasal discharge and cacosmia. [17]

Imaging Features:

A fungus ball typically appears as an intracavitatory mass surrounded by a crescent of air (Monod sign). Appearing as hyperattenuating (76%) at noncontrast CT due to dense matted fungal hyphae and may demonstrate punctate calcifications. On different positioning of the patient, the mass can be shown to be mobile. On occasion the mass may entirely fill the cavity, thus taking on the shape of the cavity, obliterating the surrounding air crescent and no longer being mobile.

Calcification is not uncommon (15%), which can range from none to heavy when compared with study by Ferguson BJ (32%). [17] Due to the inflammation and vascular granulation tissue formation, the bronchial arteries supplying the wall can sometimes be seen as markedly enlarged. [17] The adjacent pleura maybe thickened.

Conclusion

Computed Tomography of the paranasal sinuses has improved the visualisation of paranasal sinus anatomy and has allowed greater accuracy in evaluating paranasal sinus disease. It evaluates the osteomeatal complex anatomy which is not possible with plain radiographs. Anatomical variations studied on CT scan are found to cause fungal sinusitis. Malignancy differentials of acute invasion with bone erosion can be delineated. Also knowledge of vascular involvement is an important presurgical requirement depicted clearly on CT scan. This study has re-emphasized the concept that removal of disease in osteomeatal complex region is the basic principle of paranasal sinus injury which is best appreciated on CT scan. Thus our aim to clearly delineate the radiologic features of the fungal cases will direct the clinician towards expeditious diagnosis and necessary treatment.

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