Case Report

MUCORMYCOSIS: Re-emerging opportunistic fungal infections in COVID-19 pandemic times in Indian patients (South Indian) – A series of seven cases

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Abstract

Opportunistic fungal infections are associated with patients having compromised systemic health. In India, a slow rise in cases of mucormycosis has been observed as the country has seen a rising number of diabetes mellitus cases in the recent decades. This apart, an enormous increase in case numbers was seen in association with COVID-19 infections in the Asian subcontinent, Southeast Asia, markedly in India. Many cases of mucormycosis were reported in association with COVID-19 positive history and post-treatment for COVID-19. They were presented in the form of rhino-cerebral-mucormycosis, in patients with and without diabetes. The presentation of the disease differed at different times of the pandemic to some extent. Some of the cases initially came in an acute format, but at the later end of the epidemic, they presented in an indolent form. A compilation of cases is provided to illustrate the variation in presentations and findings of mucormycosis cases diagnosed at different times of infection of the COVID-19 waves.

Keywords: Acute and indolent, COVID-19 pandemic, diabetes, Indian scenario, opportunistic infection, osteomyelitis, rhino-cerebral mucormycosis

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INTRODUCTION

Fungal infections in humans are predominantly opportunistic and include a variety of fungal organisms: aspergillosis, mucormycosis, cryptococcosis and candidiasis. Opportunistic fungal infections need an early diagnosis and appropriate treatment. It becomes paramount in cases of invasive mycosis, seen as mucormycosis cases associated with the COVID-19 pandemic. In India, mucormycosis cases have been on a slow surge related to uncontrolled diabetes for close to a decade.[1-4] This has dramatically changed in the times of the COVID-19 pandemic. An acute rise in case numbers has been reported. Haematologic malignancies, transplantations, trauma, burns, alcoholism, HIV infections, diabetes, chronic corticosteroid[1] use and immuno-compromised patients are mainly predisposed individuals to the infection. The added new predisposing factor is COVID-19 infection, alleviated with different modalities of treatment, which

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has triggered torrential precipitation of mucormycosis cases in India. Here, we attempt to present and discuss cases of rhino-cerebral-mucormycosis (Zygomycosis) in different scenarios but having a common association with COVID-19 infection. This report is a revisit to mucormycosis in the COVID-19 pandemic as an emerging infection with rapid progression and high mortality. In this series, we discuss seven cases of mucormycosis.

CASE SERIES

Case 1

A 48-year-old female reported to the clinic with a swelling on the right side of the face involving the maxillary arch. She had multiple draining sinuses from the 13 to 18 teeth region. Discoloured gingiva, loose teeth and a blocked right nostril were eminent for 3 months. Dull pain, headache and numbness in the right alveolar area were the given history. The patient was a non-diabetic with a history of COVID-19 positivity, which was diagnosed only 2 weeks back. Computed tomography (CT) showed a hyper-dense lesion of the right maxillary sinus, 2 × 3 cm in size, abutting the sinus floor and lateral wall, clear of medial and orbital wall. The sinus wall appeared thickened. Ortho-pantomogram (OPG) showed a hazy right maxillary sinus. Partial involvement of the ethmoidal sinus was also noted [Figure 1].

Right maxillary sinus debridement was performed, under general anaesthesia (GA). The surgical grossing showed multiple, soft, blackish bits of necrosed tissue.

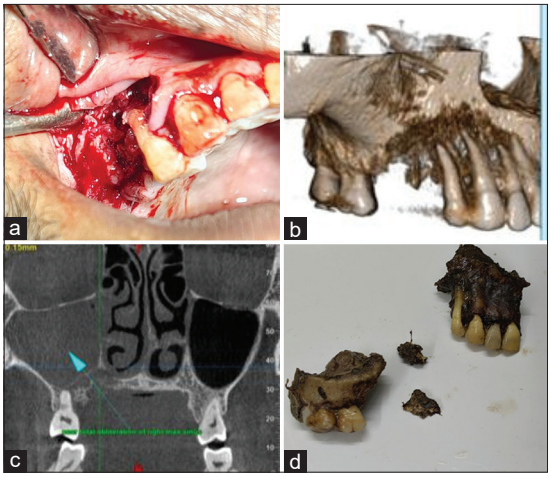

Figure 1: (a) Clinical intra-operative image showing inflamed soft tissue with friable bone, mobile teeth and missing 15. (b) CBCT image shows the right maxillary quadrant with missing 15 and 16, with peri-apical and inter-radicular bone loss. Erosion was noted along the buccal plate. (c) Radiographic image shows a hazy right maxillary sinus with communication from the palatal bone and peri-apical region of the molar tooth. (d) Surgical grossing of one of the cases showing fragmented necrotic maxillary bone with teeth attached

Histopathological sections showed sinus lining with squamous metaplasia, stratified epithelium, large areas of inflammation/infection, oedema, haemorrhage and necrosis. Loss of all structures in connective tissue, with dense inflammatory cell response and necrosis, was observed. Areas of necrosis showed a large number of bulky aseptate hyphae, branching at 90° angle. On special staining, the tissue showed periodic acid-Schiff (PAS) +ve hyphae. With clinico-pathological correlation, a diagnosis of rhino-cerebral mucormycosis was given [Table 1].

The patient was treated with hemi-maxillectomy and endoscopic curettage of frontal and ethmoidal sinus, along with medical treatment with Amphotericin. Rehabilitation was performed with fibula graft. Follow-up has been maintained for the last 3 years, with good bone regeneration [Table 1].

Case 2

A 53-year-old male reported pain in posterior teeth for 3 weeks (severe throbbing pain), ulceration on the left side of the palate, numbness on the left cheek and blurred vision. On examination, the lesion showed involvement of the left maxillary area and multiple draining sinuses for few weeks. The patient was not a known diabetic and had a history of COVID-19 positivity for a few weeks. Radiological examination on MRI showed a hyper-intense lesion involving the left maxillary sinus and ethmoidal sinus abutting the medial wall of the orbit. Surgical exploration and treatment were performed under GA.

Surgical grossing revealed multiple, dark soft tissue bits with haemorrhage and necrosis. Histopathology showed pseudo-stratified ciliated epithelium with dense inflammation in the connective tissue, large areas of haemorrhage and necrosis. Aseptate bulky hyphae in clusters along with bacterial colonies were evident which were PAS +ve. Diagnosis based on clinico-pathological correlation was given as mucormycosis-rhino-cerebral type [Table 1].

The patient was treated with left hemi-maxillectomy along with primary closure and later rehabilitated with cast partial denture and medically treated with fluconazole and Amphotericin. Follow-up maintained for last 3 years, with radiography, showed well-healed bone and soft tissue [Table 1].

Case 3

A 28-year-old male reported pain in the right maxillary arch, long-standing headache, multiple sinuses draining on the alveolar area on the right side, pain and mobility in the upper

right posterior molars teeth. The patient gave a history of COVID-19 infection, almost 1 year back. The patient was a diabetic, under treatment and in control. The patient showed right and left maxillary sinus involvement.

CT scans in axial and coronal views exhibited hyper-dense lesions of both the right and left maxillary sinus. Lateral and orbital walls appeared intact. Thickening of the sinus wall was evident. The right and left meati appeared to be hazy.

A partial maxillectomy was performed along with surgical debridement of the right and left sinuses under GA, followed by antifungal therapy. Later, prosthetic rehabilitation was carried out [Table 1].

Histopathology of hematoxylin and eosin (H&E) stained sections on the right side revealed ciliated pseudo-stratified antral lining with acute sinusitis, oedema and haemorrhage with necrosis. Multiple areas of abscess with dead bone and clusters of fungal hyphae that were broad bulky and non-septate along with giant cells were evident [Figure 2]. Large areas of resorption and non-vital bone were observed. The left side showed chronic inflammation of the soft tissue along with osteomyelitis [Figure 3]. A diagnosis of fungal osteomyelitis – mucormycosis for the right side was given. Lesion of the left side was reported as non-specific osteomyelitis as no fungal hyphae were detected.

Case 4

A 38-year-old male reported severe pain in the right maxillary region with a large ulcer on the right posterior palatal mucosa. He gave a history of COVID-19 infection 1 year back and a history of diabetes. Radiological examination on CT scan showed a thickened sinus wall of the right and left maxillary sinus and involvement of ethmoidal sinus. The orbital wall was intact. Maxillary alveolus was not involved.

The patient was treated medically with Amphotericin B and later shifted to fluconazole. He also underwent surgical debridement followed by prosthesis [Table 1].

Histopathology of the right side showed pseudo-stratified ciliated epithelium with chronic maxillary sinusitis, along with haemorrhage and oedema. Bone showed the presence of the aseptate bulky fungal hyphae and multiple areas of abscess with osteomyelitis. Haemorrhage and necrotic areas also showed clusters of aseptate bulky hyphae along with a large number of giant cells. Compact bone with resorption, dead bone and filamentous hyphae that were non-septate and branching at right angles were noted. On the left side, osteomyelitis was observed but devoid of any fungal hyphae. On clinico-pathological co-relation fungal, osteomyelitis associated with mucormycosis was reported for the right side [Table 1].

Case 5

A 45-year-old male reported pain in the right maxillary region for the past 2 months, which was continuous and radiating. The extraction sockets of 15 and 16 showed draining pus. A diffuse extra oral swelling was observed on the right side. The patient had a positive diabetic history for 10 years and was under medication. No history of COVID-19 infection was evident. Radiological examination revealed erosive lesions involving the right maxillary alveolar process, hard palate and anterior wall of the maxillary bone. CT scan showed right maxillary sinus wall thickening, with lateral wall involvement and meati. The orbital wall was uninvolved.

The case was treated by primary debridement and medication.

Surgical grossing revealed bony pieces and soft tissue from the right maxillary sinus [Figure 1]. On histopathological examination, soft tissue sections showed stratified epithelium with inflammatory cells and oedema. Chronic inflammation/infection, giant cells, areas of degeneration, necrosis and haemorrhage were evident. Hard tissue sections showed large areas of necrotic bone/osteomyelitic bone with hyphae and inflammatory cell response. The hyphae were PAS +ve. On clinico-pathological correlation, the case was reported as fungal osteomyelitis-rhino-cerebral type [Table 1].

The patient did not return for further treatment and thus lost follow-up with the patient [Table 1].

Case 6

A 49-year-old female patient reported pain and pus discharge in the left maxilla for the past 4 months. She gave a history of previous COVID infection, treated with the use of steroids. She had a known case of diabetes mellitus and was under medication for the same. Radiological examination revealed destruction along the left posterior maxillary region with communication with the left maxillary antrum.

Surgical grossing revealed multiple small, fragile soft and hard tissue specimens, along with antral tissue. On histopathological examination, the section showed trabecular bone with associated soft tissue. The mature trabecular bone showed resorptive bays at multiple foci, with infection and inflammation in the marrow space. Multiple bulky aseptate hyphae were noted in the soft tissue and also in the marrow areas. The hyphae showed

branching at 90° and were present in large clusters. A dense chronic inflammatory cell response was observed in the marrow space and the soft tissue, along with oedematous connective tissue and haemmorhagic patches. The antral lining was evident with ciliated pseudo-stratified epithelium and multiple secretory units in the connective tissue. On PAS staining, the section showed the presence of darkly stained bulky aseptate hyphae in the marrow space and the soft tissue [Figure 4]. A diagnosis of fungal osteomyelitis, mucormycosis type, was established [Table 1].

The patient was treated with complete debridement of the involved tissue, and primary closure was achieved. However, the patient did not return for long-term follow-up.

Case 7

A 55-year-old male presented with intra-oral draining sinus in the left infra-orbital region for the past 2 weeks. The patient had a known case of diabetes mellitus for 10 years. Radiological examination revealed gross destruction along with the anterior and left posterior maxilla, the maxillary sinus, the left zygomatic bone and the medial canthal region.

Surgical grossing revealed multiple small and hard tissue specimens, curetted from the left maxilla, sinus, zygomatic bone and canthal region. On histopathological examination, sections showed mature trabecular bone with multiple foci of osteoclastic activity and resorption bays. Large areas of bone destruction were noted. Marrow spaces show inflammation with the presence of numerous fungal hyphae. Large bulbous and non-septate hyphae branching at 90° were detected along with inflammatory cells, predominantly plasma cells and lymphocytes. Sub-mucosa showed inflamed minor mucous salivary glands. On PAS staining, the presence of PAS +ve non-septate hyphae with branching at 90° was observed in the soft and hard tissue. On Grocott-Gomori silver methanamine (GMS) staining, dark brown-black fungal hyphae were noted in the marrow spaces and soft tissue wall of the antrum [Figure 5].

The patient was treated with complete debridement of the involved regions, and primary closure was achieved; later, the patient underwent complete denture fabrication. The patient was also medically treated with Amphotericin B and later shifted to fluconazole for 6 months. The patient has been on regular follow-up for the last 2 years with no reported complications so far [Table 1].

DISCUSSION

Phycomycetes is a saprophyte that is omnipresent. The fungus belongs to the class-mucorales, with the common genera being *Mucor* and *Rhizopus*[5] which are pathogenic to man.[1] *Rhizopus arrhizus* is the most common cause of

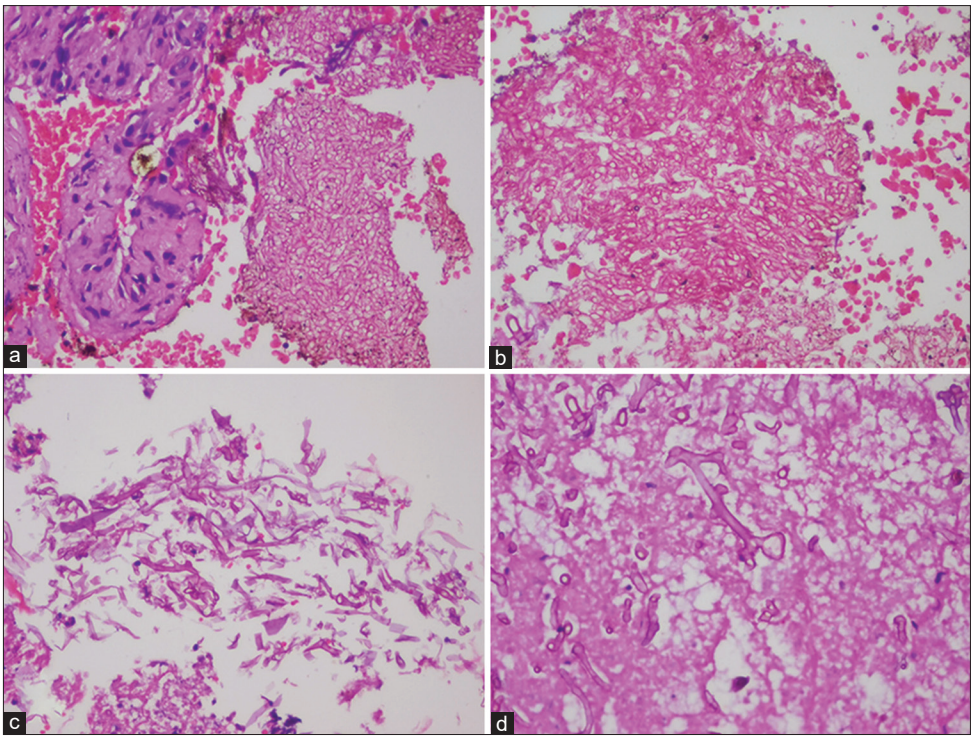

Figure 2: (a) H&E-stained slide images show numerous fungal hyphae which are seen in oedematous necrosed connective tissue. x100. (b) H&E-stained slide images show numerous fungal hyphae that are clustered together into a fungal ball. x200. (c and d) H&E-stained sections show prominent darkly stained bulky aseptate hyphae branching at right angles interspersed in the soft tissue in a necrotic background x100

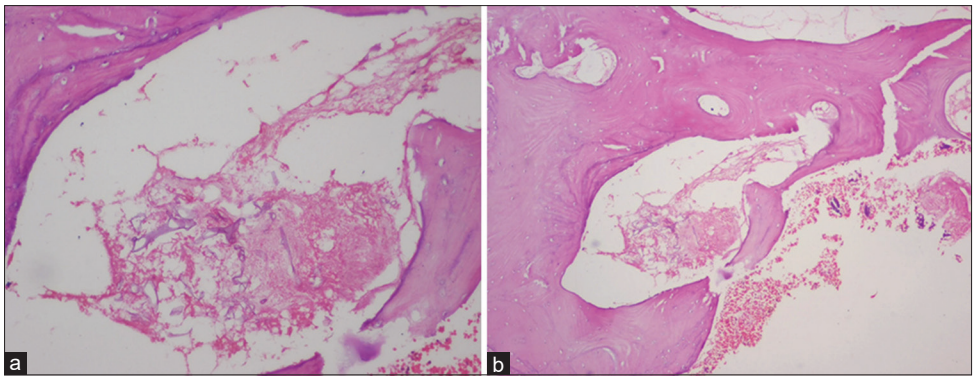

Figure 3: (a) H&E-stained decalcified section of bone showing an indolent infection with few fungal hyphae infiltrated into the marrow spaces with haemmorhagic areas and minimal inflammation surrounded by mature trabecular bone. x100. (b) Section shows marrow spaces with fungal hyphae along with resorptive activity along the inner wall and empty lacunae. x200

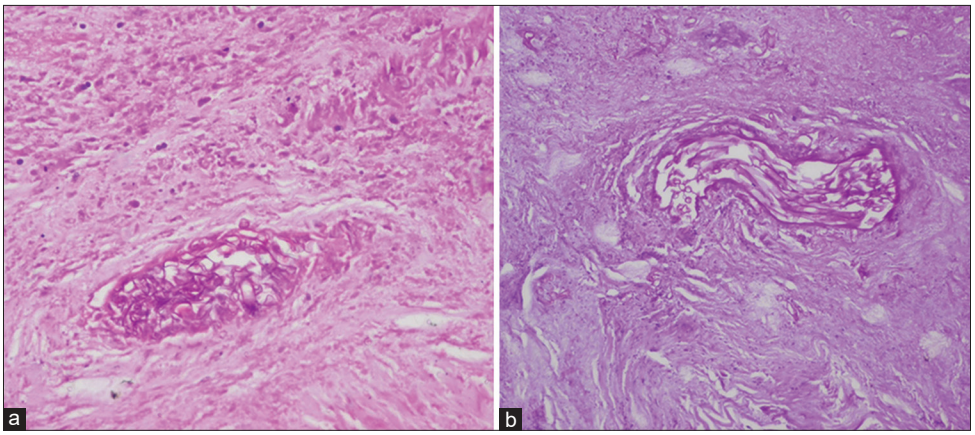

Figure 4: (a) H&E-stained section shows fungal hyphae clustered together in the soft tissue. x200. (b) PAS-stained section confirming prominent aseptate bulky fungal hyphae. x200

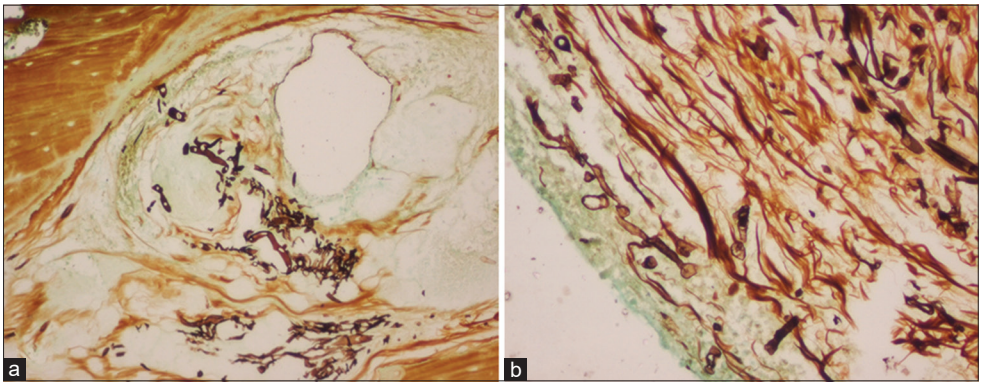

Figure 5: (a) Gomori's methamine silver-stained section shows dark brown-black fungal hyphae in the marrow spaces. x100. (b) Multiple fungal hyphae seen as brown, black branching filamentous organisms in a background of degenerating collagen fibres (yellowish brown) x400

mucormycosis globally, but the *Apophysomyces*[6] species ranks second in India. Infections due to *Rhizopus microsporus* and *Rhizopus homothallicus* are rising in India.[3,4,7]

Most of the mucormycosis infections are categorized into different clinical forms, namely pulmonary, disseminated, gastrointestinal and rhino-cerebral.[8] The rhino-cerebral-orbito mucormycosis (RCOM) is considered to be the most common with 45–74% of the cases.[3] The mortality of the RCOM is around 49–50%, and morbidity ranges around 46%.[9,10] Manifestations of mucormycosis usually depend on the route of entry of fungal spores into the body which is mainly by inhalation or ingestion or direct skin injection and also depends on the co-morbid diseases of the infected patients.[10] In this series, all our cases are presented in the form of RCOM.

Table 1: Clinical details, diabetic status, treatment, histopathological diagnosis and follow up for all seven cases

Case No	Age/ Gender	Location and side	Diabetic status	Other co-morbidities	Treatment done	Histo-pathological diagnosis	Treatment and recall
1	48/Female	Right Posterior maxilla	Non-Diabetic	None	Hemi-maxillectomy with fibula reconstruction	Mucormycosis-Rhino-cerebral type	3 years follow-up. Bone reconstruction maintained well
2	53/Male	Left palate and posterior maxilla	Non-diabetic	None	Hemi-maxillectomy with primary closure and CPD fabrication	Mucormycosis-rhino-cerebral type	3 years follow-up. Bone morphology and prosthesis maintained well
3	28/Male	Right maxillary arch	Diabetic	None	Partial maxillectomy with surgical debridement of the antrum. rehabilitation with denture prosthesis.	Mucormycosis-rhino-cerebral type	3.5 years follow-up. Bone height maintained with prosthesis.
4	38/Male	Right maxillary region with palatal ulceration	Diabetic	None	Surgical debridement followed by prosthesis.	Mucormycosis-rhino-cerebral type	Well-maintained prosthesis.
5	45/Male	Right maxillary region	Diabetic	None	Patient did not follow-up after the incisional Biopsy	Mucormycosis-rhino-cerebral type	Lost to follow-up.
6	49/Female	Left maxillary region	Diabetic	None	Complete debridement of the necrosed tissue, along with maxillary sinus, primary closure was achieved.	Mucormycosis-Rhino-cerebral type	Lost to long term follow-up
7	55/Male	Left posterior maxilla and left infra-orbital region.	Diabetic	None	Complete curettage of the necrosed tissue, along with maxillary sinus, zygoma and medial canthus, primary closure was achieved. A complete denture was fabricated	Mucormycosis-rhino-cerebral type	2 years follow-up. Bone morphology and prosthesis maintained well

The infection in the form of mucormycosis is fulminating and can be lethal. The reported cases are frequently associated with diabetes mellitus (DM) and acidosis related to diabetes. There could be a strong link between DM, sinus involvement and *Rhizopus* spp. Indeed, sinus involvement is the preferential site in diabetic patients, and *Rhizopus* spp. more frequently leads to rhino-orbito-cerebral involvement.[11] Recently, case numbers have increased which can be attributed to an increase in cases of diabetes and also an increase in patients with immuno-compromised states and debilitating diseases.[1,9] Diabetes is the most common metabolic disorder and is an independent risk factor for severe COVID-19 and mucormycosis.[12] In patients with diabetes, COVID-19 super-infection with mucormycosis will lead to adverse clinical outcomes and prolonged hospital stays. Hyperglycemic patients are more susceptible to infections due to reduced number of dendritic cells in circulation, increased apoptosis of NK cells and neutrophilic dysfunction. Diabetic patients are immuno-compromised and lack normal functioning of immune cells. Therefore, diabetic patients are more susceptible to develop mucormycosis. The availability of free iron and acidic pH in uncontrolled diabetes makes diabetic patients more prone to mucormycosis.[4] The reported mortality of rhino-cerebral mucormycosis in patients with diabetes is 40–50%. Overall, COVID-19, diabetes and corticosteroid usage lead to a high risk for invasive fungal mucormycosis.[13] We saw in our series that five cases had an association with diabetes for more than a decade but two of our cases were young and non-diabetic.

Along with diabetes and an immuno-compromised state, several other risk factors are being highlighted. A few to be noted are hypertension, chronic kidney disease, haematological malignancies, human immuno-deficiency virus, auto-immune disorder, burns, iron overload, organ transplantation and malnutrition.[1,8,9] Our series highlights the significant immuno-compromised state of diabetes and COVID-19 which made the patients more susceptible to mucormycosis.

An increase in the survival of these patients, along with improvised diagnostic approaches by clinicians, is leading to better recognition of this disease entity. The COVID-19 pandemic has increased the case numbers of mucormycosis enormously. The rhino-cerebral form is often associated with the maxillary jaw, nose and paranasal sinus. It spreads to the eye and orbital region with further involvement of the intracranial area. Hence, an early recognition and institution of appropriate treatment is imperative for survival and control of the disease. The COVID-19 pandemic has triggered rhino- cerebral mucormycosis cases in large numbers in acute and chronic forms. The mucormycosis cases reported and discussed here are all related to COVID-19 pandemic, some with a history of COVID-19 positivity, a few with the use of steroids and some with a history of hospitalization and DM.[9] Out of

seven cases, two of our cases did not present with a history of diabetes.[14] None of the cases entered an acute state with loss of function or functionality associated with the eyes and surrounding area.

A diagnosis of rhino-cerebral-mucormycosis requires early recognition of the signs and symptoms and a mandatory biopsy for confirmation of the diagnosis.

The initial signs and symptoms of rhino-cerebral mucormycosis are related to the nose, paranasal sinus, face and maxillary jaw. The common symptoms of the RCOM are headache, facial pain, lethargy, black palate, palatal ulceration[5,12] and sores,[6] osteomyelitis, dysfunction of cranial nerves, multiple painful mobile teeth, tenderness and pain in the maxillary alveolar bone, bad odour, multiple draining intra-oral sinuses and discoloured mucous membrane in the associated area which is common in the oral cavity.[1,9] Nasal discharge, nasal blockade, sinusitis, discolouration and pain along with the tenderness of the face in the maxillary area are the early signs of the infection in nasal and paranasal areas. The orbital findings can fall in the spectrum of mild proptosis,[6] peri-orbital oedema, blurred vision, numbness in the orbital and peri-orbital area, eyelid swelling and increased lacrimation.[1] A more pronounced involvement can cause exophthalmos, ophthalmoplegia, conjunctival haemorrhage, fixed, dilated pupils and blindness.

In the Indian scenario, the most common complaints intra-orally were dull pain in the alveolar ridges, multiple draining sinuses, multiple loose teeth, halitosis and antral involvement with stuffy nose, discharge from the nose with or without blood, heaviness of head and headache.[3]

In our case series, all seven cases were symptomatic. Among seven cases, four cases were reported with acute symptoms, whereas three cases were reported with a chronic state of symptomatology. The most common symptoms were intra-oral draining sinuses, pain in the involved region, loose teeth, swelling, blurred vision, palatal ulceration and stuffiness in the nose and sinus area. A few uncommon symptoms included mobile teeth as the only presentation; one case presented with a draining sinus in the infra-orbital region, discoloured gingiva and numbness on the cheek.[1]

The COVID-19 association with this wave of mucormycosis was not incidentally coinciding. It emerged as a complication in association with COVID-19 infection and the treatment related to it. Increased mucormycosis cases post the second wave of COVID-19 infection showed a mortality rate that was as high as 31–50%, which is comparable to the global data. Morbidity levels were also high.[3] RCOM is considered to be the most common form of mucormycosis in India, with a prevalence that is 80% times more than the other developed countries.[3,7] Almost 14/100,000 population is affected in India as compared to a global count of 0.02–9.5/100,000 population.[2]

The association of mucormycosis with COVID-19 in the pandemic times might be associated with the following reasons:

1. Hyperglycemia because of uncontrolled pre-existing diabetes. Limited access to specialists and doctors because of the lockdown and pandemic, led to poor control over the disease – diabetes, which arose as a post-treatment complication for COVID-19 treatment.[1,9,11,13]
2. Irrational and unjustified overuse of proposed medications for COVID-19 treatment, which include as follows:[9]
   - Steroids[1,9,15]
   - Broad spectrum antibiotics[15]
   - Antiviral and antifungal drugs[7,15]
3. Long intensive care unit (ICU) stays/nonambulatory state with ventilation.[3]
4. Oxygen (0_2) – therapy with compromised equipment and sterilization.[15]
5. Pre-existing co-morbidities in the form of immunosuppression.[10]
6. Irrational use of steam inhalation and hot water consumption for rinsing/gurgling injudiciously.[15]
7. Use of unclean mask/unsterilized/soiled for a long period.[15]
8. Self-medication[3,8] and delayed reporting to hospital/clinic.[12]
9. Non-sterile products like bandages, nitroglycerin patches and wooden tongue depressors.[7]
10. Medical devices such as catheters, insulin pumps and finger sticks.[7,8]
11. Procedures like tooth extraction, surgery and insertion of tubes.[7]
12. Environmental sources such as air, dust, water or any surfaces in the hospital.[7]

Further evaluation with imaging modalities such as ortho-pantomogram, CT scan[8] and magnetic resonance imaging evaluation[4,12]; The findings were typical and presented as destruction of the alveolar bone, displacement of teeth and erosion along the sinus wall. CT scans presented with hyper-dense areas in the maxillary and ethmoidal sinuses predominantly. Meati appeared blocked with a hazy appearance. In all our cases, the clinical presentation and the imaging were significant contributors towards a clinico-pathological correlation for diagnosis.

Surgical notes, grossing

These cases need to be evaluated histologically for a confirmatory diagnosis. Histopathological examination of these cases was mandatory for confirmation of diagnosis and to put the patients on the antifungal treatment protocol. All the specimens received post-surgical procedure in the form of incisional and excisional biopsy (in all the seven cases) were grossed meticulously.

The grossing showed that most of the lesional specimens were a combination of hard and soft tissue. The soft tissue was in the form of small and large chunks of the antral lining, along with smaller fragments of tissue that were largely haemorrhagic and necrotic friable bits. Hard tissue was received in the form of segmental sections and partial/total maxillectomy along with the involved teeth. Large fragments of the bone were necrotic. Multiple tissue bits were selected for processing from these hard and soft tissue specimens of each case from different representative areas. In soft tissue bits, necrotic tissues were selected which yielded areas of high mycotic colonies. Hard tissues, frequently necrosed bone, fractured very easily and were very friable. These were picked up for hard tissue analysis histologically.

Histopathological findings

Conventional H&E findings – soft and hard tissues

Soft tissue histopathological examination showed the presence of partial or total sinus lining with pseudo stratified columnar ciliated epithelium. Only in one case, the total lining was destroyed. The connective tissue showed inflammatory oedema with haemorrhage and inflammation. A large number of fungal hyphae was noted in the connective tissue and in relation to the necrotic areas.[12] The hyphae were bulky and non-septate with some showing branching at right angles.[6] The fungal hyphae were of variable diameters ranging from 6–25 microns[1] or 5–20 microns.[7] The hyphae were clustered close to the vascular spaces. Prominent angio-invasion was noted in the majority of the cases.[1] The hyphae were clustered in small groups, in large clusters (Case 4,7) and along with microbial colonies (Case 2). Abscessed areas with neutrophils, chronic inflammatory cells and giant cells were also noted. Hard tissue showed the presence of compact and trabecular, mature bone, devoid of osteocytes and osteoblastic rimming. Large sections of bone were non-vital dead bone, with extensive resorption and prominent osteoclastic activity. All the cases showed involvement of marrow spaces almost completely with the presence of chronic inflammatory cell response. Predominantly lymphocytes and plasma cells were encountered in large clusters in acute cases, whereas in indolent presentation, very few inflammatory cells were observed in a bland fibrous marrow space. The marrow spaces exhibited few hyphae in cases 3,4,5,6 and 7.

All the sections, with the presence of hyphae, were further confirmed by using PAS staining, on both soft and hard tissue sections.

Special stains

Stains that can help highlight the fungal wall include Grocott methenamine-silver (GMS) and PAS stains, although PAS gives a better visualization of the surrounding tissue compared to GMS.[7] Sometimes, optical brighteners like Calcofluor and Blancofluor are also used.[1,7]

In our case series, PAS showed boldly stained magenta hyphae that were non-septate, appeared bulky, hollow and in clusters in large numbers. In some cases, the fungal hyphae were mixed with degenerating collagen fibres. In those instances, we used GMS staining. On GMS staining, dark brown-black hyphae were noted both in the marrow cavity and antral walls on a pale light green to grey background.

Diagnosis and call on treatment

Successful management of mucormycosis is usually a multi-modal approach, including reversal or discontinuation of underlying predisposing factors, early administration of active antifungal agents at the optimal dose, complete removal of all infected tissues and the use of various adjunctive therapies.[2] The treatment of mucormycosis involves the early initiation of therapy with the surgical debridement of infected tissue,[8] for managing the underlying disease.[3] In diabetic patients with mucormycosis, hyperbaric oxygen therapy is another alternative that increases the survival rate.[4]

On histopathological confirmation, the patients were put on antifungal regimes. In our cases, the majority of the cases were medically treated with Amphotericin B,[5,8] and later continued with fluconazole. Surgically four cases underwent complete debridement with primary closure. Two of our cases underwent hemi-maxillectomy, one of which was followed by fibula reconstruction. Prosthesis, complete dentures and partial dentures were fabricated in almost all cases.

Post-treatment follow-up of patients

Post-surgical recall was instituted for each patient. Follow-up after every 2 months has shown good healing

and no signs of recurrence. Five of the seven cases have maintained a regular follow-up for a minimum of 3 years.

CONCLUSION

An opportunistic infection, mucormycosis, had a huge impact on the health of patients in COVID-19 pandemic, especially post-second wave in India.[9] Similar scenarios were observed in the United States of America (USA) but not in other Asian or European countries. The Indian subcontinent showed an acute surge in the number of cases and the presentation spectrum, involving an acute and fast-progressing version as compared to the conventional forms and presentation.

A quick and confirmatory assessment is paramount in the timely treatment of these cases to lower morbidity and mortality. A histopathological confirmation is mandatory for diagnosis. It allows learning about the presentation and progression of the disease in association with the COVID-19 infection and pandemic.

The clinical signs and symptoms caught at an early stage will help treat patients better. This case presentation intends to add more valuable data on signs, symptoms and variations observed clinically and the significance of surgical notes and surgical grossing along with detailed analysis histopathologically, which will help in the future to understand the disease, its natural history and response to treatment. It will further aid us/clinicians to be better prepared and help in keeping the susceptible patients disease-free and in providing more systematic treatment.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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