



Post Covid-19 Acute Invasive Fungal Rhinosinusitis (AIFR): A Study of Histopathological Findings After FESS in Radiologically Diagnosed AIFR

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Abstract COVID-19 pandemic has led to a concerning surge of post-COVID-19 AIFR. Mucormycosis (BLACK fungus) is a rare but severe and life-threatening fungal infection occurred by mucormycetes, a family of moulds. More than 49,000 cases of AIFR were reported in three months in India. It primarily affects diabetics and spreads from the nasal cavity and paranasal sinuses (PNS). It also involves eye, palate, or brain. It is diagnosed clinically followed by radiological and pathological findings. We aimed to compare and analyse the pre-operative imaging with postoperative histopathological findings. The study was conducted in ENT department of tertiary care hospital, Rajkot. 200 patients were randomly selected who were presented to ENT OPD with clinically suspected Post COVID-19 AIFR. All patients underwent detailed ENT examination and radiological modality like MRI PNS, Brain, and Orbit. After proper pre-op evaluation, all patients underwent Functional Endoscopic Sinus Surgery (FESS). MRI findings were confirmed with that of histopathological findings done on KOH mount. All the patients were showing AIFR on MRI findings whereas 49% of patients had mucormycosis on Histopathology. Various other fungal infections like aspergillosis (7%), candidiasis (1.5%) were also found on HPE. 9% of patients showed combined infection with mucor and aspergillus species. Rest of the patients showed non-fungal rhinosinusitis. Inflow of the epidemic, plenty of patients were shown invasive fungal sinusitis in MRI patterns whereas many of them were HPE negative. Thus this study was done to know the efficacy of

radiological features with pathological diagnosis. We have considered both procedures standard in our study.

Keywords AIFR · Covid-19 · FESS · Radiology · Mucormycosis · Histopathology

Introduction

COVID-19 infection is caused by novel severe acute respiratory syndrome coronavirus 2 (SARS Cov-2). COVID-19 may be associated with a variety of bacterial and fungal co-infections and may be associated with pre-existing morbidity or may develop as a hospital-acquired infection. It has many complications out of which the exponential rise of cases of fungal sinusitis catches the attention. The COVID-19 pandemic has led to a concerning resurgence of mucormycosis. More than 49,000 cases of mucormycosis were reported in three months in India.

Mucormycosis is a wide spectrum of subacute or acute, and devastating infections, caused by angiotropic fungi, and is associated with high morbidity and mortality. Mucormycosis is an infection caused by a group of filamentous molds within the orders Mucorales and Entomophthorales. Mucorales occupy environmental niches including soil, decaying vegetable matter, bread, and dust. The order Mucorales comprise numerous genera (e.g., *Rhizopus*, *Mucor*, *Lichtheimia* [formerly *Absidia*], *Rhizomucor*, *Cunninghamella*, *Apophysomyces* spp., and *Saksena*) and others. Acute invasive fungal rhinosinusitis (AIFR) is a rapidly progressive and life-threatening fungal infection involving the nasal cavity and paranasal sinuses [1–3]. A disease's early stage is limited to the nasal cavity and paranasal sinuses (PNS), with lower mortality rates and better prognosis after debridement, while intracranial extension increases the mortality.

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Mucor and aspergillus were found predominant organisms in AIFR. Mucormycosis also called as BLACK fungus is a rare but severe fungal infection occurred by the mucormycetes family of molds. AIFR incidences showed a sudden rise after the second peak of COVID-19 in India. Judicious use of steroids and humidified oxygen in the management of COVID-19 results in uncontrolled DM and immunosuppressant state which is ultimately responsible for the development of mucormycosis.

Early diagnosis and treatment of AIFR are important to decrease morbidity and mortality of patients. Emergent imaging is vital in confirming the diagnosis and assessing the extent of fungal invasion and associated complications. Early diagnosis is done in clinically suspected AIFR patients with a recent history of COVID-19. The most valuable diagnostic tool is Magnetic Resonance Imaging (MRI) for early evaluation and for surgical planning. The most common MRI findings were mucosal thickening of PNS, air/fluid levels, soft tissue infiltration of the periantral fat planes, and black turbinate sign. Orbital invasion, bony dehiscence, erosion of alveolus, hard palate, and intracranial extension were found in advanced disease [4]. The efficacy of anti-fungal treatment depends on early and aggressive debridement of necrotic and unviable tissue to decrease fungal load with functional endoscopic sinus surgery (FESS) [5].

Radiological findings were confirmed with the histopathological examination (HPE) on the KOH mount of tissue which was removed during debridement with FESS. Histopathological examination plays a key role in diagnosing mucormycosis. This study was done to compare radiological findings with that of HPE results. We aimed to find possible different identification of organisms on HPE results that were eventually found AIFR with the possibility of mucormycosis in a majority of patients.

Aims and Objectives

- To compare and analyze MRI patterns with HPE results
- To diagnose different species of fungal organism in suspected AIFR patients
- To know the risk factors for developing mucormycosis after COVID-19

Materials and Methods

The study was conducted on 200 clinically and radiologically suspected AIFR patients presented to the outpatient department (OPD) of ENT at tertiary care hospital, Rajkot. All the patients presented with headache, facial pain, nasal blockage, and foul-smelling from the nose. In this study, we have included patients who came with rhinosinusitis.

Patients with orbit, palate, and cranial extension were excluded from the study. All the patients were primarily investigated at OPD with nasal endoscopy and detailed ENT examination. Suspected AIFR on nasal endoscopy patients were admitted to mucor ward under ENT department and underwent radiological and preoperative assessment for FESS. After surgery, all the tissue removed from the sinuses was sent for HPE on the KOH mount. So ideally this study represents the teamwork of ENT surgeons, Radiologists, and Pathologists.

All imaging was done in our institute, using institutional craniofacial MRI protocol. According to our protocol images were acquired in 16 channels 1.5 T MRI machine. Soft tissue and bone algorithm reconstructions were performed. Scans were obtained in an axial and sagittal plane including the brain, orbit, paranasal sinus, and hard palate.

Imaging was reviewed by the radiologist of our institute blinded to the patient's clinical information. It graded mucosal thickening in all PNS as mild, moderate, severe, or Soft tissue infiltration as present or absent in the following sites: peri-antral fat, sphenopalatine foramen, pterygopalatine fossa, inferior and medial orbital fat, bone marrow edema, rarefaction and erosion of alveolus and hard palate. Black turbinate sign, seen in postcontrast T1 sequence was defined as nonenhancement of nasal turbinates and nasal mucosa. Sinus mucosal thickening was graded as mild, moderate, and severe on a score of 0 to 3 (0=absent, 1—mild, 2—moderate, 3—severe). We have included patients diagnosed with rhinosinusitis. Orbit, palate and brain extension showed in patients were excluded from the study. Sino-nasal disease fungal involvement shows in Figs. 1.

Removed polypoidal tissue after FESS sent for HPE preserved in saline for rapid diagnosis and 10% neutral buffered formalin solution for routine histopathologic examination. KOH preparation was prepared from fresh tissue received in saline and examined under a microscope. The smears were prepared from tissue, fixed with 95% ethyl alcohol, stained with haematoxyline and eosin (H&E) stain, and examined under a microscope. The tissue, which was received in formalin was fixed overnight and processed with autotechnicon and stained with H & E stain. Pathologists of our institute confirmed mucormycosis diagnosis by microscopic examination. There were other different organisms also found in microscopic examination [6]. Special stains for fungus namely Periodic Acidic Schiff (PAS) and Gomori Methenamine silver (GMS) were utilized to confirm and/or differentiate the fungal organisms and to highlight the cell wall of the fungus.

Mucorales were identified on HPE with findings like non-pigmented, wide (5–20 μm), thin-walled, ribbon-like hyphae with pausi septations or aseptate, and right angle branching [7, 8] (Fig. 2b). Aspergillus species identified by nonpigmented (hyaline), narrow, septated hyphae with

Fig. 1 MRI findings shows mucosal thickening in PNS. **a** shows black turbinate sign (red arrow), **b** shows enhancement of the mucosa limited to ipsilateral maxillary and ethmoid sinuses

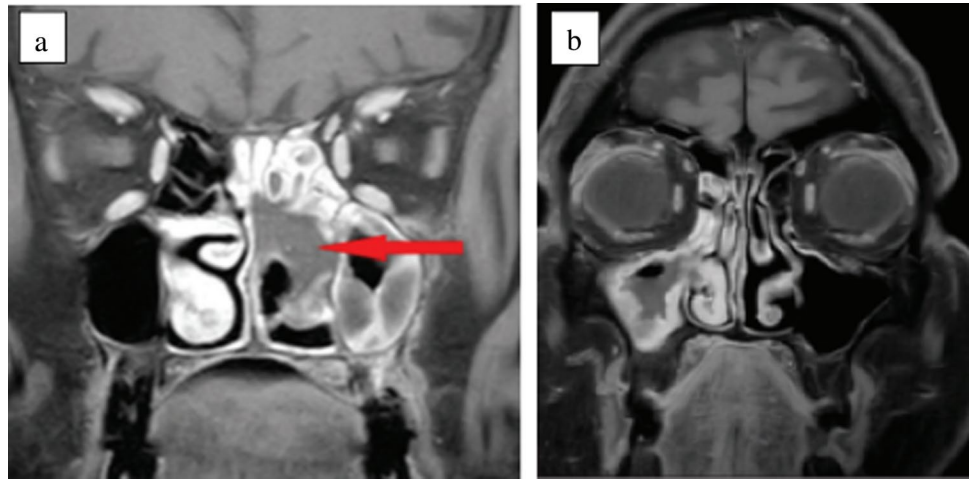
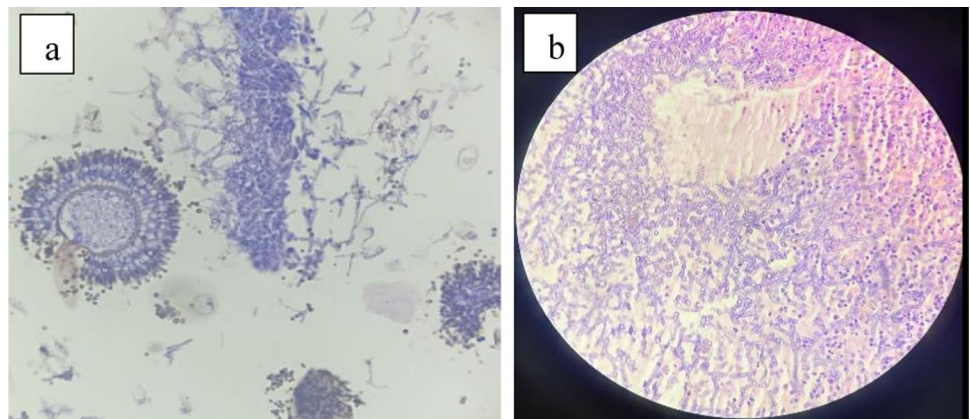


Fig. 2 Histopathological appearance of fungi. **a** Shows aspergillus with fungus ball, **b** shows mucor species



acute angle branching (Fig. 2a). Candida was demonstrated by yeasts (3–5 μm) forms of smaller size admixed with pseudohyphae [9]. Two pathologists independently analyzed the histopathological slides and parameters like site of biopsy, type of inflammation as acute, chronic, mixed suppurative and granulomatous. The presence of necrosis, fibrino purulent exudates, angio, soft tissue, neural and bony invasion were studied.

Results

The study included 200 patients with clinically suspected AIFR and subjected to radiological assessment and histopathological examination and all data were compared and analysed. Out of 200, 125 were males and 75 were females (Table 1) with age ranges from 22–80 years with a mean age was 51.35 years (Table 2). Patients were presented with comorbidities like DM (39.5%), Hypertension (4.5%), Both (10.5%) and haematological abnormalities (0.5%) (Table 3). The majority of patients have diabetes mellitus (DM). Radiological assessment with MRI showed

Table 1 Gender distribution of patients

Gender	No. of cases
Male	125
Female	75
Total	200

Table 2 Age distribution of patients

Age (in years)	Male	Female	Total no. of patients
21–30	4	1	5
31–40	18	12	30
41–50	43	16	59
51–60	46	32	78
61–70	10	10	20
71–80	4	3	7
81–90	0	1	1
Total	125	75	200

Table 3 Distribution of patients according to co-morbidities

Co-morbidity	Male	Female	Total	Percentage (%)
DM	56	23	79	39.5
HTN	2	7	9	4.5
DM+HTN	8	13	21	10.5
Others	0	1	1	0.5
None	59	31	90	45
Total	125	75	200	100

Table 4 Sinus involvement in radiological findings

Sinuses	No. of patients	Percentage (%)
Maxillary	12	6
Ethmoid	0	0
Sphenoid	0	0
Frontal	0	0
M+E	25	12.5
M+S	12	6
M+E+S	61	30.5
M+E+F	8	4
M+E+S+F	82	41

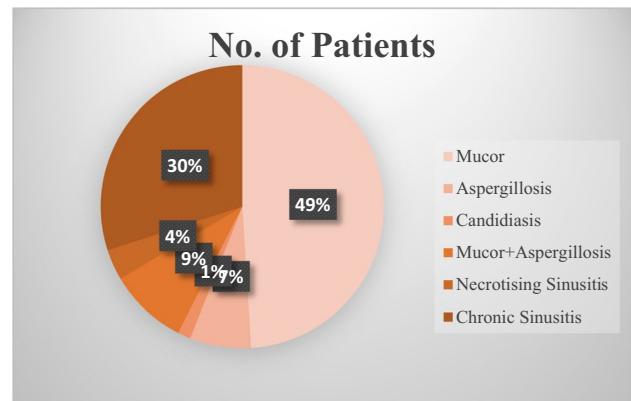
Table 5 Surgical debridement by FESS

FESS surgery	No. of patients	Percentage (%)
B/L	160	80
U/L	40	20

the involvement of paranasal sinuses in terms of mucosal thickening. Most commonly pansinusitis (41%) was found on MRI followed by the involvement of combination of maxilla, ethmoid, and sphenoid (30.5%). Only maxillary sinus was involved in 6% of all patients. Isolated involvement of sinus was not found in other sinuses (Table 4). According to radiological findings, patients underwent unilateral (20%) or bilateral (80%) functional endoscopic sinus surgery (Table 5). In histopathological findings, 133 out of 200 were reported positive for AIFR, while patients were found negative and showed chronic sinusitis (30%) in HPE reports. Mucormycetes (49%) were found most common fungal organism followed by aspergillosis (7%) and candidiasis (1.5%). Some patients also found combined infection with mucor and aspergillus (9%). Some of the patients showed necrotising sinusitis (3.5%) (Table 6, Fig. 3).

Table 6 Histopathological findings

HPE findings	No. of patients	Percentage (%)
Mucor	98	49
Aspergillosis	14	7
Candidiasis	3	1.5
Mucor + Aspergillosis	18	9
Necrotising Sinusitis	7	3.5
Chronic Sinusitis	60	30

**Fig. 3** Histopathological findings

Discussion

Covid-19, a pandemic results in various manifestations of comorbidities in patients after recovering from covid-19. The tremendous increase in mucormycosis following the COVID-19 pandemic resembles the re-emergence of rare pathogens such as Pneumocystis following the HIV pandemic. Notably, a significant proportion of individuals with CAM (covid-19 associated mucormycosis) lacked the traditional risk factors for invasive mold diseases. In the second peak of covid-19, irrational and judicious use of steroids and humidified oxygen in diabetic patients caused immunocompromised status which was a risk factor for mucormycosis. Patients developed AIFR within 5 days to 3 months with covid-19 infection. The incidence is higher in the 5th and 6th decade of life with 34.52% due to the high incidence of diabetes, hypertension, and use of the steroid.

Risk Factors for COVID-19 Associated AIFR

In our study, oxygen requirement was observed in 80% of patients in terms of either nasal prongs/masks or non-invasive/mechanical ventilatory support. Most of these patients had DM and received corticosteroids as a treatment. So these factors are favored in nosocomial infection. Remdesivir and tocilizumab were used for COVID-19 management with

specific indications of both drug usage. Tocilizumab was used rarely. Remdesivir is used in 18% of patients and only 1.7% received tocilizumab, and may not have role in increasing the risk of AIFR.

Corticosteroids have been found to predispose immunocompromised patients to mucormycosis. Methylprednisolone at a dose of 0.5–1 mg/kg in two divided doses for a duration of 5–10 days. According to literature rate of use of steroids is higher about 88% [10]. In our study, 90% of patients received systemic corticosteroids. Irrational and judicious use of steroids and oxygen can be a possible cause of mucormycosis.

In our study, the majority of patients were present with either pre-existing DM or New-onset DM. The SARS Cov-2 virus is said to damage the pancreatic islet cells leading to the development of New-onset DM, and worsening of pre-existing DM or DKA. In DM, impaired dendritic cell responses delay the timely activation of adaptive immune responses. Cytokine storm of COVID-19 increases insulin resistance via enhanced secretion of stress hormones like cortisol and other cytokines [10–12]. Hyperglycemia causes glycosylation of transferrin and ferritin and reduces iron findings. By reducing the ability of transferrin to chelate iron, acidosis causes an overall increase in free iron levels, allowing mucor to thrive. Rhizopus also interacts with GRP78 on nasal epithelial cells via CoH3 to invade and damage the nasal epithelial cells [13]. DM has been identified as an independent potential risk factor for mucormycosis [14].

The etiology of COVID-19-associated AIFR appears multifactorial including Pre-existing DM; new-onset COVID-19-related hyperglycemia; impaired mucosal immunity, mechanical breach in the nasal mucosa and mucosal necrosis, hypoxia, and increased ferritin levels all attributed to COVID-19; systemic corticosteroids; nosocomial infections in hospitalized patients, specifically those in the setting of intensive care, all seem to conjure up a vicious combination of risk factors. Apart from all these predisposing factors, the tropical Indian climate may itself predispose vulnerable patients to AIFR.

Symptoms and Signs and the Site of Involvement of COVID-19-Associated AIFR

Overall prognosis is poor in the case of mucormycosis with other co-morbidities. Onset of symptoms of mucormycosis after COVID-19 infection was 0–90 days with meantime was 8 days. Majority of patients presented within 8–10 days after COVID-19 infection. The most common presentation was headache and facial pain. Black nasal crusting with foul-smelling fungal spores was the most common finding on nasal endoscopy of a patient. Patients with intra-orbital involvement presented with ophthalmoplegia, vision loss,

ptosis, and restriction of eye movement, while palatal involvement showed loosening of teeth, black colored patch over palate, or palate necrosis. Altered sensorium or hemiparesis was found in cases of intracranial involvement. We have only studied patients with rhinosinusitis. Infection harbors the nasal cavity initially and gradually spreads to PNS, orbit, and CNS.

Diagnosis of COVID-19-Associated AIFR

Contrast-enhanced MRI is the imaging modality of choice. It allows delineation of soft tissue involvement earlier and is better than a CT scan, especially in the setting of orbital and cerebral involvement. In our series, MRI is predominantly used for diagnostic modality. Sino-nasal disease is identified on imaging by opacification of paranasal sinuses with high attenuation content, nodular mucosal thickening, and absence of fluid level. The sinus content invariably appears hypointense on T2 images secondary to the presence of iron and manganese in the fungal elements.

Diagnostic nasal endoscopy allows a quick inspection and sampling of the nasal cavity. It is a simple, bedside yet powerful tool to diagnose suspected cases. Nasal-endoscopy-guided swabs from the area of discharge, nasal mucosal inflammation, ulcer, necrosis, or eschar are likely to yield a better representative sample for direct microscopy using KOH wet mount with or without fluorescent brighteners. Culture is done for the identification of genus, species, and antifungal susceptibility. Histopathology of the biopsied tissue may be necessary for the definitive diagnosis of mucormycosis, to detect angioinvasion, and to distinguish an infection from a contaminant. It can also reveal co-infection. Mucor and aspergillosis species had a rapidly progressive course of disease.

Rhizopus arrhizus is responsible for most cases of mucormycosis worldwide, followed by fungi of other genera, including Mucor, Rhizomucor, Lichtheimia, Apophysomyces, Saksenaia, Cunninghamella, and others. Mucormycosis infiltrates blood vessels and bone trabeculae as wide, aseptate or slightly septate ribbon-like hyphae ranging from 5 to 20 microns (Fig. 2b). Septate hyphae with acute-angle branching ranging from 3 to 5 microns appear as Aspergillus sp. or other hyaline moulds (Fig. 2a). These organisms can be spotted on microscopy in sites of suppurative tissue necrosis. In our study, the majority of cases showed mucor species on histopathological findings followed by aspergillosis and Rhizopus.

Management of COVID-19-Associated AIFR

The management of mucormycosis essentially involves control of hyperglycemia or any other risk factor, optimal surgical debridement, and medical management with antifungal

agents. In our series, all the patients underwent extended surgical debridement. Debridement facilitates anti-fungal agents to penetrate vital mucosa by removing devitalized tissue.

In our study, we have found that infection with mucor and aspergillus requires extensive clearance of disease. The majority of patients had bilateral involvement. In case of chronic sinusitis, there was no intra-operative findings similar to fungal sinusitis.

Amphotericin-B is a drug of choice for AIFR. Patients with HPE positive reports for mucormycosis and aspergillosis were initially treated with intravenous liposomal Amphotericin—B 5–10 mg/kg/day for a minimum of 3 weeks followed by step-down therapy of oral Posaconazole 300 mg twice a day on day 1 followed by 300 mg once a day for a minimum of 6 weeks following clinical regression or stabilization. Those who came negative for mucormycosis on HPE were treated with intravenous liposomal Amphotericin—B 5–10 mg/kg/day for a minimum of 14 days followed by step-down therapy of oral Isavuconazole 200 mg thrice a day on days 1–2 followed by 200 mg once a day for a minimum of 6 weeks. This treatment was monitored with alternate day serum creatinine and serum electrolytes levels. The liposomal form is preferred since it is less nephrotoxic than deoxycholate type. In our series, 66.5% of patients received oral posaconazole and about 33.5% of patients received oral isavuconazole.

DeGuadio et al [4] compared CT findings of 23 patients with AIFR (9 patients with Mucor and 14 with Aspergillus species) with those of 10 control patients with acute myelocytic leukaemia (AML) and nonfungal rhinosinusitis.

Middlebrooks et al [15] analysed 23 variables of CT findings from 42 patients with AIFR (10 patients with Mucor, 18 with Aspergillus, and the rest with various fungal species) versus 42 control patients proved negative for AIFR, in order to design a diagnostic imaging model.

In our study, we have found 133 (66.5%) patients out of 200 confirmed AIFR on Histological findings with different fungal species. 98 (49%) patients showed mucor in histopathological findings from 133 patients whereas 14 (7%) patients had infection with aspergillus. 18 (9%) patients have combined infection with mucor and aspergillus species. 67 (33.5%) patients had non-fungal rhinosinusitis on Histological examination that was showed invasive fungal sinusitis on MRI.

Conclusion

COVID-19 is frequently associated with secondary infections, both bacterial and fungal possibly due to immune dysregulation. Besides this, the widespread use of broad-spectrum antibiotics, steroids, or monoclonal antibodies in

the management of COVID-19 may lead to the development or exacerbation of pre-existing fungal diseases. The clinician should be aware of the possibility of invasive fungal infections in patients with COVID-19, especially in patients with risk factors, and should enable early diagnosis and treatment to reduce morbidity and mortality.

SARS-CoV-2 is constantly undergoing genetic mutations and variations, whereas the genetic profile of fungi is generally stable. Genus-specific differences in the interaction of fungi and host immune cells are known in Mucorales. Whether the mucorales have acquired hypervirulence factors contributing to the current epidemic needs to be studied. To establish the role of SARS CoV-2 in modulating the interaction between mucorales and human host cells further studies are required.

Mucormycosis, coined and reclassified by R.D.Baker, is an insidious, life-threatening opportunistic mycotic infection caused by ubiquitous mold, mucormycetes, which belongs to the family of mucoraceae, order Mucorales, class zygomycetes [16]. There is an exponential rise in the incidence of mucormycosis of the second wave of covid-19. The burden of mucormycosis (COVID-19-associated) is exceptionally high in India. According to literature, the annual incidence of mucormycosis is very low around 1.7 per 1 million people [17]. In India, this incidence is almost 80 times higher accounting for 0.14 per 1000 population. Mucormycosis can manifest in 7 types of clinical presentation syndromes such as Rhino-orbito-cerebral, pulmonary, gastrointestinal, central nervous systems, cutaneous, disseminated, miscellaneous (bones, joints, heart, kidney, mediastinum, glands). Among all Rhino orbito cerebral mucormycosis (ROCM) is the commonest type accounting for about 30–50% of cases [18].

Diagnosis of mucormycosis is done radiologically and clinically. MRI is the investigation of choice for mucormycosis. MRI shows mucosal thickening of sinuses and bony wall erosion. Most commonly involved sinuses are maxillary and ethmoid followed by sphenoid. Most of the patients had pansinusitis. Surgical debridement is done by functional endoscopic sinus surgery. Radiological findings were confirmed with histopathological findings. Tissue biopsy is the gold standard for diagnosing and classifying the pathogen in AIFR, with histology demonstrating fungal invasion. Early diagnosis and prompt treatment are crucial, as a delay of even 6 days is associated with a doubling of mortality [19].

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Declaration

Conflicts of interest Not applicable.

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