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Original Article

Imaging features of rhinocerebral mucormycosis: A study of 43 patients

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ABSTRACT

Background: Rhinocerebral mucormycosis is a life-threatening infection caused by saprophytic fungi seen almost exclusively in immunocompromised patients.The objective of this study was to describe the imaging findings in patients with rhinocerebral mucormycosis.

Materials and methods: The case records of patients with biopsy/culture proven invasive rhinocerebral mucormycosis were reviewed. Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) images were retrieved from the Picture Archiving and Communication System (PACS) and analyzed. Statistical analysis was performed using descriptive statistics.

Results: CT and MR imaging of 43 patients showed predominant involvement of the ethmoid (37, 86%) and maxillary (34, 79%) sinuses. Extension to the orbit (32, 76%) and face (24, 57%) preceded involvement of the deep skull base (5, 12%) and brain (13, 31%). CT showed minimally enhancing hypodense soft tissue thickening as the predominant finding in involved areas, while MRI showed T2 isointense to mildly hypointense soft tissue thickening and heterogeneous post contrast enhancement as the main finding. Bone erosion was seen less often (17, 40%), with rest (26, 60%) of the patients showing extrasinus extension across grossly intact appearing bones on imaging.

Conclusion: CT and MRI shows a spectrum of findings in rhinocerebral mucormycosis. Imaging plays a major role in assessing the extent of involvement and complications.

1. Background

Rhinocerebral mucormycosis is a life-threatening infection caused by saprophytic fungi belonging to the genera *Mucor*, *Rhizopus* and *Absidia* [1,2]. All of these belong to the order *Mucorales* and class *Zygomycetes* [3]. The disease is seen almost exclusively in immunocompromised patients since normal phagocytic activity in immunocompetent hosts provide an adequate barrier against infection [1,2]. The clinical presentation in the early stages is typically with fever, headache, facial pain, nasal discharge, nasal obstruction and crusting. The disease progresses rapidly within a period of a few hours to days leading to cranial nerve palsies and features of CNS involvement [1]. Early imaging is helpful in assessing the extent of involvement of this lethal disease which requires prompt and aggressive treatment. In order to study the imaging findings in patients who were diagnosed with rhinocerebral mucormycosis who presented to us at various stages of the disease, we performed a retrospective study of all patients with this diagnosis who presented to our hospital. We also studied the imaging findings of those patients who reported for follow up after successful therapy.

2. Materials and methods

The case records of patients with culture and histological evidence of acute invasive rhinocerebral mucormycosis were retrospectively evaluated for relevant clinical data. The Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) images were retrieved from the Picture Archiving and Communication System (PACS) (GE Healthcare, Milwaukee, Wisconsin). CT scan was performed on a Siemens (Emotion 16 slice Siemens Medical system, Erlangen, Germany) or Philips (Brilliance 6 slice Philips Medical system, Best, the Netherlands) machine using a routine CT Paranasal sinus (PNS) protocol with 130kVP and 150–220 mA tube current. Intravenous contrast medium (low osmolar, non-ionic, 300 mg/mL iodine content) was used

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routinely at a dose of 1 ml/kg administered by pressure injector. Conventional MR Neck imaging including axial, coronal and sagittal T1 weighted (TR/TE 40/12 ms), T2- weighted images (TR/TE 4000/100 ms) and fat suppressed post contrast T1 weighted images were acquired. MRI imaging was performed using 1.5 T Siemens (Avanto: Siemens Medical system, Erlangen, Germany) or 3 T Philips (Achieva: Philips Medical system, Best, the Netherlands).

Image analysis- Retrospective review by consensus was performed by 3 staff radiologists to look for sites and extent of involvement, signal characteristics and complications.

2.1. Image interpretation

The sinuses showing opacification on CT or MRI were recorded in each case. The appearance on plain T1 and T2 images were documented. On post contrast CT and MRI, the type of contrast enhancement and involvement of any extra sinus structures including orbit, face, pterygopalatine fossa, masticator space, brain and cavernous sinus were noted. Presence of bone involvement was evaluated on the CT. Any complications like arterial thrombosis was noted on CT and MRI.

Fat stranding and soft tissue extension similar in appearance to the intrasinus soft tissue was taken as evidence of orbital, retroantral, masticator and pterygopalatine involvement. Orbital cellulitis was seen as stranding in the retrobulbar fat, without overt abscess formation. Cavernous sinus and internal carotid artery involvement was seen as thickening and non enhancement on post contrast scans with presence of abnormal surrounding soft tissue. Patients with intracranial extension were evaluated for dural enhancement, presence of extradural collections, infarcts, cerebritis and intracerebral abscess.

As patients presented to us at various stages of the disease, the patients in the study were divided into three groups based on the extent of regional involvement according to classification suggested by Rupa et al. Table 1 [4].

2.2. IRB clearance

Institutional ethics committee clearance was obtained for the conduct of this study.

2.3. Statistical analysis

Descriptive statistical methods were used for statistical analysis.

3. Results

A total of 43 patients with rhinocerebral mucormycosis having preoperative contrast CT and/or MRI imaging and histopathology confirmation were identified. All 43 patients underwent contrast-enhanced CT examination while 19 patients also had MRI. Out of the 19 patients who had MRI, only 14 underwent contrast imaging with gadolinium, primarily because of inability to use contrast in those patients with impaired renal function.

Table 1
Extent of regional involvement.

Stage	Areas involved	Number (%)
Stage 1	Nose & paranasal sinuses alone	2 (4.7)
Stage 2	Paranasal sinuses with immediate adjacent areas which are surgically resectable with minimal morbidity eg. orbit (extraconal), palate & oral cavity	16 (37.3)
Stage 3	Intracranial extension (extradural/intracerebral) or partially resectable with extension to pterygopalatine fossa, cavernous sinus, cheek and periorbital region	25 (58.1)

3.1. Demographic and clinical findings

Our study group comprised of 30 males and 13 females with ages ranging from 2 to 75 years (mean = 55 years). The majority of patients (83.7%) were aged over 40 years, with those aged 40–60 years (55%) being most affected.

Thirty nine patients (91%) had a history of uncontrolled diabetes, with 38 patients (88.4%) having type 2 diabetes mellitus and 1 patient with type 1 diabetes mellitus. Four patients (9.3%) had a predisposing haematological condition, one patient each with acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia and post bone marrow transplant status for aplastic anemia.

The clinical symptoms reported in our series were headache (38, 88%), nasal discharge (30, 69%), facial swelling (30, 69% patients), facial pain (28, 65%), decreased vision (9, 21%), fever (6, 14%), and epistaxis (4, 9%). Eleven patients (25%) presented with cranial nerve palsy with 6 patients having multiple cranial nerve palsies at presentation.

3.2. Imaging findings

(a) Sinonasal involvement

The ethmoid sinus was the most common paranasal sinus involved in our study (37, 86%). In the majority of patients (34, 79%) multiple sinuses were involved. The combination of maxillary, ethmoid and sphenoid (21, 49%) was most frequently seen. Unilateral sinus involvement was more common (79.1%) than bilateral sinus involvement (20.9%). The sinuses involved in mucormycosis is detailed in Table 2.

(b) Signal characteristics and imaging appearances

CT

On CT three types of contrast enhancement were seen, with mild enhancement being the most common form. Other types included low density opacification with no post contrast enhancement and heterogeneously enhancing intrasinus abscess like appearance with variable enhancing and non enhancing areas. The various enhancement types are shown in Table 3. In cases with non-enhancing opacification of sinuses, presence of retroantral, facial and orbital fat stranding and hypodense soft tissue extension indicated the aggressive nature of the infection (Fig. 1). Surrounding walls of the involved sinuses were normal in 26 cases (60%) with spread of infection across uninvolved bone into the perisinus fat. Bone involvement (Fig. 2) in the form of bone rarefaction, erosions and permeative destruction was seen in 17 cases (40%), involving the sinus walls and the contiguous bony structures. Nasal cavity involvement on CT was seen in the form of non specific inflammatory turbinate hypertrophy and inflammatory fluid in the nasal cavity (17, 39%). Nasal septal involvement was seen in the form of septal perforation in 3 patients.

MRI

On MRI, the lesions were isointense or mildly hypointense on T1W images in all cases. On T2W images rhinocerebral lesions (Table 3)

Table 2
Sinuses involved in mucormycosis infection.

Sinuses involved	Number (%)
Maxillary	34(79%)
Ethmoid	37(86%)
Sphenoid	26(60%)
Frontal	1(2%)
Maxillary + ethmoid	10(23%)
Ethmoid + sphenoid	2(4%)
Maxillary + ethmoid + sphenoid	21(49%)
Pansinusitis	1(2%)

Table 3
CT and MR features of paranasal sinus involvement.

CT feature	N (%)	MR feature	N (%)
Mucosal thickening	43(100%)	T1 W signal	
		Hypointense	19(100%)
Osseous erosion	17(40%)	T2W signal	
		Isointense/Hypointense	7(37%)
		Heterogenous	6(32%)
		Hyperintense	6(32%)
Enhancement pattern		Enhancement pattern	
Non enhancing	10(23%)	Intense homogenous enhancement	4(29%)
Mild enhancement	30(70%)	Heterogeneous enhancement	5(36%)
Heterogeneous	3(7%)	Central non enhancement with rim enhancement	5(36%)

(Fig. 3) were seen as (a) T2 isointense to mildly hypointense soft tissue lesions in 7 cases (37%) (b) T2 heterogeneous soft tissue lesions in 6 cases (32%) (c) T2 hyperintense mucosal thickening and intrasinus T2 hyperintense fluid in 6 cases (32%). In two cases involving the sphenoid sinus, bulky non enhancing extrasinus soft tissue was seen in the surrounding cavernous sinus which was intensely T2 hypointense. In one similar case involving the maxillary sinus, bulky hypointense soft tissue was seen in the pterygopalatine fossa.

Only 10 out of 19 patients with MRI images underwent diffusion weighted imaging through the para nasal sinuses. 7 out 10 patients showed diffusion restriction. These patients had either intracranial extension or soft tissue collections.

On post contrast scans, patterns of enhancement (Fig. 4) included intense homogenous enhancement in 4 cases (29%), heterogeneous enhancement with variable enhancing and non enhancing areas in 5 cases (36%) and as complete central non enhancement of the lesion with or without thin irregular rim of peripheral enhancement in 5 cases (36%). Enhancement of the lesions and pattern of extension of infection were best delineated on fat suppressed post gadolinium images. The black turbinate sign described by Safder et al. to be a feature of early nasal mucormycosis was found only in 2 patients out of the 14 patients with available post contrast MRI [5].

(c) Extrasinus extension

The most common site of extrasinus involvement was orbit (76%) and face (57%), followed by orbital apex, masticator space, pterygopalatine fossa, bone, skull base, cavernous sinus, brain and internal carotid artery. Further details of extrasinus extension including the type of involvement is given in Table 4 (Fig. 5).

Based on the classification by Rupa et al. most of the patients (25, 58%) appeared to have advanced disease (stages 3) at presentation. Further details regarding type of extension is given in Table 1.

(d) Chronic post-treatment bone findings

In some cases of acute mucormycosis following treatment and improvement of blood glucose control, a chronic persistent form of bone involvement (5 cases) was seen in the surrounding bones of the involved sinuses. The involved bones showed variable expansion, sclerosis, erosions and irregular lytic destruction on follow up imaging.

4. Discussion

Mucormycosis is an invasive fungal infection first described by Paulltauf A in 1885 [6]. Even though it can involve different body organs the most common type is the rhinocerebral form [1]. The infection is usually picked up by inhalation of the spores of the Phycomycetes fungi, most commonly belonging to the genera Mucor, Rhizopus and Absidia [1]. These fungal spores are freely seen in the environment in the skin, soil, air, dust and spoiled food. In immunocompromised patients as well as patients with poorly controlled diabetes mellitus and diabetic ketoacidosis, these organisms can become pathogenic. Immunocompromised states include organ transplantation, hematologic malignancies, chronic corticosteroid treatment and haemochromatosis [1]. However, Acquired Immune Deficiency Syndrome (AIDS) is only rarely associated with mucormycosis.

Disease spreads from the paranasal sinuses and nasal cavity to the extrasinus sinus sites including the brain. Orbital involvement results from spread through the nasolacrimal duct and medial orbital wall. The fungi invade the adjacent blood vessels causing thrombosis and infarction, as well as dissemination to the brain parenchyma

Imaging helps in assessing the extent of disease, identification of complications like ICA thrombosis and is indispensable for surgical planning [7]. But, imaging techniques including MRI show only nonspecific features during the early stage of the disease like mucosal thickening which may delay diagnosis. Hence a high clinical suspicion is mandatory for early pick up of this condition.

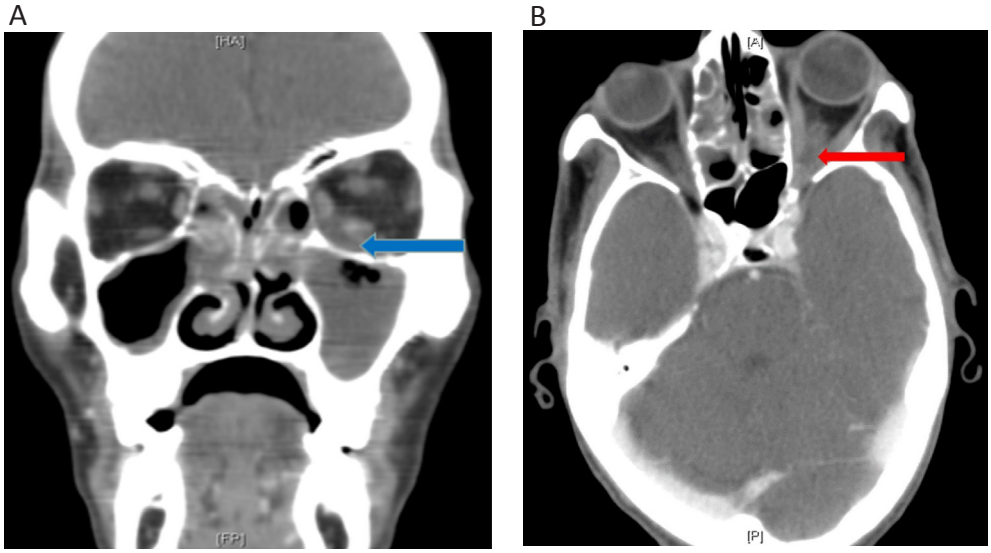

Fig. 1. 73 year old patient presenting with pain in the left side of face and orbit. (A) Coronal CT hows soft tissue density involving both ethmoid sinus and left maxillary sinus with extension into extraconal space of the left orbit (blue arrow). (B) Axial CT shows soft tissue density in the orbital apex region (red arrow).

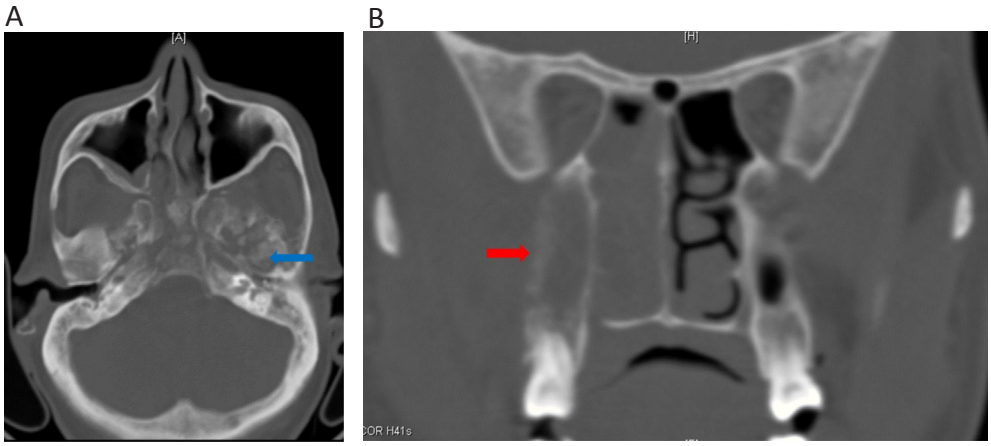

Fig. 2. Multiple patients with bony involvement in chronic mucormycosis A - CT shows mixed areas of sclerosis and irregular lysis involving the anterior and middle skull base (blue arrow). B - Coronal CT shows rarefaction and thickening of the maxillary sinus with adjacent soft tissue density (red arrow).

Mnif et al. and Herrera et al. have previously shown that the disease causes aggressive sinonasal and orbital changes on imaging [6,8]. Mohindra et al. has shown that MRI can detect cavernous sinus invasion and vascular complications such as thrombosis and ischemia [9]. According to Razek and Castillo involvement of cavernous sinus appears hypointense on T1 and T2 with intense inhomogeneous post contrast enhancement [10]. The 7 variable CT based model proposed by Middlebrooks et al. was found to be effective as a screening tool to triage patients at risk for acute invasive fungal sinusitis [11]. The variables included periantral fat, bone dehiscence, orbital invasion, septal ulceration, pterygopalatine fossa, nasolacrimal duct and lacrimal sac.

Our study with 43 patients of proven mucormycosis, also shows many of the findings described previously. Patients initially present with sinonasal involvement which later spread to the orbits, masticator space, face, pterygopalatine fossa, hard palate, maxillary alveolus, zygomatic process, skull base involving the clivus and pterygoid process and intracranial extension to involve the cavernous sinus, internal carotid artery and cerebral hemispheres.

CT predominantly showed minimally enhancing hypodense sinonasal soft tissue which was either isodense or slightly hypodense to surrounding masticator muscles. As Silverman et al. described, presence of retroantral, facial and orbital fat stranding indicated the aggressive

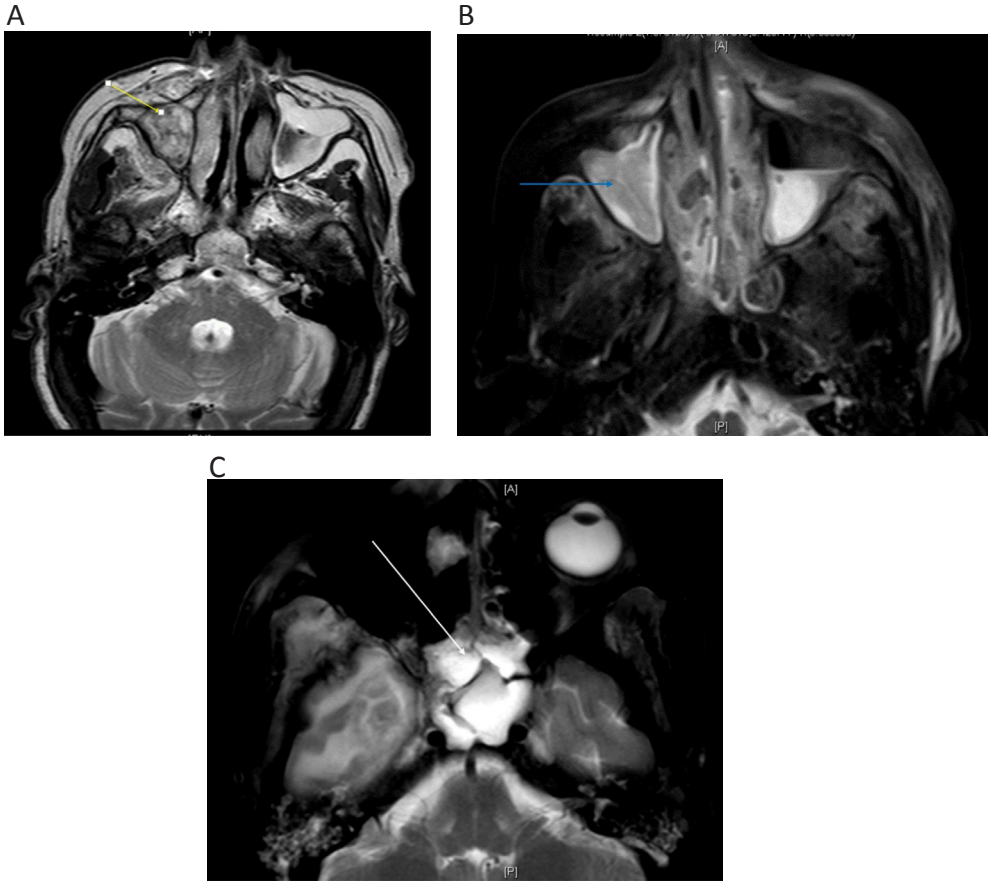

Fig. 3. T2 patterns in mucormycosis. T2 MRI showing A. Heterogeneous pattern involving the maxillary sinus (yellow arrow). B. Isointense pattern involving the maxillary sinus (blue arrow). C. Hyperintense pattern involving the sphenoid sinus (white arrow).

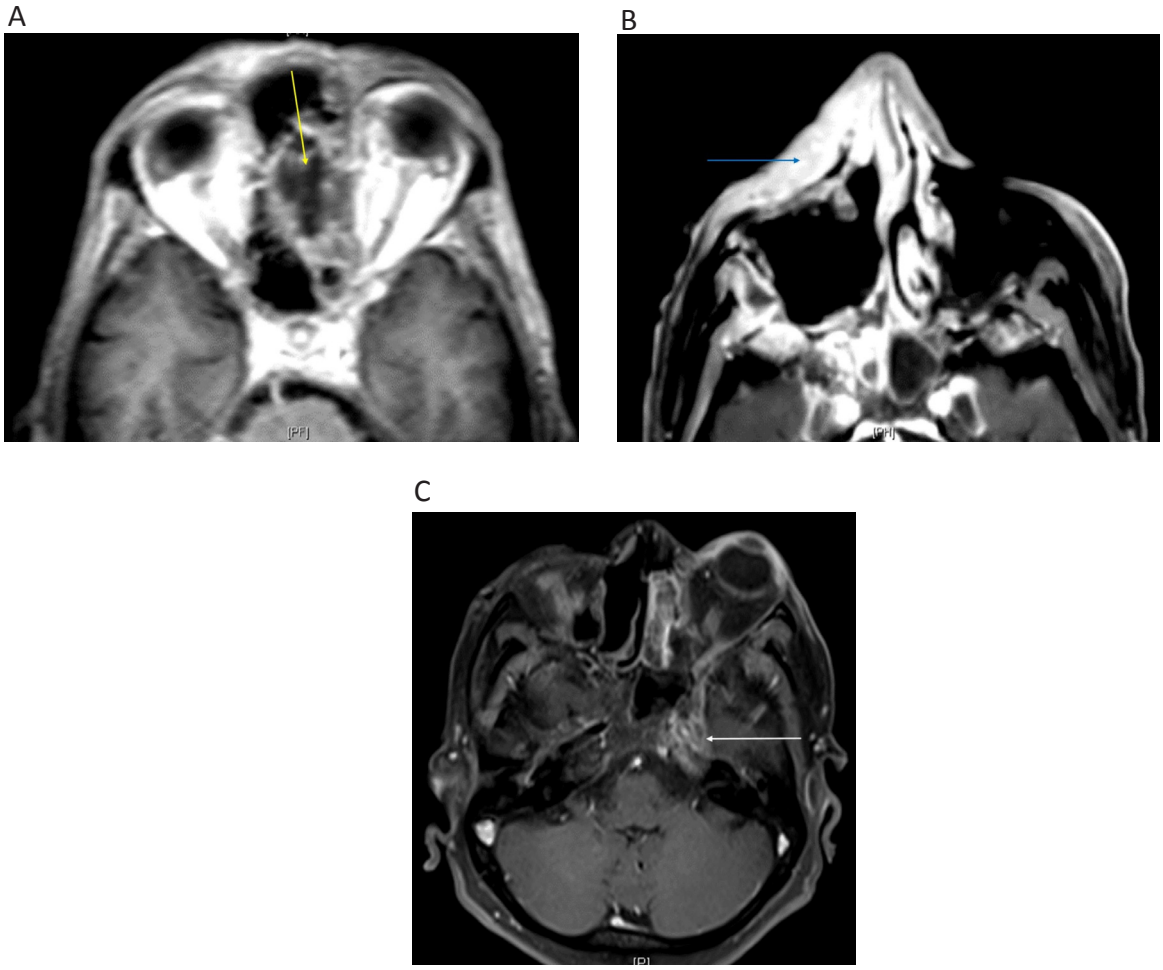

Fig. 4. MRI post contrast enhancing patterns in mucormycosis. T1 post contrast MRI showing A. Hypointense pattern involving left ethmoid sinus (yellow arrow) B. Intense enhancement pattern in the left premaxillary region (blue arrow). C. Heterogeneous enhancement pattern in the left ethmoid and surrounding the left internal carotid artery (white arrow).

Table 4
Involvement of extrasinus structures.

Site of involvement	Number (%)	Type of involvement
Face	24(57%)	Soft tissue infiltration and fat stranding
Orbit	32(76%)	Orbital cellulitis, optic neuritis
Orbital apex	21(50%)	Soft tissue infiltration and fat stranding
Pterygopalatine fossa	20(48%)	Fat stranding
Skull base	5(12%)	Rarefaction, lytic destruction, erosions and sclerosis
Cavernous sinus	6(14%)	Thrombosis
Internal carotid artery	4(10%)	Thrombosis
Brain	13(31%)	Cerebritis (3), infarcts (4), epidural (2) and intracerebral abscess (2)

nature of the infection [12]. In most patients, the extrasinus involvement occurred with intact bones, indicating the perineural/perivascular invasion of the organism, without destroying bone [12]. However, in some patients, CT also showed bone involvement in the form of bone rarefaction, erosions and permeative destruction. Gamba et al. had previously showed that early disease manifested as mucosal thickening on CT scans, usually without air fluid levels [13]. Recognition as mucormycosis was facilitated by knowledge of the clinical setting or by identification of invasive disease.

MRI of the sinuses and orbits showed three patterns as noted above with largest number of cases showing iso to hypo intense appearance on T2. The T2 hypointense appearance may be due to presence of iron and manganese in the fungal elements [14] Post contrast images showed three patterns, namely, intense enhancement of soft tissue, heterogeneous with variable enhancing and non enhancing areas and complete central non enhancement of the lesion with or without thin irregular rim of peripheral enhancement. Notably, T2W signal or enhancement patterns are variable and not reliable markers for invasive fungal infection. Careful attention to often subtle extra-sinus extension in the form of fat stranding in the premaxillary, retromaxillary fat, orbital fat stranding and altered fat in pterygopalatine fossa is more important to suggest the diagnosis of invasive fungal infection on imaging, in the appropriate clinical setting. As described in previous literature MRI proved to be very useful in detection of complications like orbital cellulitis, cavernous sinus thrombosis and ICA thrombosis [15,16].

Due to the angio invasive nature of the disease, skull base osteomyelitis and bone involvement is usually not seen or seen only late in the disease [17]. Only few case reports of chronic mucormycosis involving bone are available [17,18]. However in our series 5 patients presenting with acute mucormycosis went on to develop chronic infection with bone involvement following the initial treatment. The involved bones showed expansion, sclerosis, erosions and irregular lytic destruction. Also many of our patients showed destructive bony changes in the acute phase of the disease suggesting early bone involvement can also occur.

Limitations of this study included the absence of plain CT sections as part of the protocol in our institution preventing the evaluation of

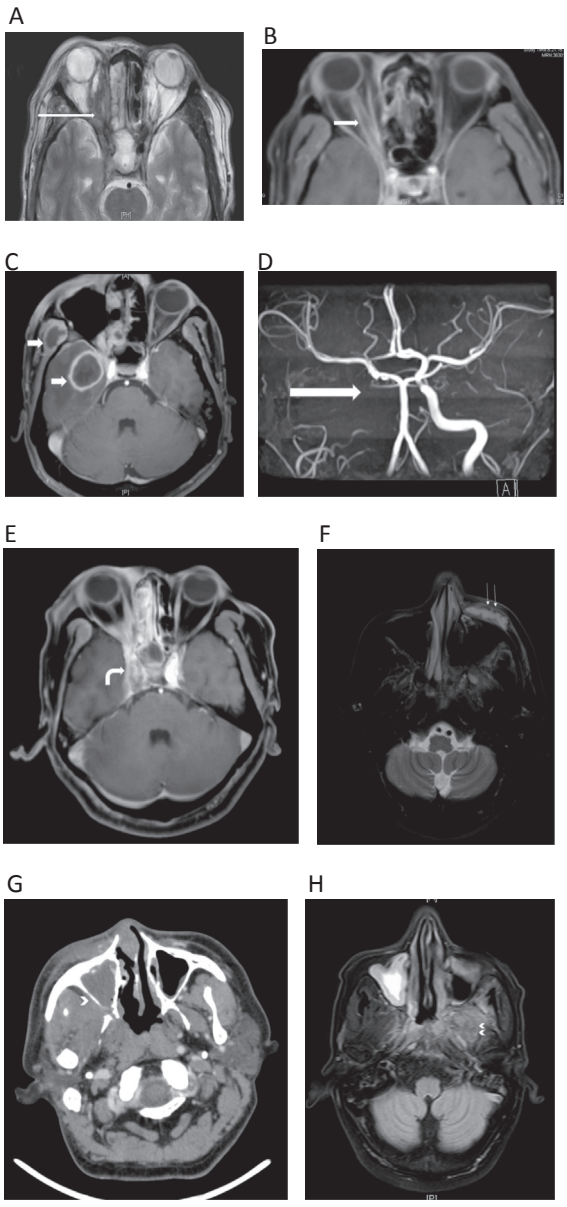

Fig. 5. Involvement of regional structures A. Ill defined iso to hypointense soft tissue in the orbit (long thin arrow) B. Thickening and peripheral enhancement of the right optic nerve (short thin arrow) C. Abscess involving the right temporal lobe and right temporalis muscle (short thick arrow) D. Non visualisation of the right internal carotid artery, suggestive of thrombosis (long thick arrow). E. Non enhancing soft tissue in the right cavernous sinus, suggestive of thrombosis (curved arrow). F. Abscess formation involving the left premaxillary region (double arrow) G. CT showing soft tissue opacification of the right maxillary sinus with involvement of retromaxillary fat (arrowhead) H. ill defined hyperintensity involving the left masticator space and pterygopalatine fossa (double arrowhead).

density of the tissues without contrast. The retrospective nature of our study led to some variation in the imaging protocol used for evaluation of suspected mucormycosis cases. Also since the study was retrospective ADC values of the areas of diffusion restriction could not be obtained. This prevented comparison with the values reported by Razek et al. who compared ADC values in malignant versus benign masses of the paranasal sinuses [19].

5. Conclusion

Based on our study, imaging of rhinocerebral mucormycosis show heterogeneous variable T2W signal intensity, different enhancement patterns and involvement of different sinuses. In our study group patients tended to chiefly present in the advanced stages of the disease when there is extensive extrasinus involvement. CT and MRI are invaluable tools which are complementary to clinical evaluation in assessing the extent of disease and diagnosis of complications.

Conflict of interest

We have no conflict of interest to declare.

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