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Case Series of Mucormycosis in Post COVID 19 Patients with Hematological Malignancies in Ongoing Pandemic

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ABSTRACT

Rhinocerebral mucormycosis is a lethal infection caused by saprophytic fungi in immunocompromised patients. Haematological malignancy patients with superseeded COVID 19 infection are more predisposed to mucormycosis with high mortality.

KEYWORDS: mucorrnycosis, antifungals, endoscopic surgery, haematological malignancy, COVID 19

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INTRODUCTION

Mucormycosis is an aggressive rapidly progressing opportunistic fungal infection caused by filamentous fungi of family Mucoraceae, Order Mucorales[1]. It comprises genera of Rhizopus, Mucor and Absidia[2]. It typically affects patients with uncontrolled Diabetes with ketoacidosis[3,4], Hematological malignancies[5-8],organ transplant[9], patients on prolonged use of steroids[10] or patients on Deferoxamine[11].

Any medical condition resulting in prolonged lymphopenia status will prone a patient to the lethal infection of mucormycosis.

It is categorised as Rhinocerebral, Pulmonary, Cutaneous, Gastrointestinal and Disseminated, depending on the organ involved[12]. Most common form is Rhinocerebral which constitutes about 39% of cases. This is further divided into following subtypes- Rhinonasal, Rhinoorbital, Rhinoorbitocerebral. The overall prevalence is about 4 per 100 in patients of hematologic malignancies[13,14]. Among the hematologic malignancies, Acute myeloid leukemia (AML) is the most common constituting about 62% of cases.

CASE REPORTS

CASE 1

A 31 year old male adult was admitted in our tertiary care institute, in the month of feburary 2021, with the complaints of fever for last one month along with shortness of breath and gum bleed for 2 days. He was investigated and Hemogram showed haemoglobin of 5mg/dl, TLC as 5000/mm^3 and peripheral smear showed no atypical cells.

Bone marrow aspiration showed 65% of blasts and bone marrow biopsy as consistent with Acute myeloid Leukaemia. Flow cytometery showed blasts positive for CD34, CD117, CD33, CD13, CD38, HLADR and cytoplasmic MPO suggestive of AML with intermediate risk. Cytogenetics and Karyotyping was normal. Patient was then started on induction regimen (3+7) of injection Daunorubicin 60mg/m^2 and injection Cytarabine 100mg/m^2 under medical oncology department. After which bone marrow went into remission(4%)

Paitent was then planned for consolidation chemotherapy which was completed in the month of june but during this phase he developed neutropenic sepsis. Blood culture was positive for gram negative bacteria with pseudomonas species. Patient was managed with appropriate IV antibiotics, blood transfusion and Random Donar platetets transfusion. Following this he developed high grade fever of 102.2 degree

F and tested positive for COVID 19. He was started on injection Remdesivir and antibiotics with supportive management. There was no history of oxygen ventilatory support or use of steroids and tested negative in the month of April,2021.

Patient later developed nasal block for about 20 days and toothache for 2days. The CT scan of PNS, orbit and brain was suggestive of bilateral maxillary and ethmoidal sinusitis. KOH mount was negative for fungal elements and other blood investigations were within normal limits.

Figure1a: CT PNS Coronal reconstruction shows mucosal thickening in bilateral maxillary sinus causing OMC block with bilateral ethmoids sinuses.

Figure 1b,1c: In soft tissue and bone window shows mucosal thickening in left maxillary sinus and abnormal soft tissue in the retromaxillary fat with rarefraction in postero-lateral wall of maxillary sinus.

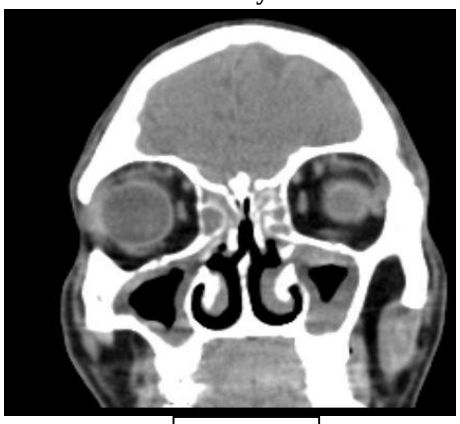

Fig. 1a

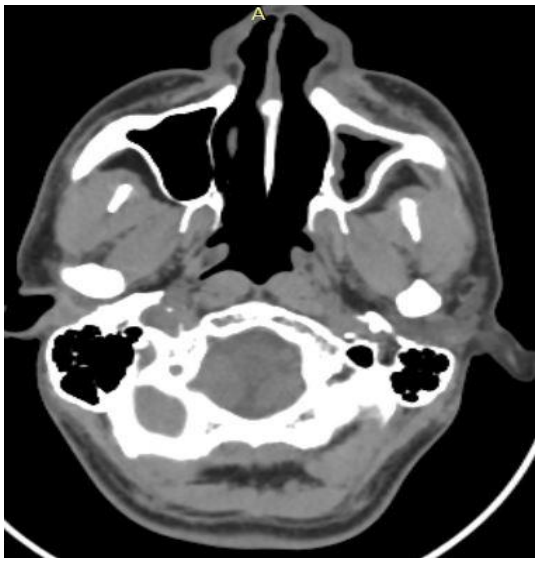

Fig.1b

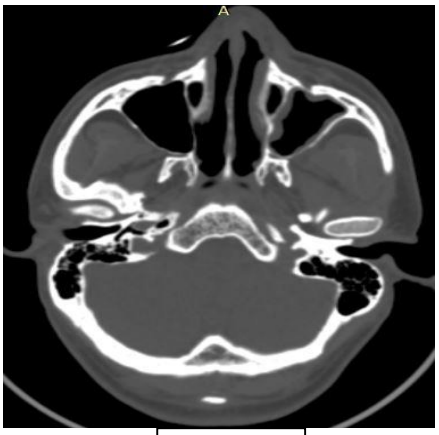

Fig.1c

Patient underwent endoscopic sinus surgery with surgical debridement with left partial maxilectomy followed by antifungal treatement with injection Posoconazole 300mg OD dosage for a period of 14 days followed by oral Posaconazole. Paitent post period was uneventful with no recurrence of disease.

Histopathological report was suggestive of broad aseptate hyphae of mucormycosis

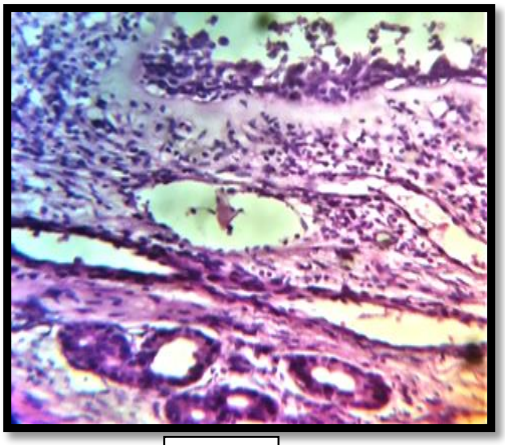

Fig.2a

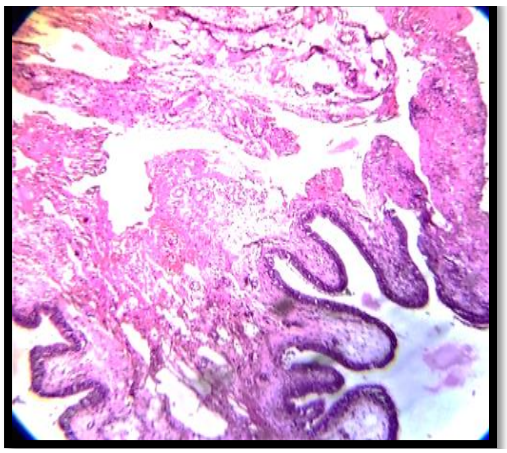

Fig.2b

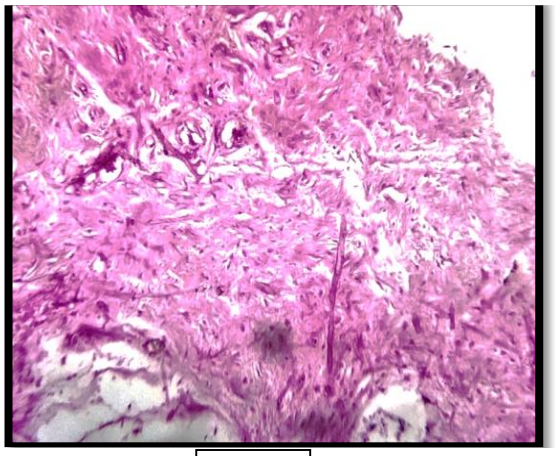

Fig.2c

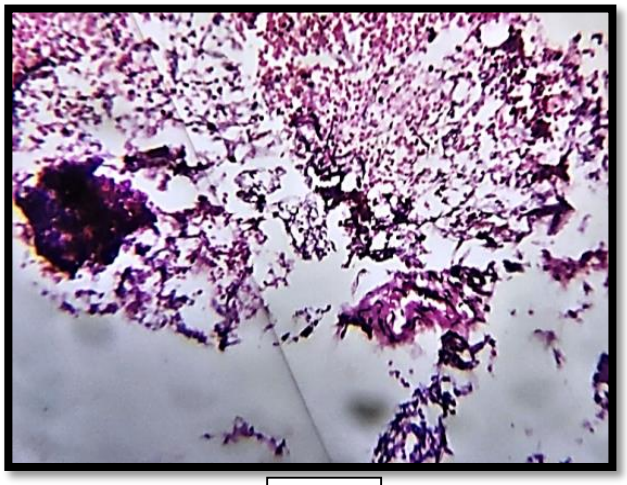

Fig.2d

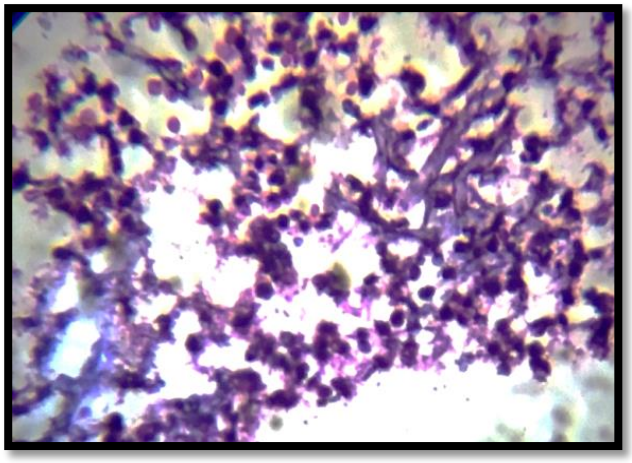

Fig.2e

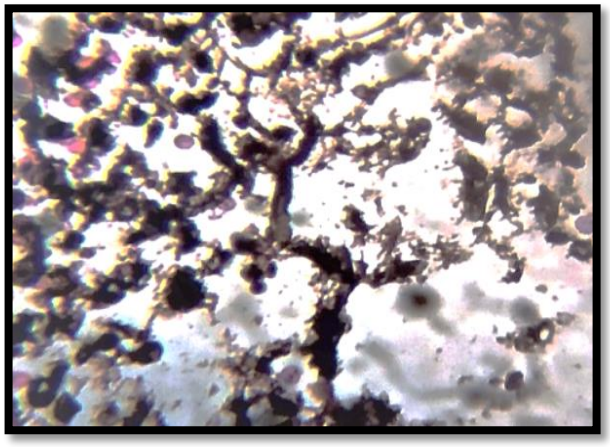

Fig.2f

Figure 2a, 2b,2c,2d,2e,2f:
2a)Shows polypoidal nasal mucosa with lining pseudostratified ciliated columnar epithelium, subepithelial stroma showing edema, haemorrhages and inflammatory cells (H&E 100X).2b) nasal mucosa with lining pseudostratified ciliated columnar epithelium, subepithelial stroma showing congested blood vessels, mucinous glands, stroma showing miced inflammatory infiltrate.(H&E400X).
2c)showing fibrocollagenous tissue and broad aseptate hyphae of mucor.
(H&E 100X) 2d), shows bony trabeculae haemorrhagic exudates and fungal elements of mucor. (H&E100X). 2e), showing broad aseptate acutely branching hyphae of mucor. (H&E 400X). 2f)Gomori's Methanamin silver(GMS) stain highlighting fungal hyphae. 400X

CASE 2

A four year old male child of Acute lymphoblastic leukaemia with Lansky score of 80/100, was on maintenance chemotherapy with oral 6-MP (Mercaptopurine) and Methotrexate.

He developed recurrence with 94% of blasts and was started on BFM-85 protocol.

During this course of treatment paitent developed right orbital cellulitis with persistent high grade fever, tested positive for COVID 19. Patient was subjected to computed tomography of paranasal sinuses which was suggestive of enhancing mucosal thickening in bilateral maxillary, right ethmoid, right sphenoid sinusitis with focal erosion lamina papyracea on the right side, enhancing soft tissue right preseptal and extraconal compartment. Routine blood investigation showed haemoglobin 8.3g/dl, RBC-2.80mill/cumm, platelets-0.17lakhs/cumm and others parameters were within normal limits. Blood parameters were corrected with fresh frozen plasma transfusion.

Patient then underwent endoscopic sinus surgery with right orbital decompression. Histopathological studies were suggestive of broad aseptate obtuse fungal hyphae, mucormycosis. GM and PAS stain was positive for fungus. Patient was then started on injection posoconazole for next

fourteen days. Repeat bone marrow aspirate blasts -73% with persistence of disease. Periorbital cellulitis resolved in 2 days.

Figure 3a: CT PNS Coronal section shows opacification of bilateral maxillary and right ethmoidal air cells with illdefined soft tissue in the intra and extraconal compartment inferiorly, suggestive of orbital cellulitis.

Figure 3b: CT PNS Axial section shows complete opacification of right ethmoid air cells with proptosis right eye ball. Abnormal soft tissue in the extraconal compartment medially and in preseptal region with lid edema.

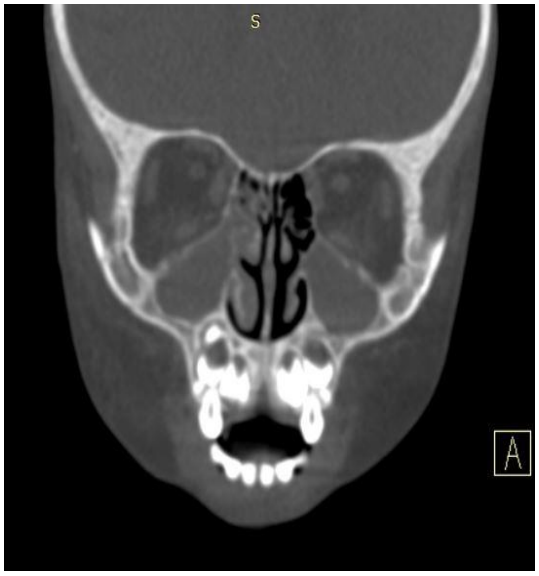

Fig.3a

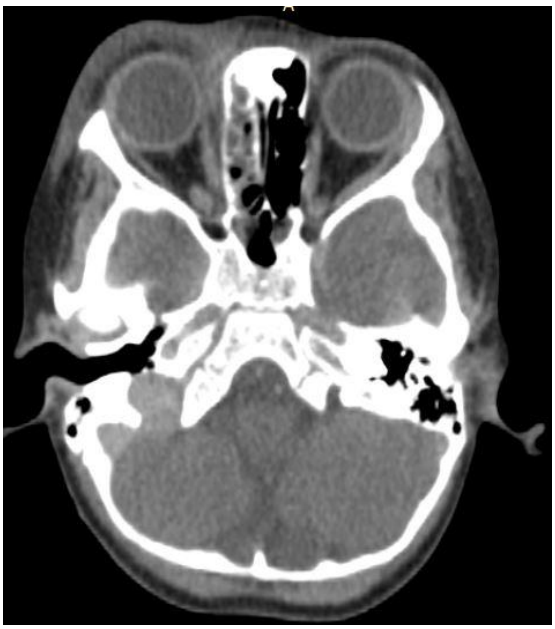

Fig.3b

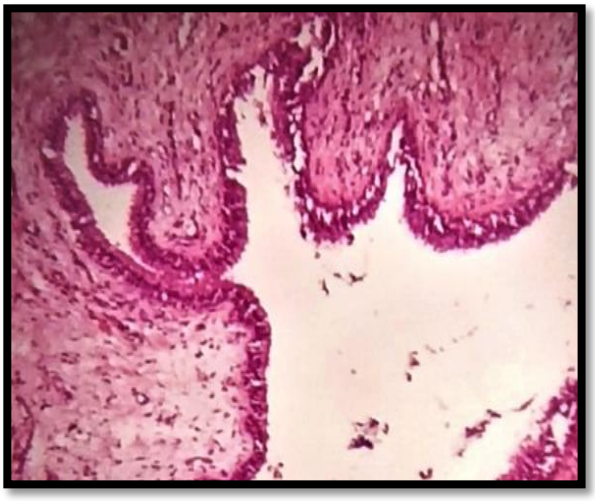

Fig.4a

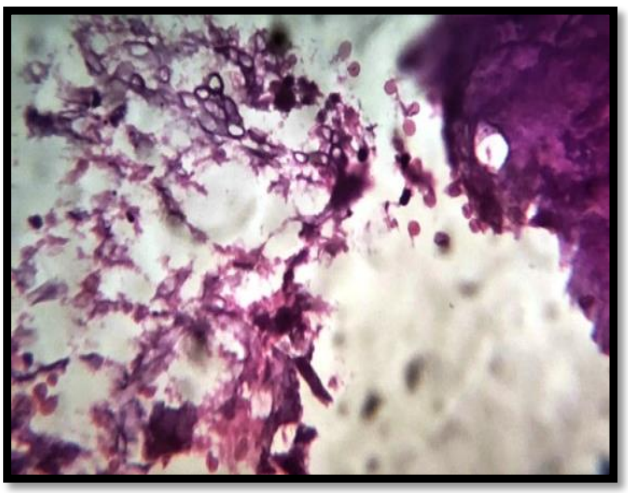

Fig.4b

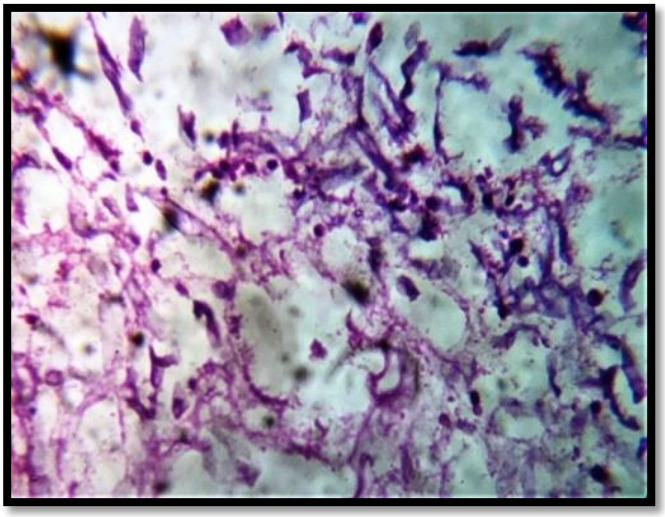

Fig.4c

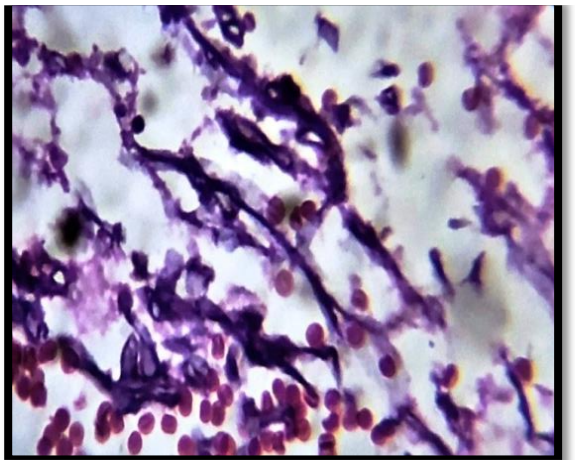

Fig.4d

Figure 4a,4b,4c,4d:
4a) showing polypoidal nasal mucosa with lining pseudostratified ciliated columnar epithelium, subepithelial stroma showing edema inflammatory cells (H&E 100X). 4b), showing necrotic bony spicules with closely associated fungal elements showing broad aseptate hyphae.(H&E 100X). 4c), showing fungal elements with broad aseptate acutely branching hyphae. (H&E100X). 4d) showing broad aseptate hyphae of mucor (H&E400X).

CASE 3

A 45 year old female presented with complaints of right hemifacial pain and unilateral nasal obstruction (right side) with history of COVID 19 infection about 3months. She is known case of Acute Myeloid leukaemia on chemotherapy.

Patient was on consolidation phase therapy with tablet 6 MP as 25mg/m^2 from D1-D56 and injection Methotrexate on D8,D22,D36,D50. Bone marrow aspiration was in remission phase. Routine Blood and urine investigation was within normal limits.

CT PNS was suggestive of bilateral maxillary and right ethmoidal sinusitis.

Patient was then planned for endoscopic sinus surgery with surgical debridement.

KOH mount was suggestive of broad aseptate hyphae and fungal culture showed growth of Mucor. Histopathology showed features of mucormycosis.

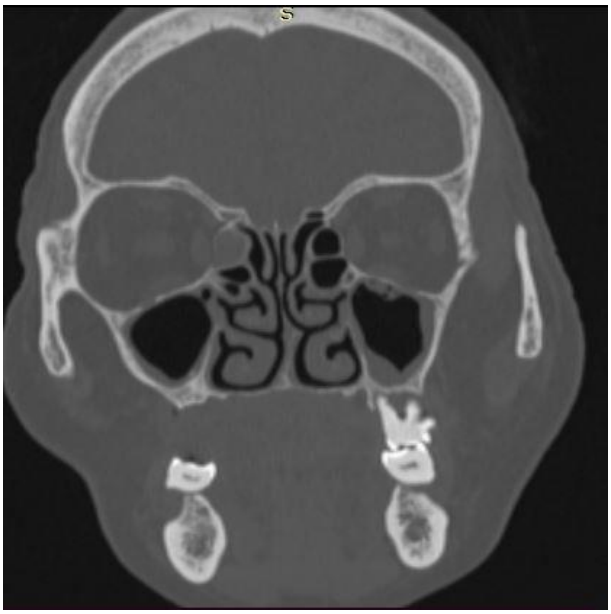

Fig.5a

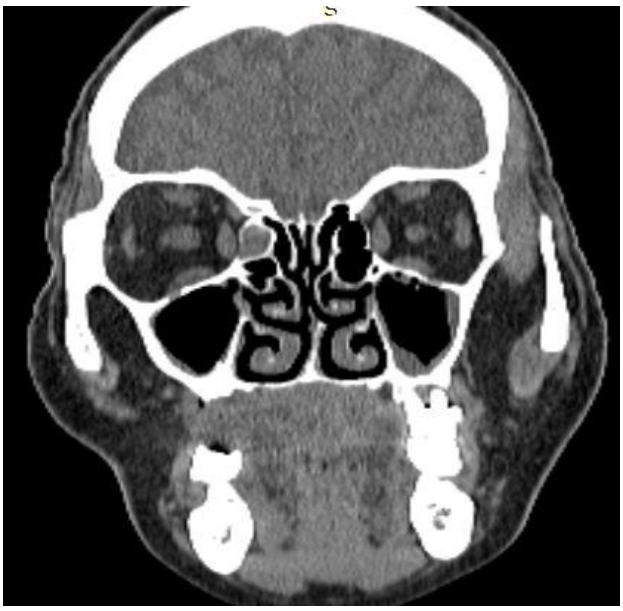

Fig.5b

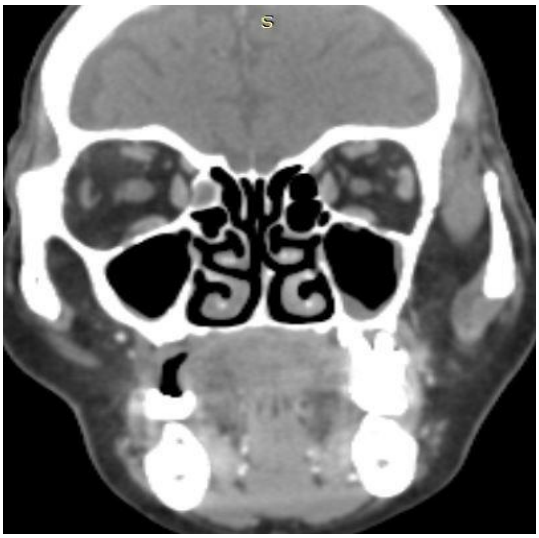

Fig.5c

Figure 5a,5b,5c: CT Coronal reconstruction shows mucosal thickening in bilateral maxillary sinus and few right ethmoidal air cells. Bony window shows erosion of right ethmoidal cells in lateral wall,near lamina papyracea. Mottled lucency in left maxillary sinus roof area.

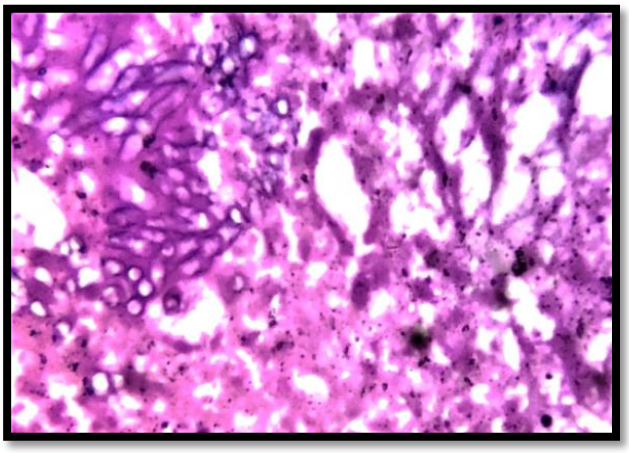

Fig.6a

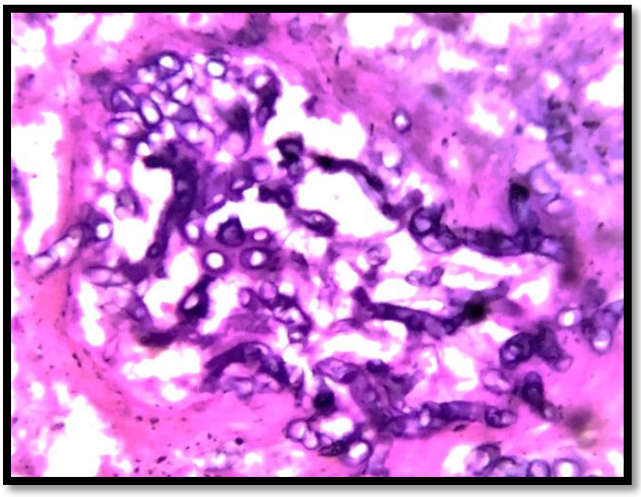

Fig.6b

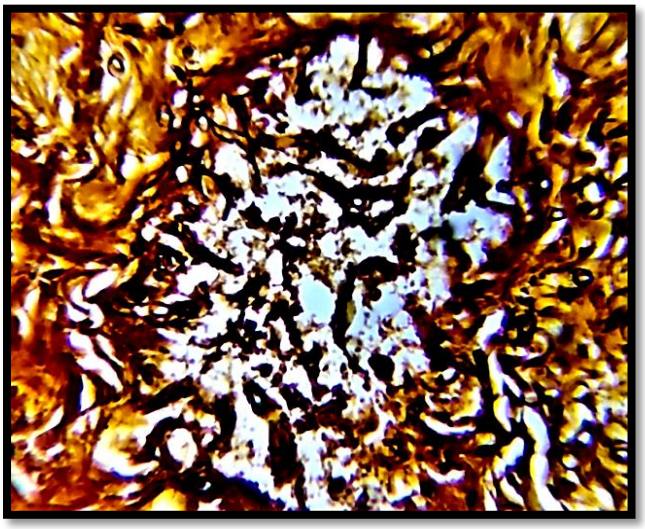

Fig.6c

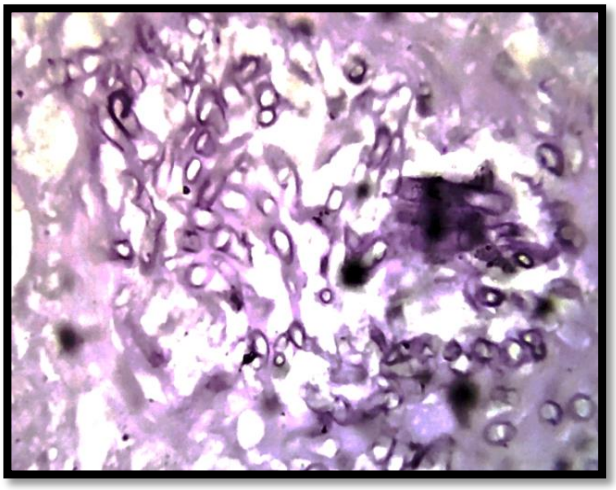

Fig.6d

Figure 6a,6b,6c,6d: 6a) showing fungal elements of mucor with broad aseptate hyphae and cross sections of fungi, the background shows necrotic stroma. (H&E 400X).6b) , showing vascular invasion by mucor fungus. (H&E400X) 6c) Gmomori's Methanamin silver (GMS) stain shows fungal hyphae. 400X. 6d) Periodic Acid Schiff (PAS) stain highlighting fungal hyphae. 400X.

Case 4

A 68 year old female presented to our OPD with severe headache, left nasal obstruction, foul smelling nasal discharge and malaise. She is diagnosed case of chronic lymphocytic leukaemia on mantainence therapy, Tablet. Methotrexate as 20mg/m^2 weekly once and 6Mercaptopurine as 50mg/m^2 daily. She has past history of COVID 19 infection about 7 months back. Routine blood and urine investigations were within normal limits.

CT PNS was suggestive left maxillary and ethmoidal sinusitis.

Patient then underwent endoscopic sinus surgery with surgical debridement and was started on induction therapy with inj. Amphotericin B with dose of 5mg/kg iv OD dosage. KOH mount was suggestive of broad aseptate hyphae and fungal culture showed growth of Rhizopus. Histopathology showed features mucormycosis.

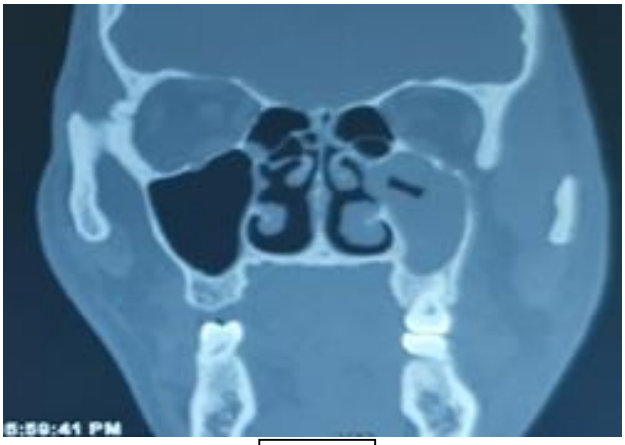

Fig.7a

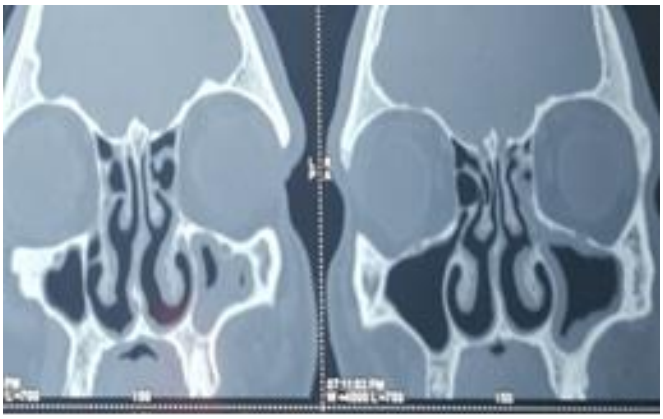

Fig.7b

Figure 7a,7b: CT Coronal section shows opacifiaction of left maxillary sinus with mucosal thickening in few ethmoidal cells.

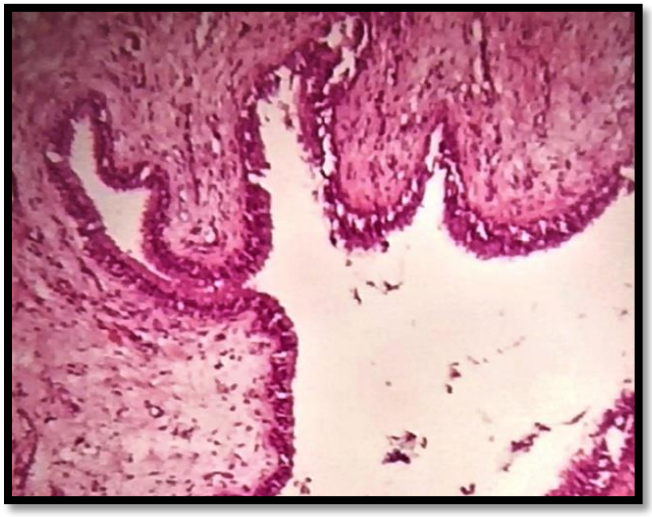

Fig.8a

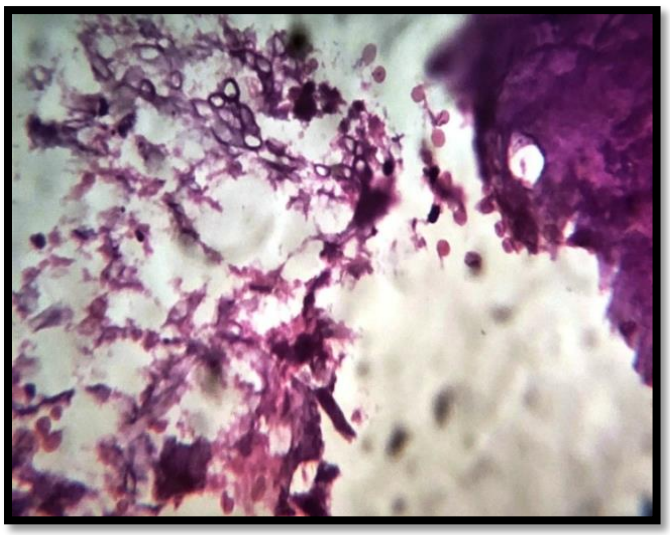

Fig.8b

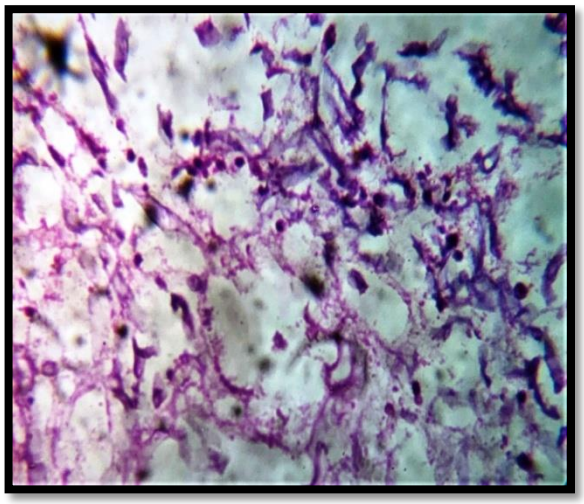

Fig.8c

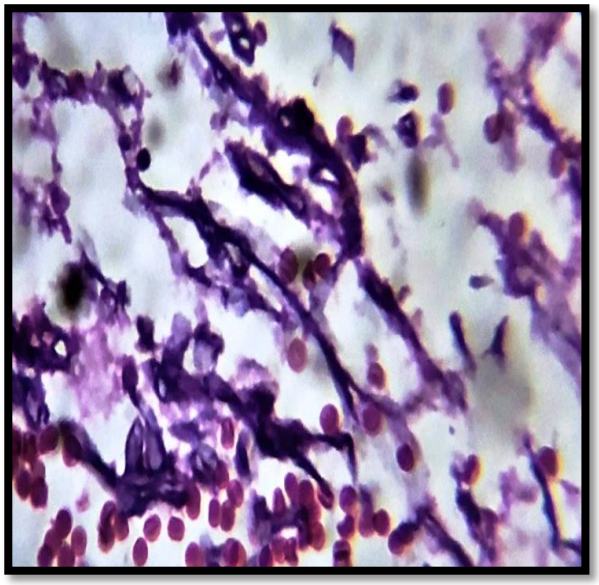

Fig.8d

Figure 8a.8b,8c,8d: 8a) showing polypoidal nasal mucosa with lining pseudostratified ciliated columnar epithelium, subepithelial stroma showing edema inflammatory cells (H& E 100X).8b) showing necrotic bony spicules with fungal elements.Cross section and broad aseptate hyphae. (H&E 100X).8c), showing fungal elements with broad aseptate acutely branching hyphae. (H&E100X). 8d) showing broad aseptate hyphae of mucor (H&E400X).

DISCUSSION

Mucormycosis is also known as Phycomycosis or Zygomycosis. A devastating disease caused by Mucor. Mucor was first described by Paltauf in 1885[15]. These fungi are ubiquitous saparophytes found in the environment.They are broad (5 -50micrometers), aseptated hyphae with right angle branching.

Rhinocerebral mucormycosis was first described by Baker in 1957[16]. The disease is though rare in normal scenario but it has burdened many states of India in ongoing COVID 19 pandemic, where it is declared as epidemic especially in immunocompromised states like haematological malignancies.

Mucormycosis is an aggressive angioinvasive fungal infection in patients with hematologic malignancy, especially who are on chemotherapy or immunosuppressive therapy.

It is sudden in onset and carries high mortality rate. The mycotic spores are found mostly in soil, rotten fruits, vegetables, fallen leaves and compost matter. Spores enter sinuses through inhalation or by direct contact with nose and paranasal sinus mucous membrane causing invasion, vascular occlusion, and diffuse tissue necrosis in the vascular endothelium in patients of impaired phagocytosis and neutrophil functions.

The mortality rate is as high as 65% inspite of aggressive medical and surgical intervention. Early diagnosis is very crucial for adequate management. Diagnostic Nasal endoscopy, KOH mount, CTscan and CE MRI of PNS, orbit and brain and biopsy are important tools for diagnosis.

Prompt surgery in hematologic malignancy patients sometimes becomes difficult due to factors, such as thrombocytopenia, anemia, and deranged coagulation profile, therefore induction therapy with antifungals play a vital role in prognosis[17].

Mucormycosis is characterized by angioinvasion, thrombosis and tissue necrosis which causes poor penetration of antifungals in the diseased sites. Therefore surgery plays an important role debridement of necrotic tissues.

Surgery reduces the local fungal burden in the tissues and permits the normal immune response to eliminate the fungal antigens. Early appropriate surgical debridement decreases the rate of disease progression and provides a period for underlying disease reversal in immunocompromised patients.

Endoscopic sinus surgery provides a conservative approach for clearance of disease and to widened the sinus ostia for irrigation and easy access for further FESS cleaning and debridement even as a outpatient office procedure. External procedures include medial maxillectomy, partial maxillectomy,total maxillectomy with or without orbital exenteration or craniofacial resection[18,19]. The surgeries should be planned according to the prognosis.

The early diagnosis and management is very essential in terms of prognosis. Patient in whom treatment starts within 6 days of onset of disease have a better survival rate of 76-81%. It falls down to 36-42% if treatment is delayed for more than 12 days[17].

The combined approach with intravenous antifungals and surgical debridement decreases the mortality in immune-compromised patients[20].

In our study all patients were immunocompromised due to haematological malignancy and SARS COV 19 infection, on chemotherapy. Therefore prone to the deadly opportunistic infection of mucormycosis. All were started on intravenous antifungal therapy prior to Endoscopic sinus surgery and surgical debridement. One of patient underwent left partial maxillectomy also, due erosion of maxilla. Prompt surgical debridement, repeated if necessary, is considered a crucial component of successful therapy. Surgery before disease progression to cerebral structures improves the chance for a successful outcome.

Recently, posaconazole has been used as a salvage therapy aganist Mucorales especially in patients with poor immune response and blood parameters.

CONCULSION

Our cases showed severe rhinomaxillary involvement which was dealt with combined surgical approach and antifungals. Patient were switched to oral Posaconazole therapy for next 1 month and are performing well with no recurrence of disease till date. Early diagnosis and treatment with reversal of underlying neutropenic state and co-morbidities plays a vital role in improving prognosis of mucormycosis.

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