17 Clinical Profile and Management of a Series of Rhino-Orbital-Cerebral Mucormycosis Cases at Otorhinolaryngology Department of a Tertiary Hospital

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The years from 2020 until July 2021 were a nightmare to the human race due to the pandemic caused by COVID-19, which gripped the whole world, not once but twice. No living person could have ever comprehended the damage caused to the human race by this tiny, invisible enemy called 'the coronavirus'. The health system worldwide has gone topsy-turvy since the first human case was detected in December 2019.

The first wave in 2020 caused many causalities but gave doctors and the health care system worldwide insight into developing and practising protocol-based treatment for COVID-19. In 2021, the second wave hit the world with more force, speed, and vengeance. This time, the virus was more virulent and associated with numerous complications that were not part of the first wave. These complications were attributed to the side effects of overzealous treatment of COVID-19 infection.

During the first wave, the complications were mainly related to the lungs and the central and peripheral nervous systems. The second wave was accompanied by an altogether different complication called 'mucormycosis' which is though, a systemic disease, but this time, it was explicitly 'rhino-orbito-cerebral mucormycosis (ROCM)'.

17.1 Background

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been proven to be the causative organism of the novel coronavirus disease (COVID-19).

COVID-19 is known to cause respiratory system complications, primarily pneumonia (mild to severe), with superadded bacterial and fungal co-infections.

The second wave of the COVID-19 pandemic in India created grounds for fungus (mucormycosis) to grow and infect the human race with grave severity. ROCM, which was found to be associated with COVID-19, is the most common form of mucormycosis and a life-threatening opportunistic fungal infection characterized by rapidly progressive invasion of the nose, paranasal sinuses, orbit, hard palate, and brain. In the past, this angioinvasive fungal infection, which was noticed very rarely, suddenly saw an acute spurt in post-COVID patients during the second wave.

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17.2 Spread

The fungi that cause ROCM are ubiquitous in the environment, and human beings are constantly exposed to them. In immunocompromised patients, the airborne fungal spores attach to the nasal and oral mucosae and start proliferating and germinating into hyphae. From the nasal, oral, and nasopharyngeal mucosae, the spores/hyphae invade the paranasal sinuses. The further spread of this infection can be classified into different stages.

17.3 Classification of ROCM

Depending upon the anatomical spread and severity:

1. Sino Nasal Mucormycosis
   (a) Disease can be limited to nasal mucosa, middle turbinate, inferior turbinate and the ostium of nasolacrimal duct (NLD).
   (b) Disease can extend to paranasal sinuses and involve mostly a single sinus or more than one sinuses mucosa and bony walls, as well as the opposite-sided sinuses, which hold a grave prognosis.
2. Extra Sinus Extra Cranial Mucormycosis
   (a) It includes the involvement of palate, maxilla/facial tissue/retro antral spaces like pterygopalatine fossa, infratemporal fossa and masticator space.
   (b) Involvement of the orbit
   Orbital spread via NLD/medial orbital wall (thin lamina papyracea/congenital dehiscence/along perivascular spaces)/ Infarorbital foramen.
3. Intracranial Mucormycosis

Intracranial spread can be through three potential pathways: Shreshtha

1. *Direct extension*: From sinonasal cavities through osteolytic defects in the base of skull-like cribriform plate (CP). Infection from Sphenoid sinus (SS) can extend into cavernous sinus (CS), or invade internal carotid artery (ICA) and from there embolize the frontal and parietal lobes.
2. *Perivascular and perineural invasion*: Perivascular spread can occur through spaces around vessels in CP of ethmoid bones to frontal lobe or through spaces around emissary veins in lamina papyracea (LP) into orbit, superior orbital fissure/orbital apex to cavernous sinus and ICA. Posterior fossa involvement can occur through perineural spread from the cavernous sinus along the trigeminal nerve.
3. *Haematogenous Spread*: From invasion of arterial wall due to its occlusion, leading to ischemia, infarct and/or abscess formation.

17.4 The Important Areas Involved During Spread of ROCM Are

17.4.1 The Pterygopalatine Fossa

The pterygopalatine fossa plays a very important role in spreading the fungal hyphae to areas beyond the paranasal sinuses. It actually acts as a reservoir from where the spread of infection takes place to areas like the orbit, soft tissues, in the pre and post maxillary areas, the palate, infratemporal fossa, and cavernous sinus. Infection reaches the pterygopalatine fossa through either the posterior maxillary wall or the sphenopalatine foramen and from here spreads in different directions. Debridement of diseased tissue with complete clearance of mucor from the pterygopalatine fossa becomes mandatory to prevent further spread of disease.

17.4.2 Palate

The palate can be directly eroded by the spread of fungus from nose and paranasal sinuses. Painful, reddish to dark-brown ulceration, well-defined irregular raised border, variegated necrotic surface, and fast progression are the main features of these lesions. The other areas around palate which get infected by mucor are the gingiva, cheek mucosa and pharyngeal surface [2].

17.4.3 Orbital Involvement [1]

The Orbital invasion is usually through the path of least resistance which is the medial wall. It includes thin lamina papyracea, nasolacrimal duct, congenital dehiscence and perivascular spaces in lamina papyracea. At times, aggressive disease from the maxillary sinus can spread to orbit through the infraorbital foramen along the infraorbital nerve. The other pathway for infection is through pterygopalatine fossa and inferior orbital fissure to the retro global space of the orbit. Orbital involvement can be categorized into:

1. In the Early stages, the disease can be involving nasolacrimal system or can infiltrate the periorbital soft tissue leading to inflammation and oedema in the retroorbital fat around the extraocular muscles. This inflammation can further cause abscess formation along the medial aspect of the orbit leading to inflammation of the medial rectus muscle and may cause its lateral displacement. Vision remains unaffected in this situation.
2. Diffuse orbital involvement in the form of infection reaching contents of both extra and intraconal compartments leading to diffused proptosis.
3. Occlusion of Central retinal artery or ophthalmic artery or thrombosis of superior ophthalmic vein leads to superior orbital fissure or orbital apex syndrome. The loss of vision is associated in this situation due to the optic nerve infarct.

17.4.4 Orbital Apex Involvement

The infection travels from the ethmoid sinus through the thin lamina papyracea into the orbit and its contents. This creates a pathway for the organism to extend posteriorly up to the orbital apex, leading to orbital apex syndrome. At this stage, there may be vision loss due to affection of the optic nerve. The progression of the infection may be very rapid because of the aggressive invasive nature of the organism.

The disease can also progress posteriorly from orbital apex, through the inferior orbital fissure across the pterygopalatine fossa into the infratemporal fossa. In some cases, it can spread to the superior orbital fissure causing diplopia, ophthalmoplegia and sensory loss to the corresponding areas of the cornea and face because of the involvement of cranial nerves III, IV and VI, and branches of V1 and V2 [3]. As it spreads more posteriorly it infects cavernous sinus and then the brain parenchyma underlying cause being vascular thrombosis and infarction.

17.4.5 Optic Nerve Involvement

The pathogenesis behind optic nerve involvement is invasion of the organism directly into either the optic nerve fibres or the walls of central retinal or ophthalmic artery causing occlusion or thrombosis of the vessels. Diffusion-weighted sequences of MRI are the right diagnostic tool for picking up optic nerve ischaemia earliest even when other MR sequences appear normal. Sudden infarction of the optic nerve leading to sudden onset blindness is a very grave situation and demands urgent treatment.

17.4.6 Cavernous Sinus and Internal Carotid Artery

The spread to cavernous sinus can happen due to the posterior extension of disease from the superior orbital fissure or fossa. Further invasion and occlusion of the cavernous part of the internal carotid artery, becomes the cause of brain infarcts.

17.5 Presentation

The presenting symptoms of patient are that of acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache and facial pain. Although it can involve all paranasal sinuses, there is a propensity for maxillary sinus followed by ethmoids, sphenoid and frontal sinus. The disease is usually seen involving unilateral sinus or sinuses, but rarely bilateral involvement can be seen, which is of grave severity. The spread to the

surrounding structures, such as premaxillary space, palate, orbit and brain, is relatively rapid within a very short period.

During this growth phase, through angioinvasion, tissue necrosis occurs due to endarteritis resulting in characteristic black eschar formation in the nasal mucosa, palate, or skin around nose and orbit gives it the title 'Black fungus'. The necrosis can involve nasal septum, soft tissue and bones of turbinates, paranasal sinuses and palate. At times, the facial skin's swelling, erythema and cyanosis overlying the involved sinuses and or orbit can be seen. In COVID-associated mucormycosis, the spread of disease was so rapid that pus and osteomyelitis were seen more than the pathognomonic 'Eshcar' formation in the affected parts of the nose paranasal sinuses. Signs of orbital involvement depend upon the extent of involvement of orbit and beyond. It includes periorbital oedema, proptosis, ptosis, diplopia and diminution of vision to complete blindness. On examination, there can be conjunctival chemosis, restricted ocular mobility, ptosis, proptosis, Infraorbital nerve and V1, V2 nerve anaesthesia, CN III, IV and VI palsy indicates orbital apex/Superior Orbital fissure/cavernous sinus involvement and complete loss of vision.

Further extension into the internal carotid artery and brain can result in paralysis, altered sensorium, focal seizures etc.

17.6 Evaluation and Assessment of ROCM

17.6.1 Primary Assessment

- Nasal endoscopy
- Craniofacial computed tomography (CT scan)
- Contrast-enhanced Magnetic Resonance Imaging (MRI)

CT scan and MRI are reviewed together by an otorhinolaryngologist, ophthalmologist and a neuroradiologist and graded according to the extent of the disease. The final correlation is done with the clinical features of the patient.

17.6.2 Confirmation of Diagnosis

The aggressive presentation of ROCM can make the diagnosis easy, but the final diagnosis depends on demonstration of fungal tissue on the KOH mount and tissue cultures.

- KOH wet mount is a primary screening tool to identify the fungal elements present in the specimen. In suspected fungal rhinosinusitis cases, nasal discharge or crusting can be sent as a sample (a. 17.1).
- *Biopsy for HPE*: Necrotic tissue from the involved site (nose, orbital) is sent for histopathological examination. The stains used are H & E (haematoxylin & Eosin), specialized fungal stains like Grocott methenamine-silver (GMS) or periodic acid-Schiff (PAS). It shows pathognomonic broad, irregular, ribbon-like, aseptate or sparsely septate hyphae with irregular acute angle branching.
- The culture of biopsy samples is done to determine species of Mucorales. Crushing or grinding of the specimen should be avoided as it leads to the destruction of fungal elements. Lactophenol cotton blue (LCB) stain demonstrates specific hyphae and spores of mucor organisms (Fig. 17.2).

17.7 Imaging

17.7.1 Craniofacial Computed Tomography (CT)

Although CT scan is not a very specific investigation to differentiate between chronic sinusitis and invasive fungal sinusitis, it serves as a valuable tool for easy identification of bony invasion, if there is any. It also helps in planning surgical approach in a case of mucormycosis.

The specific CT sequences needed in ROCM are routine and contrast-enhanced CT-Scan of paranasal sinuses, orbit and hard palate and brain, if the clinical picture suggests intracranial extension of the disease. One to three millimetre

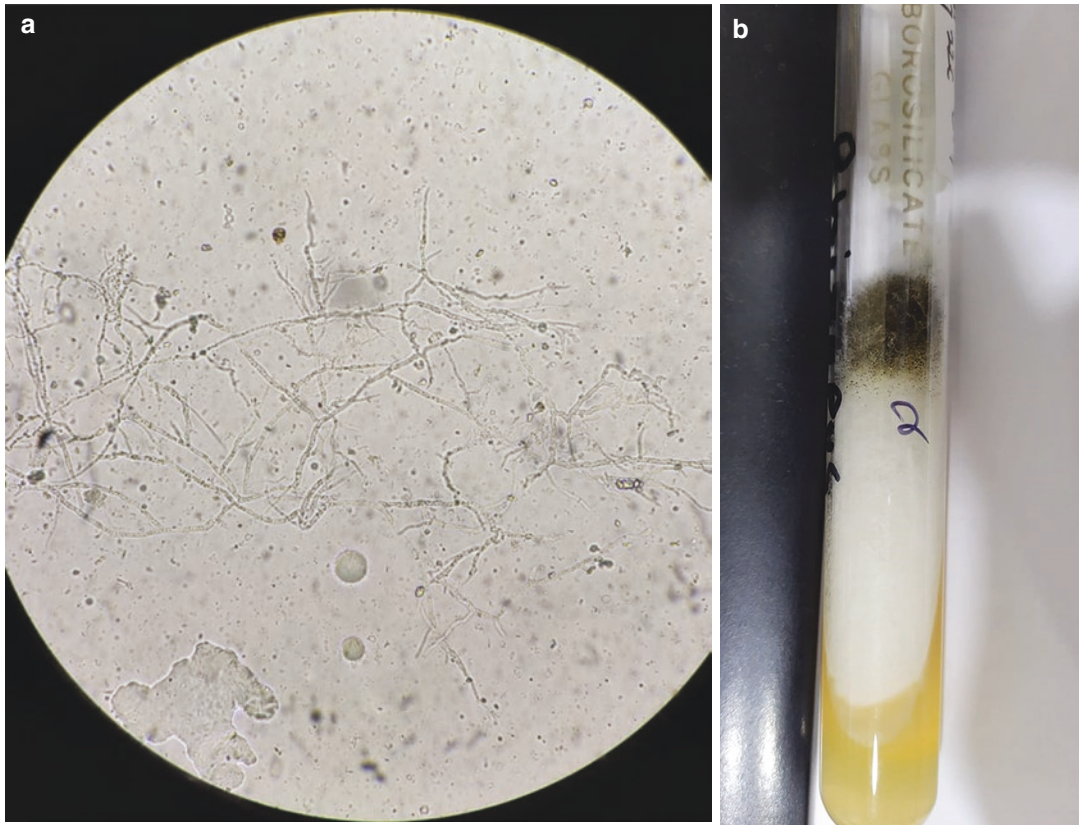

Fig. 17.1 (**a**) KOH stain showing broad, aseptate ribbon-like fungal hyphae. (**b**) Culture tube showing growth of blackish-grey colonies of mucor (Courtesy—Dr. Satish Kumar, MD pathology, Department of Pathology, Jindal institute of medical sciences, Haryana)

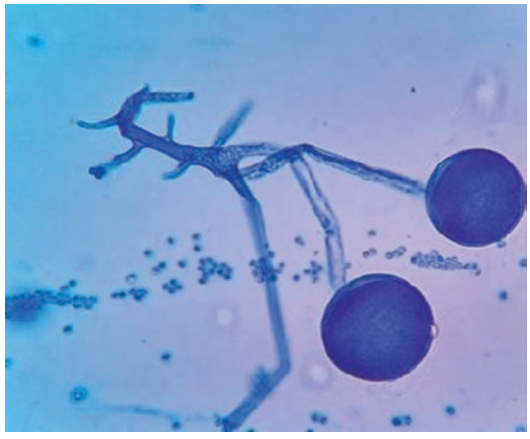

Fig. 17.2 Lactophenol cotton blue (LCB) stain showing fungal hyphae and conidiophore-specific mucor organisms (Courtesy—Dr. Satish Kumar, MD pathology, Department of Pathology, Jindal institute of medical sciences, Haryana)

sections are taken in the axial plane with reformations in coronal and sagittal planes. These are evaluated in soft tissue and bone window by a team of neuroradiologist, otorhinolaryngologist, neurosurgeon and ophthalmologist. Evaluation and grading are done for mucosal thickening in nose and paranasal sinuses and extent of inflammation and disease are evaluated in the following anatomical sites: anterior and posterior peri antral fat, sphenopalatine foramen, pterygopalatine foramen, nasolacrimal duct, medial and inferior orbital fat, facial soft tissue and the masticator space. Mucosal thickening of more than 3 mm in the nasal cavity and paranasal sinuses is recorded as present. Bony dehiscence in the sinonasal area or hard palate is recorded as present or absent.

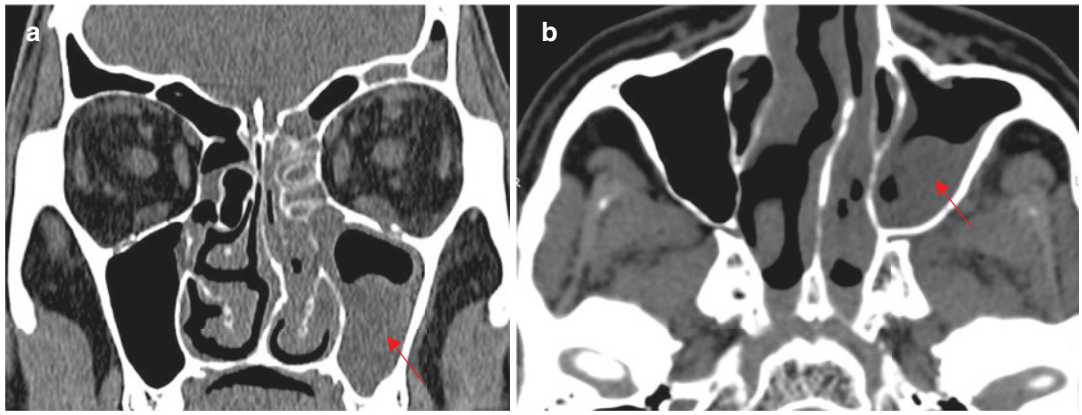

Fig. 17.3 Non-contrast CT PNS images in coronal (**a**) and axial (**b**) planes show nodular mucosal thickening in the left maxillary sinus (red arrow). Mucosal thickening was also seen in the left nasal cavity and ethmoid air cells

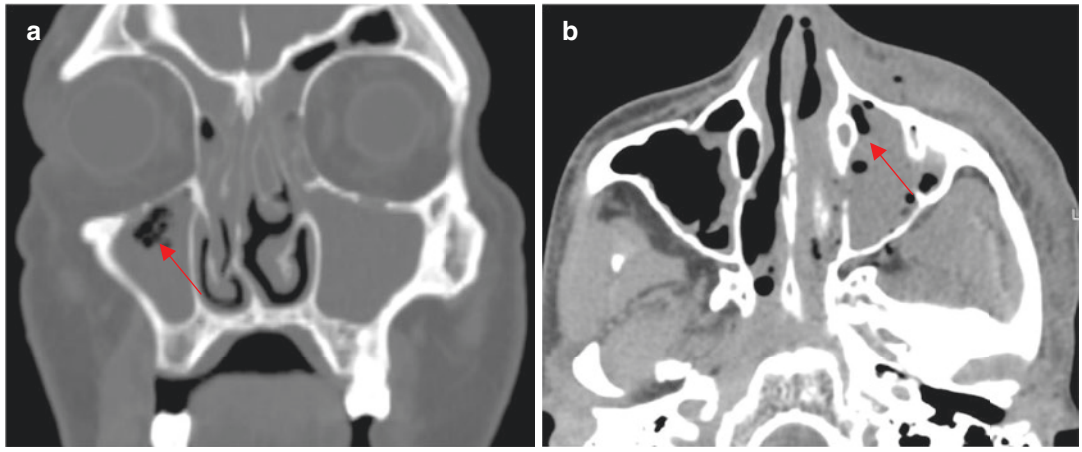

Fig. 17.4 Non-contrast CT PNS images in the coronal (**a**) and axial (**b**) planes show mucosal thickening in both maxillary sinuses, causing almost complete opacification. Air fluid levels are seen as bubble-like lucencies within soft tissue density (red arrow)

17.7.1.1 CT Findings in Early Stage of Mucormycosis

- *Nose and Paranasal sinuses (PNS)*: Mucoperiosteal inflammation presents as nodular mucosal thickening. Sinonasal mucosal thickening >3 mm recorded as present (Fig. 17.3).
- Air/fluid levels can also be seen in sinuses along with soft tissue density due to mucosal hypertrophy leading to partial to complete sinus opacification (Fig. 17.4).
- Soft tissue opacification of the sinuses with areas of increased density with well-defined, markedly hyperdense foci within inflammatory reaction: due to dense matted fungal hyphae and calcium phosphate and sulphate deposits in necrotic areas of mycetoma (Fig. 17.5).
- *Soft-tissue infiltration of peri-antral fat planes.* Infiltration can extend up to premaxillary area (peri-antral) or post-maxillary area (retro antral), sphenopalatine foramen, pterygopalatine fossa characterized by obliteration of the normal fat planes in these areas. Soft tissue infiltration can also involve nasolacrimal duct, medial and inferior orbital fat and facial soft tissue (Fig. 17.6).

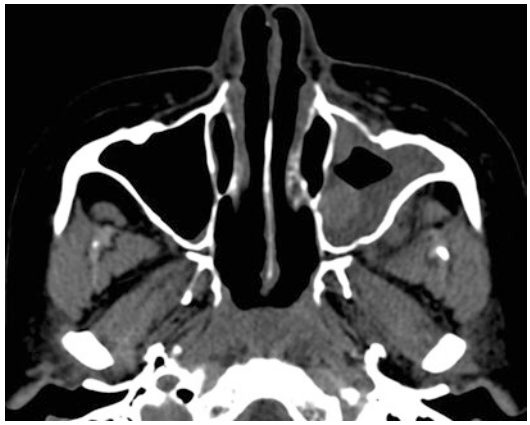

Fig. 17.5 Non-contrast CT PNS image in axial plane shows nodular mucosal thickening in left maxillary sinus with hyperdense material in sinus cavity suggesting chronic inspissated secretions or fungal ball

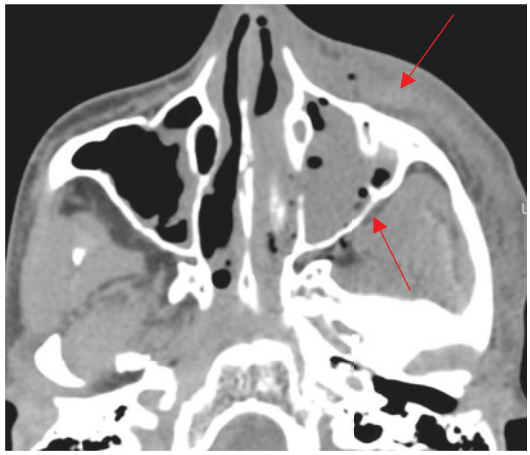

Fig. 17.6 Non-Contrast CT PNS images in axial plane show left maxillary sinus opacification with soft tissue density and air foci. There is the involvement of left middle turbinate and thickening of left premaxillary soft tissue and retroantral soft tissue (red arrow). Air fluid levels are seen as bubble-like lucencies within soft tissue density in the left maxillary sinus

17.7.1.2 CT Findings in Advanced Stage of Mucormycosis

CT scan shows bone involvement in the form of bone rarefaction, erosions and permeative destruction. Bony dehiscence in lamina papyracea (leading to orbital invasion), posterior and superior wall of the maxillary sinus, cribriform plate (leading to intracranial extension), palatine bone (leading to palate invasion) (Fig. 17.7) are recorded as present or absent. In most cases, the extra sinus involvement occurred with intact bones, indicating the perineural/perivascular invasion of the fungus without destroying bone. In such cases, retroantral, facial and orbital fat stranding without involving bone indicate the aggressive nature and advanced stage of the disease.

17.8 Magnetic Resonance Imaging

Magnetic resonance imaging is the most informative investigation in both early and late stages of mucormycosis involving the paranasal sinuses, peri antral soft tissue, orbital soft tissue, perineural spread, skull base infiltration, intracranial complications and vascular obstruction involving cavernous sinuses and internal carotid artery. It can pick up the earliest changes in soft tissue beyond paranasal sinuses, when bone involvement has not happened which is better appreciated on CT scan. The sequences of MRI most suitable to pick these early signs are fat-suppressed T2W and fat-suppressed postcontrast T1W images. The images can show enhancement of the premaxillary and retroantral fat suggesting a further extension of disease or inflammation into these regions. Further extension in the form of enhancement involving the muscles of mastication suggests extension into the infratemporal fossa (Fig. 17.4). The involvement of pterygopalatine fossa can be appreciated by the presence of enhancing soft tissue obliterating the normal fat signals surrounding the maxillary sinus posterior wall supplied by posterior branches of the internal maxillary artery.

In mucormycosis, the affected sinuses appear iso to hypointense on T1-weighted images. While on T2-weighted sequences, tissues involved have a variable enhancement pattern. The extent of necrosis determines the T2W signal intensity (causing hyperintensity) and the presence of paramagnetic elements such as calcium concretions, iron and manganese within the fungal hyphae (causing hypointensity).

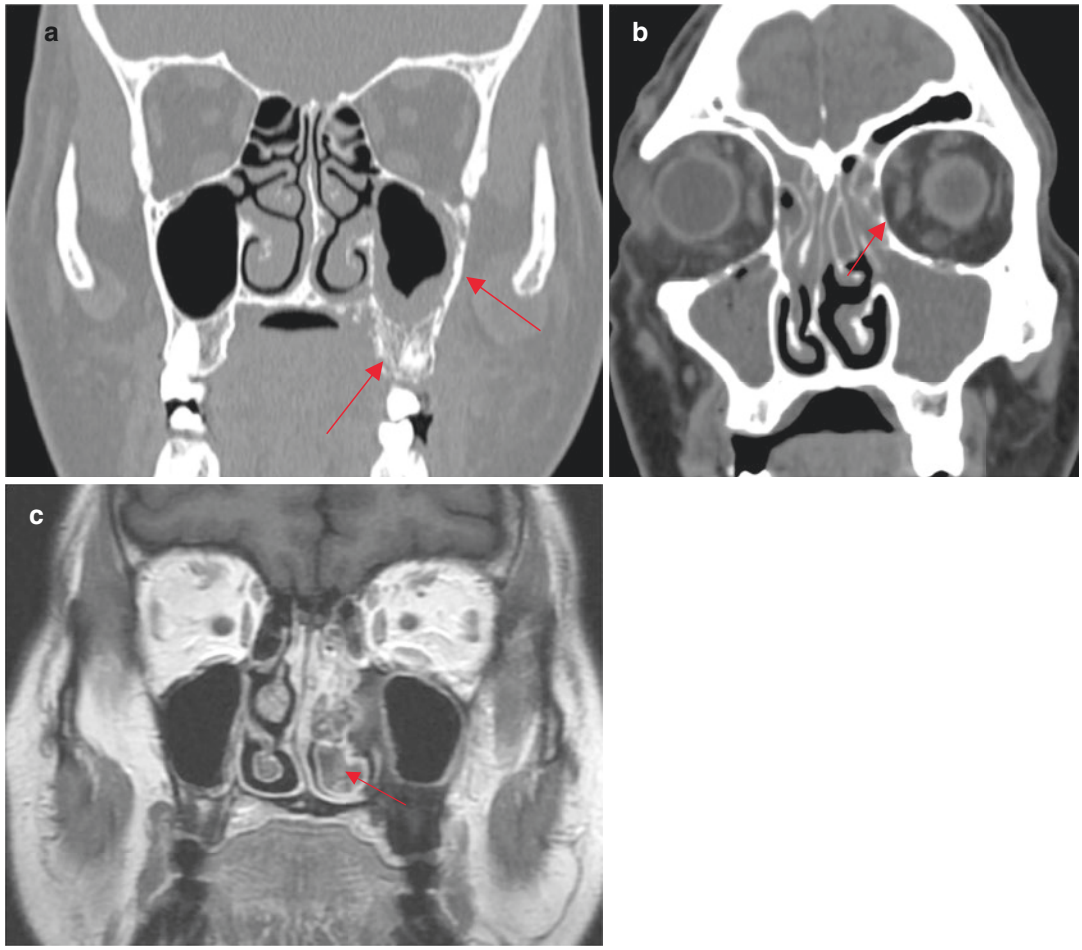

Fig. 17.7 (**a**) Non-contrast CT PNS images in the coronal plane show nodular mucosal thickening in the left maxillary sinus with bony walls erosions. Erosions are well visualized in the left half of the hard palate and the bony walls of left nasal cavity (red arrow). (**b**) Non-contrast CT PNS images in the coronal plane show almost complete bilateral maxillary opacification and visualized ethmoid sinuses. Bony erosions are seen in the left lamina papyracea. (**c**) Black turbinate sign left inferior turbinate (red arrow)

Hence not a reliable marker for mucormycosis alone.

On postcontrast (gadolinium) scans, the contents of the sinuses can show intense homogenous enhancement or variable enhancing and non-enhancing areas or complete central non-enhancing areas with or without a thin irregular rim of peripheral enhancement. An important finding in mucor although not pathognomonic, is the absence of enhancement in areas that usually do enhance. This feature is mainly because of the angioinvasion by the fungus, leading to microthrombosis and tissue necrosis in the affected regions. This appearance, if seen in turbinate bone, is termed as the 'Black Turbinate sign'[4] (Fig. 17.7c). This MRI representation of disease can be correlated to the endoscopic appearance of the necrosis and eschar seen involving the turbinate. Identification of this sign helps in the early and timely treatment of mucor.

Another important finding which is picked up on MRI is the earliest extra sinus involvement seen as fat stranding in the premaxillary or retro maxillary fat, orbital fat or altered fat signals in pterygopalatine fossa, infratemporal fossa or masticator space. This finding is suggestive of the diagnosis of invasive fungal infection in the appropriate clinical setting.

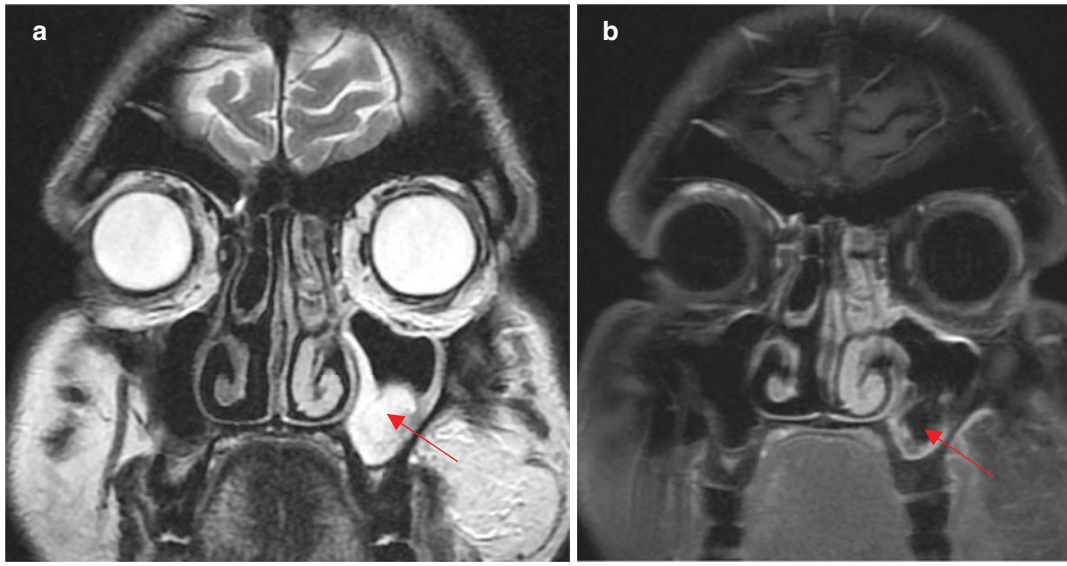

Fig. 17.8 (**a**) Non-contrast T2W image of MRI PNS in coronal plane shows hyperintense nodular mucosal thickening in the left maxillary sinus. (**b**) Contrast-enhanced fat-suppressed T1W image of MRI PNS in coronal plane shows enhancing thin mucosal lining in the left maxillary sinus and focal non-enhancing lesion in sinus cavity possibly a fungal ball or chronic inspissated secretions

Specific sequences like STIR and FLAIR can show inflammatory changes or oedema as a bright signal in involved soft tissues.

Diffusion-weighted sequences are used to evaluate areas of cerebral and optic nerve infarctions. They demonstrate optic nerve infarction (bright signal) when regular MR sequences show normal optic nerves (Fig. 17.11a).

17.8.1 MR Findings

- Non-contrast T2W MRI PNS shows sinusitis as hyperintense nodular mucosal thickening without air-fluid levels (Fig. 17.8a).
- In the same patient, contrast-enhanced T1W images of MRI PNS show mucosal enhancement in involved sinuses and focal non-enhancing areas in nasal/sinus cavities or walls, suggesting the possibility of angioinvasive fungal infection or chronic inspissated secretions (Figs. 17.8 and 17.9).
- Infiltration of the periantral fat planes with a rim of soft tissue attenuation of variable thickness along the walls of the involved sinuses is the earliest MRI finding of extra sinus extension in ROCM (Fig. 17.9). Soft tissue infiltration of premaxillary area or post-maxillary area (characterized by obliteration of the normal fat planes in the infratemporal fossa, pterygopalatine fossa and pterygomaxillary fissure) may be noted (Fig. 17.9).

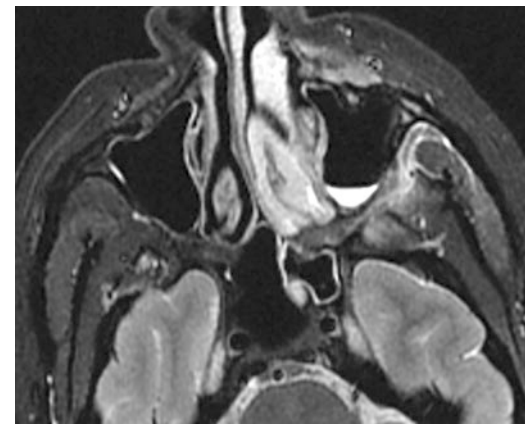

Fig. 17.9 STIR image of MRI PNS in axial plane shows hyperintense infiltration in thickened premaxillary soft tissues on the left side. Air fluid levels seen in the left maxillary sinus and hyperintensity in retro antral fat are quite specific for fungal infection

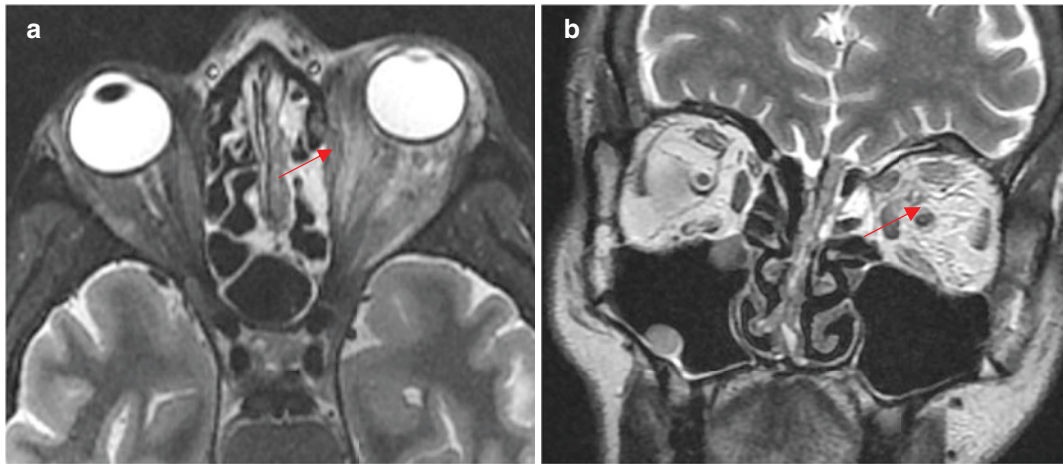

Fig. 17.10 (**a**) MRI PNS STIR image in the axial plane and (**b**) T2W image in coronal plane shows infiltration of left orbital fat, bulky and hyperintense ocular muscles suggesting orbital cellulitis (red arrow)

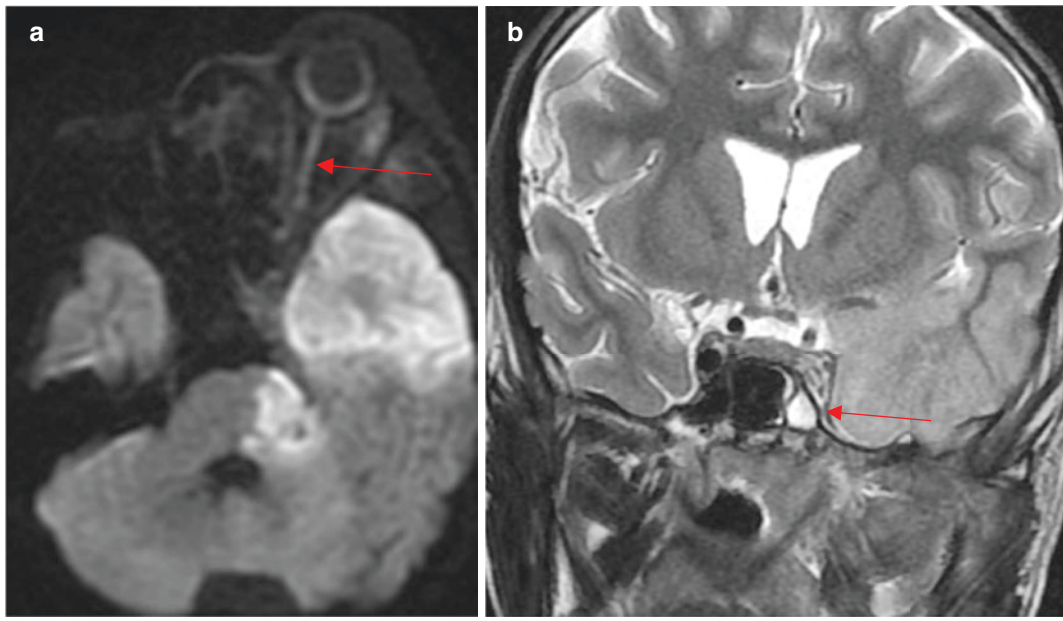

Fig. 17.11 (**a**) DW image of MRI brain shows ischaemic areas in the left temporal lobe and left pons. The bright signal is also noted in optic nerve suggestive of optic nerve infarct (red arrow). (**b**) T2W image of MRI brain of same patient shows left cavernous sinus thrombosis and occluded left ICA

Orbital invasion is seen as hyperintensity in region of retroorbital fat around the extraocular muscles suggests soft tissue infiltration and oedema. The medial rectus muscle in early stages can be seen thickened and laterally displaced (Fig. 17.10a, b). Further orbital involvement can vary in severity from cellulitis, subperiosteal abscess, an orbital abscess to central retinal artery or ophthalmic artery occlusion leading to optic nerve infarction, or there can be direct infiltration of the optic nerve (Fig. 17.11a). Patient presenting with severe proptosis and tenting of the globe suggests diffuse orbital invasion.

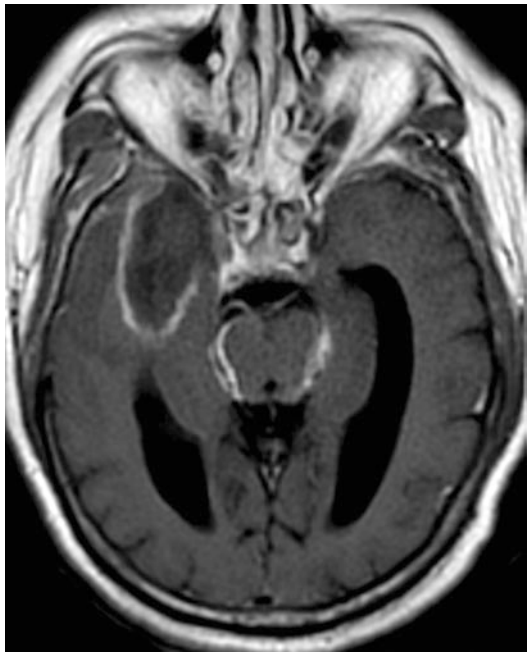

Fig. 17.12 Contrast-enhanced T1W images of MRI BRAIN in the axial plane show well-defined Intra-axial peripherally enhancing hypointense lesion in the right temporal lobe suggestive of the abscess

- Intracranial findings include infarcts due to vascular thrombosis or mycotic emboli leading to the formation of frontal/temporal lobe abscesses, epidural and subdural abscesses and central venous thrombosis (Figs. 17.11 and 17.12).
- Lack of enhancement of major vessels like the internal carotid artery, superior ophthalmic vein or ophthalmic artery is suggestive of thrombus formation due to angioinvasive nature of the fungus.

17.8.2 Management

- Early clinical diagnosis and a high index of suspicion is the key to reducing patient morbidity and mortality.
- Nasal endoscopy is performed at the earliest, and a sample from suspicious tissue or discharge is taken and sent for KOH mount. Empirical antifungal therapy is initiated in suspected cases, even when the report of KOH staining is awaited.
- Stringent control of hyperglycaemia and Ketoacidosis is achieved. In case D-dimer is raised due to associated COVID-19 infection, anticoagulant therapy is also continued. The physician's role is vital in achieving control of hyperglycaemia and post-COVID complications other than mucormycosis.
- Surgery includes an endoscopic approach in case disease is limited to sinuses, endoscopic medial maxillectomy if the disease is located in the deeper posterolateral part of maxillary sinuses or involving the pterygopalatine fossa. In case of orbital involvement, removing lamina papyracea and clearing diseased tissue and intraorbital irrigation with amphotericin B (extra and intraconal depending on the extent of disease) is performed. Once the extra sinus spread involves palate, open approach surgery in the form of subtotal, total maxillectomy (Weber Ferguson approach) with or without orbital exenteration (in case of diffuse orbital involvement with complete ophthalmoplegia) is performed.
- Early and aggressive debridement of the eschar and necrotic tissue is a must to decrease the fungal load, reduce the complications (e.g. vascular thrombosis) and also for maximum delivery of antifungal medications to remaining viable tissue. The debridement is continued and followed till its last extent, and all necrotic tissue, pus and eschar are removed till normal well-perfused bleeding tissue appears.
- Antifungal therapy (parenteral amphotericin B or *Isavuconazole*) is started at the earliest. Based on safety and efficacy data Liposomal Amphotericin B remains the drug of choice. Renal functions are monitored essentially to detect the amphotericin B-induced nephrotoxicity at the earliest.
- The recommended dose of Amphotericin is: Injection Liposomal Amphotericin B, 3–5 mg/kg/day to a total of up to 5.6 g. The drug is continued for weeks together, and once the disease is controlled, the dose is decreased to a maintenance dose of 1 mg/kg/day, followed by a step-down therapy with the antifungal

drug Posaconazole. The response to treatment is evaluated by clinical improvement, endoscopic clearance and repeated KOH staining and culture and radiological studies.

- Topical Amphotericin is also used for irrigation of the involved orbit and paranasal sinuses after surgery and in the post-operative period at regular intervals with excellent results. In cases of orbital involvement, delivery of topical amphotericin B volume 15 mL (0.5–1 mg/mL) to the infected site once or twice daily can achieve excellent results. Intraconal injection of amphotericin B (1 mg/mL) for at least a week along with intravenous amphotericin B is used in cases of extensive orbital involvement.
- Recommended dosage and schedule of the antifungal medication, Isavuconazole in case Amphotericin molecule is toxic, is a loading dose of 200 mg intravenous or oral Isavuconazole eight hourly for 48 h followed by 100 mg capsules two capsules once a day for 7 days
- Once the disease and other patient parameters are under control, maintenance therapy with oral Posaconazole 300 mg twice a day is to be given for 1 month, followed by 300 mg once a day until the patient is completely disease free.
- The patient is to be assessed clinically, regularly, with endoscopic clearance of disease and necrotic tissue every 48 h until the disease is completely cleared or eradicated.

17.9 Surgical Management

17.9.1 Case 1: Involvement of the Anterior Part of the Nasal Septum

A patient presented to us with a history of breathlessness, nasal obstruction, blood-stained nasal discharge and facial pain. He tested positive for COVID 20 days before presenting to us. He was suffering from Diabetes Mellitus, and others had systemic features of COVID at the time of presentation.

17.9.1.1 Clinical and Haematological Evaluation

At the time of admission patient was found afebrile, breathless and hypoxic. He underwent a complete systemic and laboratory evaluation. Relevant baseline investigations revealed a haemoglobin value of 10.40 g/dL (normal 13–17 g/dL), mild lymphopenia (9.60%; normal 20–40%) and elevated serum creatinine (1.57 mg/dL; normal 0.70–1.20). C-reactive protein (CRP) was 29.53 mg/l (normal <5.0), procalcitonin (PCT) was 0.34 ng/mL (normal <0.5), with a D-dimer assay of 1547 ng/mL (normal 0–243) and an IL6 level of 3439 micrograms/mL (normal 0–7.0), suggestive of a severe cytokine storm.

Other blood tests were also performed like complete blood count (CBC), kidney function test (KFT), liver function test (LFT), thyroid-stimulating hormone (TSH), glycosylated haemoglobin (HBAIC), random blood sugar (RBS), C-reactive protein quantitative, D-Dimer and serum ferritin. HBAIC, RBS, CRP and D-Dimer were found to be raised while the total leucocyte count was within the normal limit.

Twice daily evaluation of other parameters was carried out as per mucor checklist for further progression of disease.

The patient underwent a thorough assessment by a multidisciplinary team of otorhinolaryngologist, physician, pulmonologist, neurosurgeon and ophthalmologist. A diagnosis of post-COVID mucormycosis with bilateral pneumonitis and diabetes mellitus was made.

17.9.1.2 Imaging

Imaging included computed tomographic scans and magnetic resonance imaging of paranasal sinuses (PNS), orbit and brain. Chest status was also assessed by X-ray Chest PA view followed by HRCT thorax. Both X-ray and CT thorax showed central and peripheral areas of ground glass opacities. There was an interstitial septal thickening more in bilateral lower lobes and the CT severity scoring was 22/25. The radiological diagnosis was bilateral post-COVID pneumonitis with fungal infection involving anterior part of the nasal septum.

17.9.1.3 Confirmation of Diagnosis

Confirmation of diagnosis was done by collecting smear/biopsy from the lesion with appropriate precautions and sent for KOH staining. The KOH stain showed aseptate hyphae suggesting mucormycosis. Histopathological evaluation (HPE) of the nasal discharge revealed broad aseptate ribbon-like fungal hyphae on KOH wet mount. A nasal swab did not have significant findings but a nasal biopsy from the middle turbinate revealed broad aseptate filamentous fungal hyphae suggestive of mucormycosis and Sabouraud dextrose agar (SDA) media grew mucormycosis.

17.9.1.4 Treatment of COVID

The exact date of onset of COVID is noted and the treatment is started by the physician. Use of steroids and immunosuppressant drugs like tocilizumab is avoided.

1. *Evaluation and management of Diabetes*

As hyperglycaemia in mucormycosis leads to the flaring up of the disease, it needs to be treated rigorously using a strategical approach. Since the patient had a Random blood sugar of more than 200 mg/dL, fasting blood sugar more than 124 mg/dL % and HBAIC more than 6.4% diagnosis of diabetes mellitus was confirmed. Antidiabetic treatment was started immediately in the form of insulin infusion followed by oral hypoglycaemic agents and his blood glucose levels were kept well under control. All those patients who never had diabetes before covid but showed a high level of sugar owing to the steroid intake were also treated as cases of diabetes mellitus.

2. *Treatment for respiratory system*

The status of the respiratory system was assessed on HRCT chest. There was no fungal dissemination to the lungs but as HRCT chest showed severe COVID-associated pneumonia. Patient was put on supplemental high flow oxygen support, antifibrotic drugs like Nintedanib tablet formulations and anticoagulants. Steroids and immunosuppressants are avoided in these patients as they may lead to further exacerbation of mucormycosis. Broad-spectrum antibiotics were also avoided and only culture-specific antibiotics were given. Once the patient's lung condition improved, he was subjected to pulmonary function tests and 6 min walk test and finally could be weaned off the oxygen support on the 25th day of admission. Doses of anticoagulants and antifibrotic drugs were also tailored according to requirement of patient and finally tapered off after 1 month.

17.9.1.5 Treatment of Mucormycosis

1. *Medical management:*

Patient was treated with injection liposomal amphotericin B in the dose of 0.5 mg/kg/day. He was also given intravenous meropenem (1 g thrice daily) and vancomycin (1 gram twice daily) with the addition of amphotericin B.

2. *Surgical management:*

After the improvement in patient's general condition, endoscopic debridement was carried out. Since this case had limited disease involving only the anterior part of the nasal septum, the lesion was debrided and sent for histopathology and culture.

Lactophenol cotton blue (LPCB) stain after culture on Sabouraud dextrose agar (SDA) showed broad aseptate ribbon-like hyphae branching at right angles (black arrow) with sporangium.

Post-operative nasal endoscopy and cleaning were performed every 48 h and the crusts were sent for KOH till they became negative for mucormycosis (Figs. 17.13, 17.14, 17.15, 17.16, and 17.17).

17.9.2 Case 2: Involvement of the Posterosuperior Part of the Nasal Septum and Bilateral Sinuses

17.9.2.1 Imaging (Figs. 17.18 and 17.19)

The CT scan of paranasal sinuses showed pansinusitis involving all the sinuses on both sides. A post-gadolinium-enhanced MRI, however, showed mucor involving only the nasal septum in its posterosuperior part.

Fig. 17.13 Patient on high flow oxygen support as a patient suffering from post-COVID pneumonia

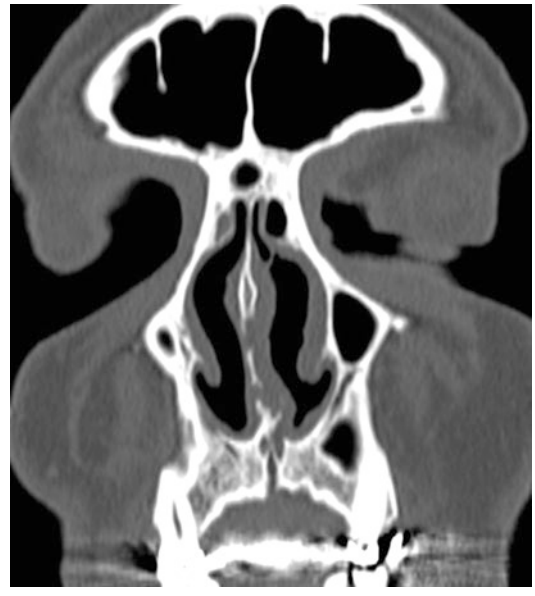

Fig. 17.14 Non-contrast CT PNS image in coronal plane shows irregular mucosal thickening with bony erosions in anteroinferior nasal septum on the left side

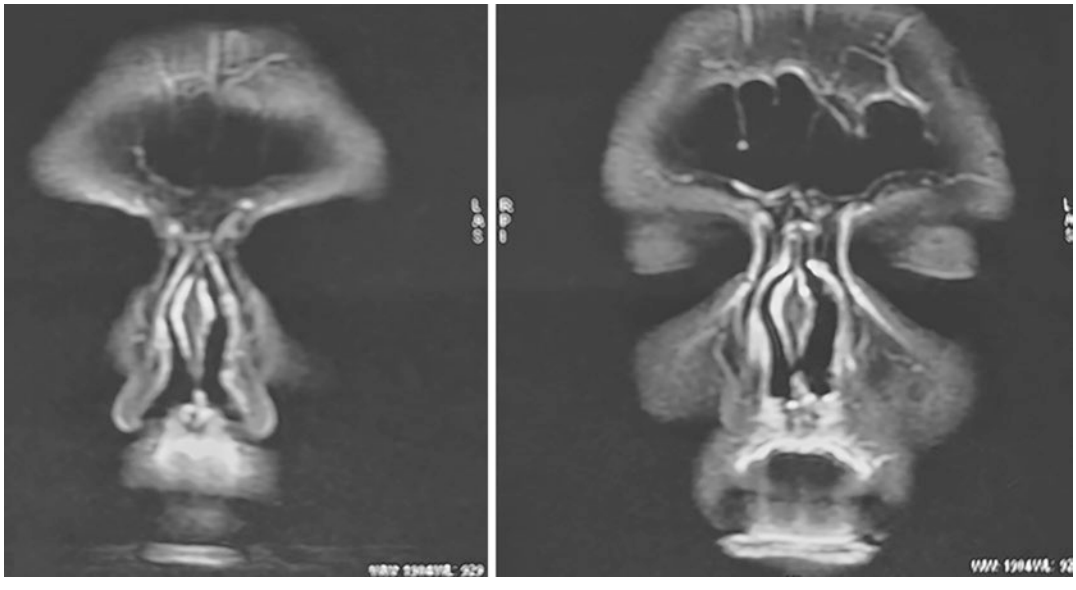

Fig. 17.15 (**a**, **b**) Contrast-enhanced MRI PNS fat-suppressed T1W images in coronal plane show mucosal irregularity and non-enhancing areas in nasal septum anteriorly

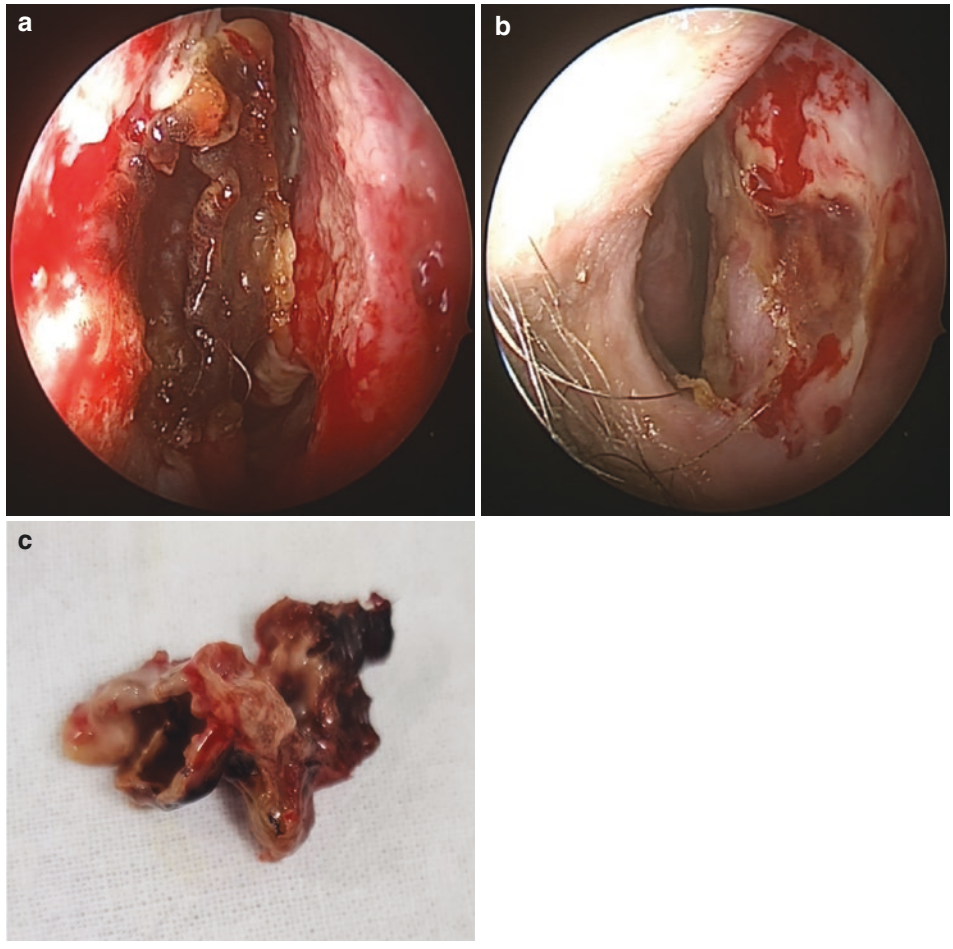

Fig. 17.16 (**a**) Eschar formation and mucor involving anterior part of the nasal septum on left and (**b**) On the right side. (**c**) Excised necrotic tissue with eschar to be sent for KOH staining and culture sensitivity

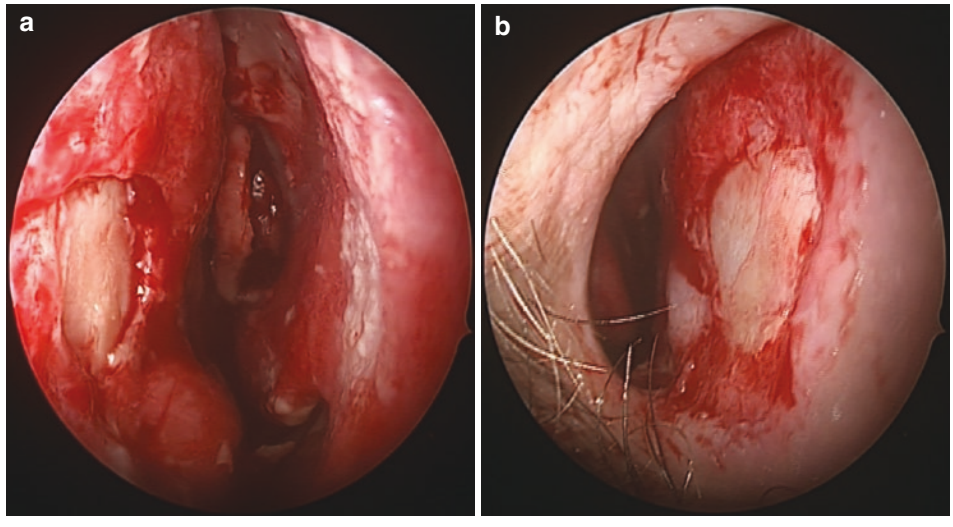

Fig. 17.17 (**a**) Clearance of disease on the left side. (**b**) Clearance of disease on the right side

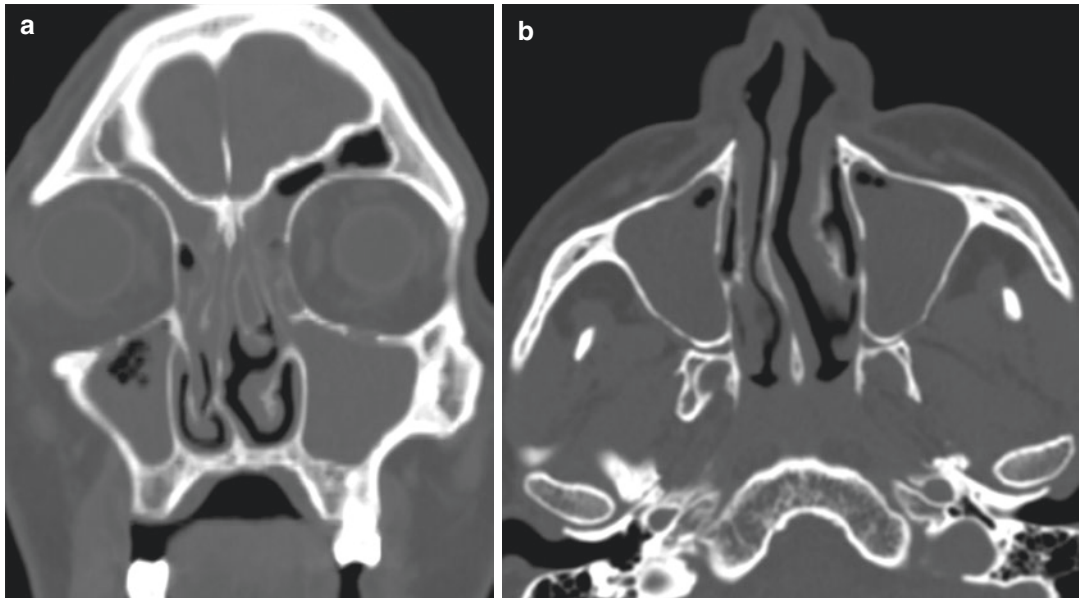

Fig. 17.18 Non-contrast CT PNS images in coronal (**a**) and axial (**b**) planes show almost complete opacification of bilateral frontal, maxillary and ethmoid sinuses. Soft tissue density is also seen in fronto-ethmoid recesses

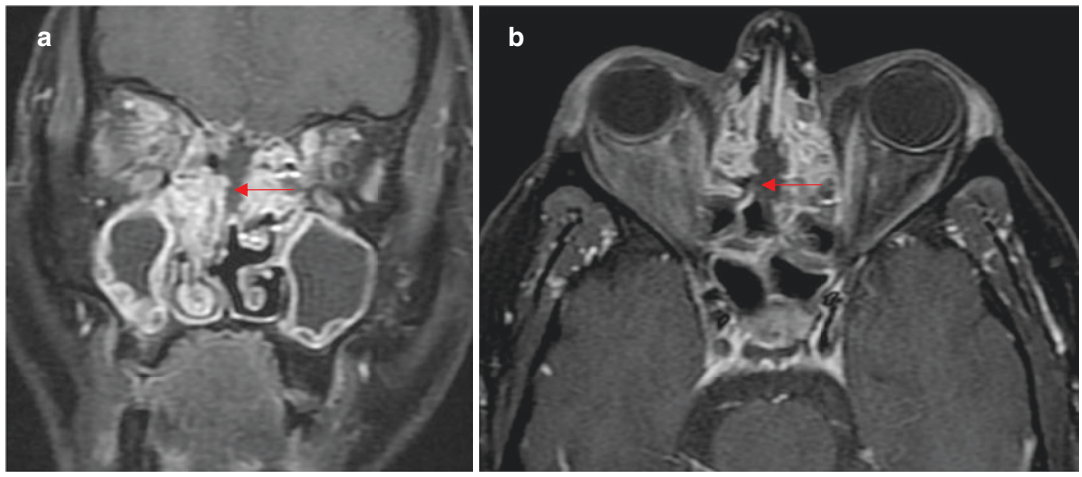

Fig. 17.19 MRI PNS Contrast-enhanced fat-suppressed T1W images in axial (**a**) and coronal (**b**) planes show enhancement of mucosal lining in bilateral maxillary and ethmoid sinuses. Non-enhancing areas are seen in sinus cavities suggesting thick secretions/pus. Focal non-enhancing area seen in the superior part of nasal septum suggests fungal infestation (red arrow)

17.9.2.2 **Surgical Findings** (Figs. 17.20 and 17.21)

On endoscopic surgical management, the sinuses were found to be filled with pus and fungal infection found to be involving only the posterosuperior part of nasal septum with involvement of both bone and cartilage. All sinuses were cleared, and the mucor infested nasal septum was excised till normal healthy septal margins were reached in all directions.

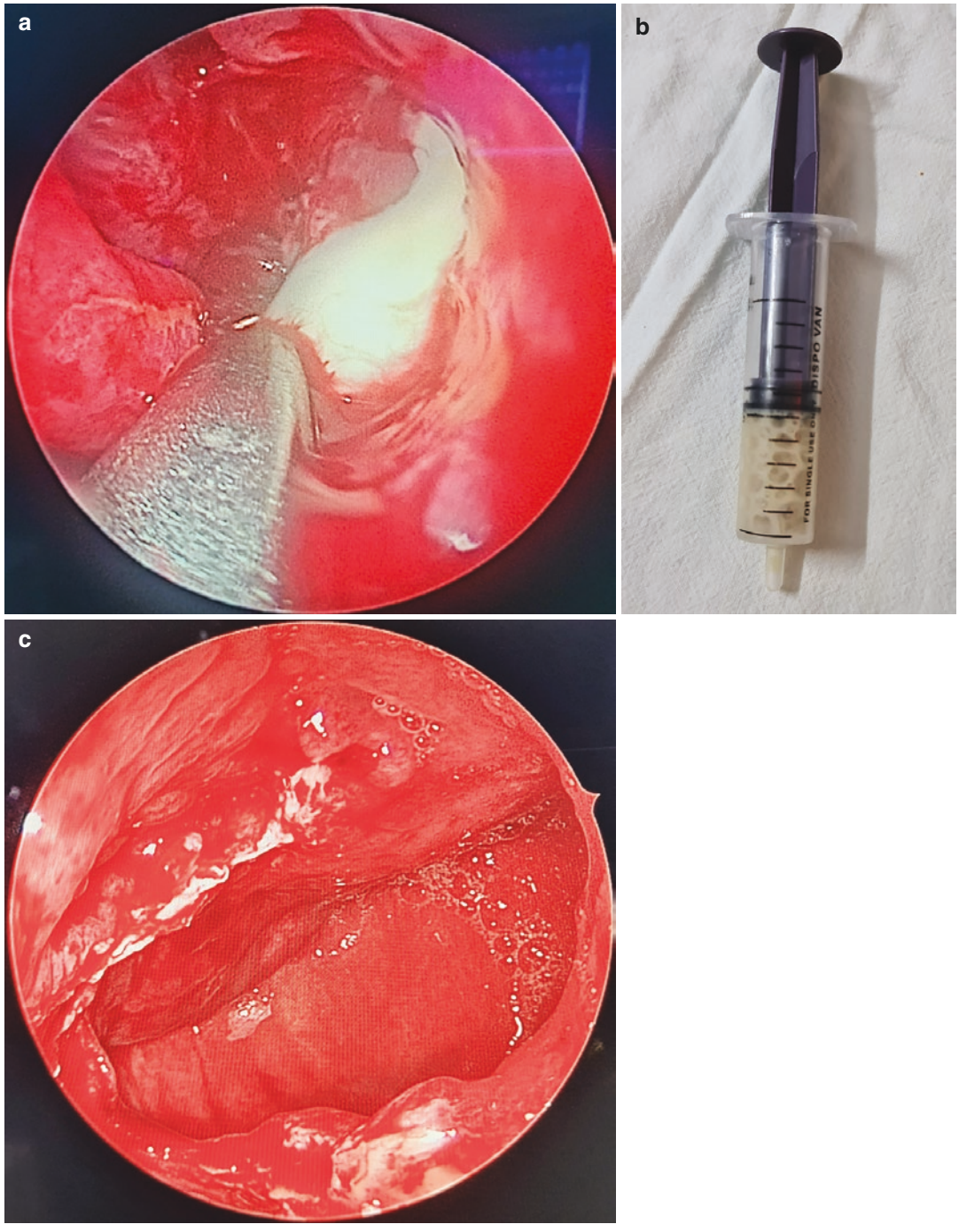

Fig. 17.20 (**a**) Left nostril: after uncinectomy, pus filling left maxillary sinus aspirated and sinus cleared of disease. (**b**) Aspirated pus. (**c**) The left maxillary sinus shows no trace of mucor

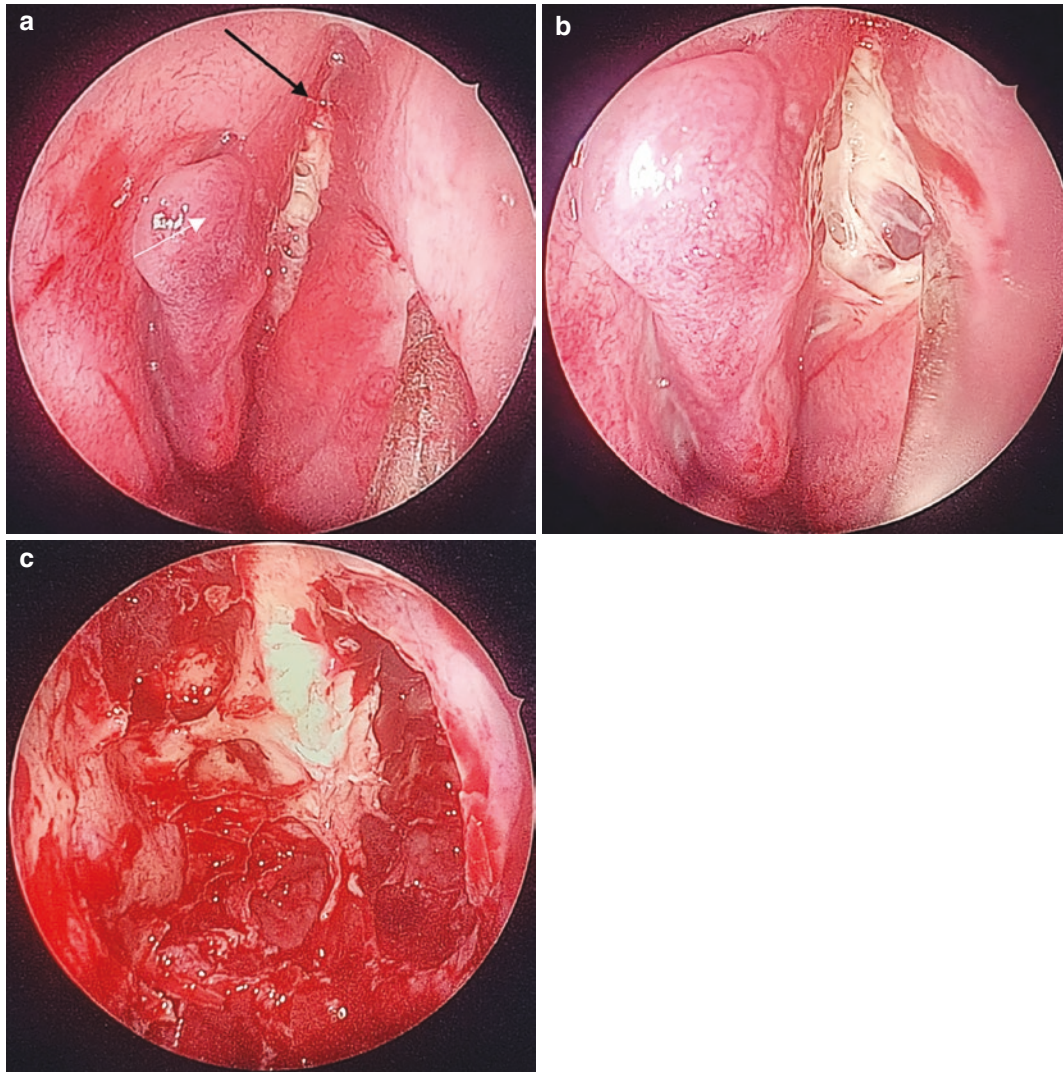

Fig. 17.21 (**a**) Right nasal cavity with healthy middle turbinate (white arrow) and involvement of posterosuperior part of septum by mucormycosis (black arrow) proved on KOH staining. (**b**) mucor involving posterosuperior part of septum. (**c**) Final picture, after clearance of disease from all paranasal sinuses on both sides and excision of diseased septum till normal septum reached in all directions

17.9.3 Case 3: Involvement of the Left Maxillary Sinus and its Lateral Wall

17.9.3.1 Radiological Findings (Figs. 17.22, 17.23, 17.24, and 17.25)

The CT scan showed polypoidal mucosal thickening involving left maxillary sinus in its medial and inferior part. The MRI T2W images showed hyperintense mucosal thickening with few hypointense areas within it, involving the medial and inferior part of the left maxillary sinus.

17.9.3.2 Surgical Management (Fig. 17.26)

Endoscopic surgery in the form of uncinectomy and middle meatal antrostomy was performed via

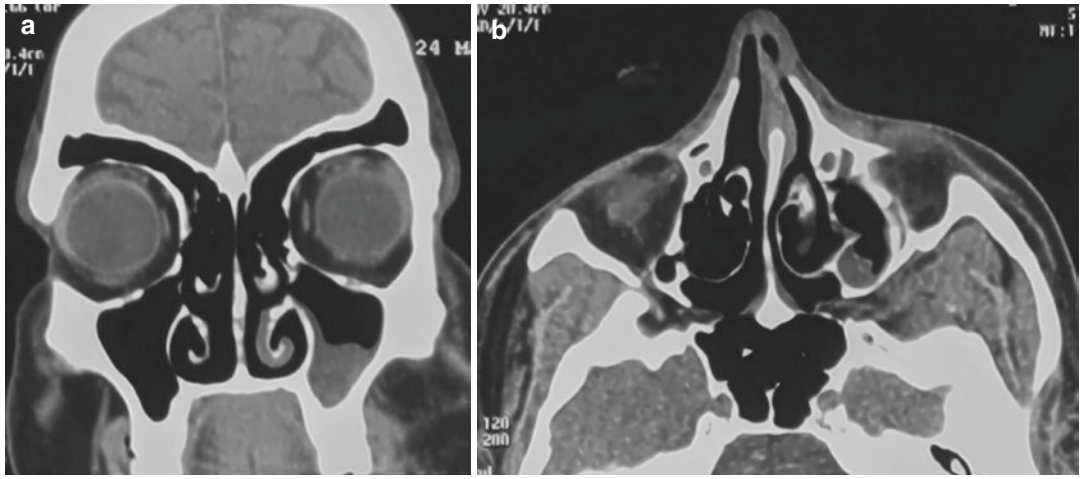

Fig. 17.22 (**a**, **b**) Non-contrast CT PNS images in coronal and axial planes show polypoidal mucosal thickening in left maxillary sinus in its inferior and medial part

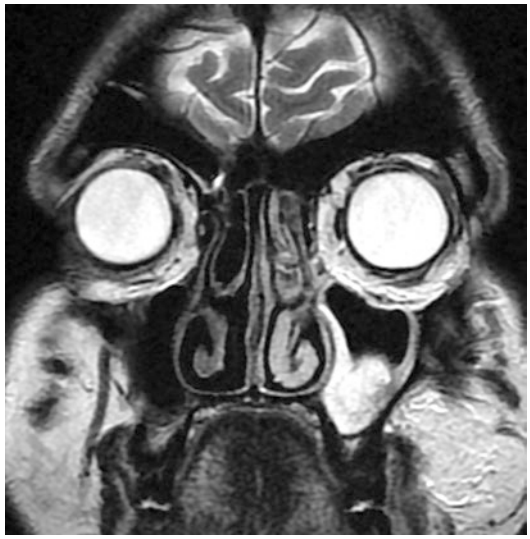

Fig. 17.23 T2W MRI PNS images in coronal plane show hyperintense mucosal thickening in left maxillary sinus with few hypointense areas within it

left nostril. Complete clearance of the disease was achieved and the necrotic tissue excised was sent for KOH mount. On receiving positive report for nucor, the patient was put on medical treatment which included Injection of Liposomal Amphotericin B. Patient became disease free within 3 weeks.

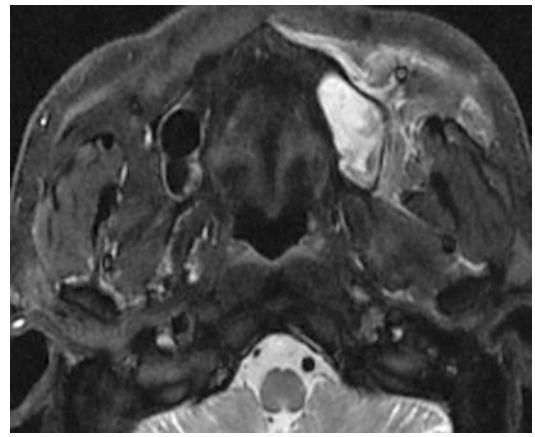

Fig. 17.24 STIR images of MRI PNS in axial plane show left maxillary sinusitis with inflammation/oedema in left premaxillary as well as periantral soft tissues

17.9.4 Case 4: Involvement of the Lateral Wall of the Maxilla

17.9.4.1 Radiological Findings (Figs. 17.27 and 17.28)

CT scan and MRI showed disease localized to maxillary sinus left side involving its lateral most part.

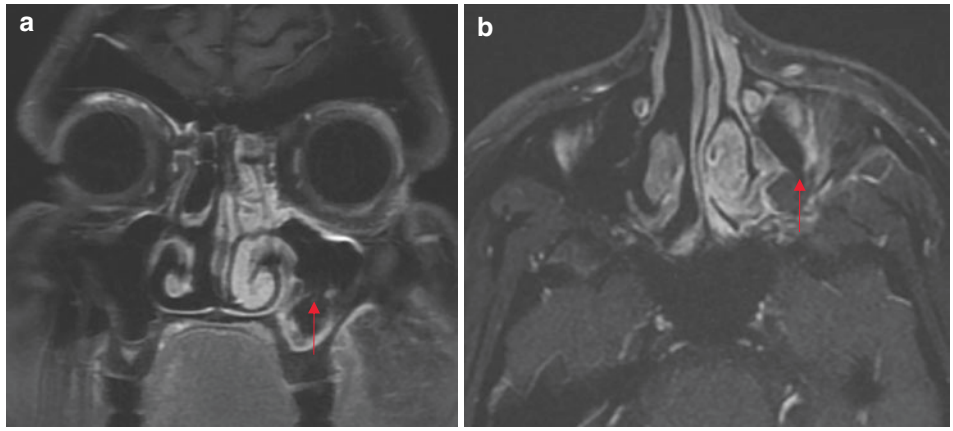

Fig. 17.25 Contrast-enhanced fat-suppressed T1W images in coronal (**a**) and axial (**b**) planes showing non-enhancing lesion involving inferior and medial quadrant of left maxillary sinus (red arrow)

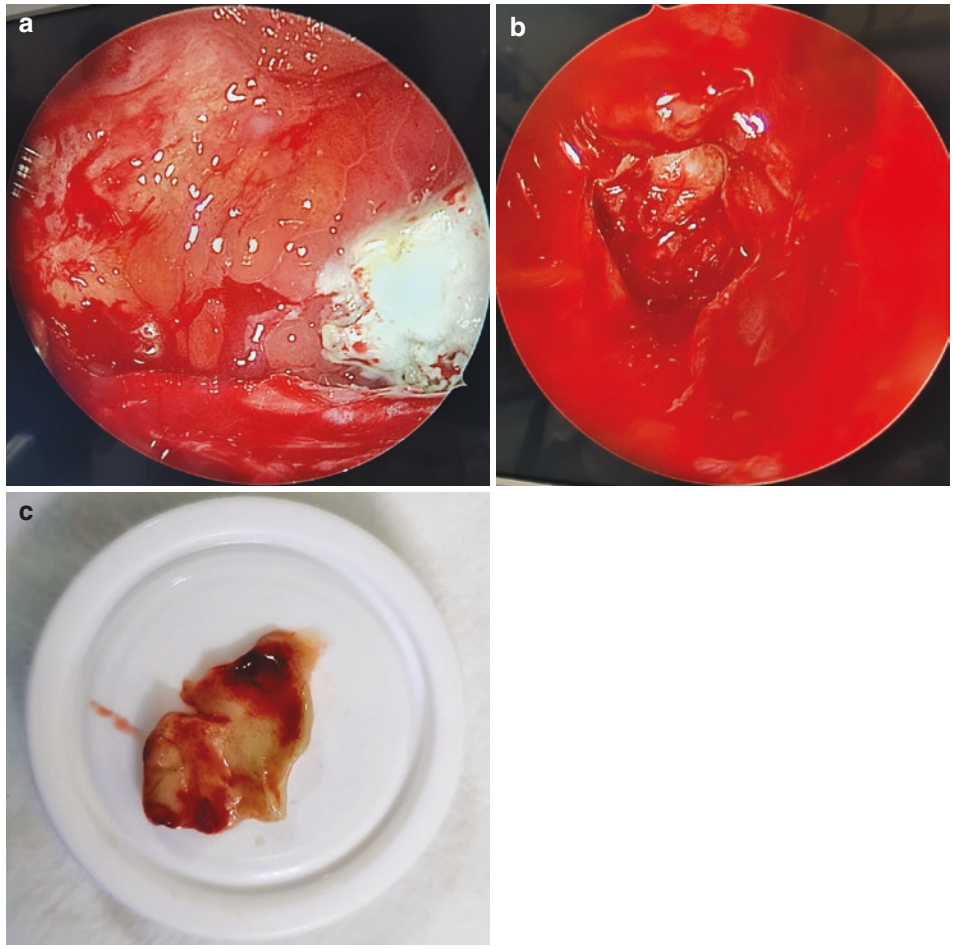

Fig. 17.26 (**a**) Uncinectomy and middle meatal antrostomy performed on left side. Per operative findings showing fungal involvement of inferior and medial part of left maxillary sinus. (**b**) After clearance of disease, the healthy though hypertrophic mucosa of maxillary sinus visible. (**c**) The mucor infested necrotic tissue

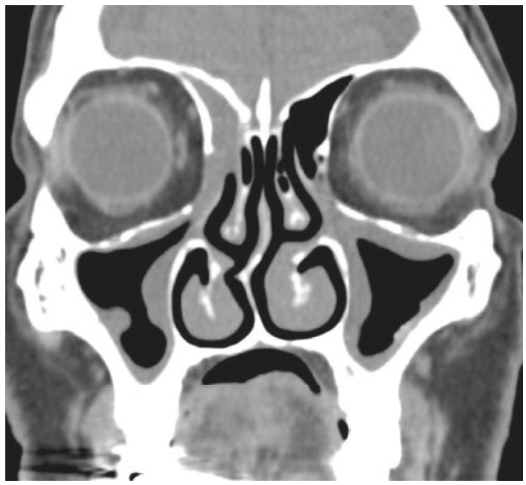

Fig. 17.27 CT PNS images in the coronal plane show nodular mucosal thickening in bilateral maxillary sinuses

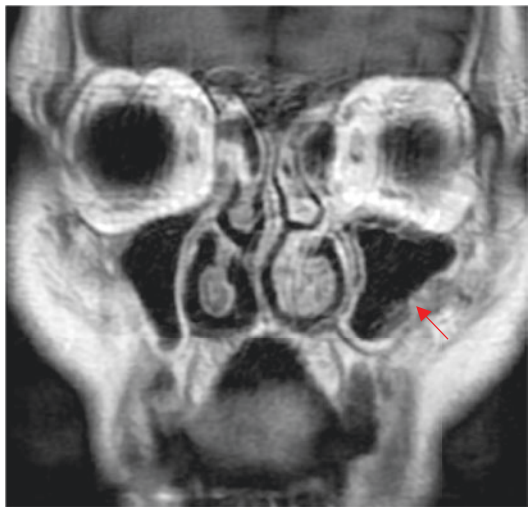

Fig. 17.28 Contrast-enhanced T1W image in coronal plane shows non-enhancing sinus mucosa in left maxillary sinus (red arrow)

17.9.4.2 Surgical Steps and Findings (Figs. 17.29 and 17.30)

Endoscopic sinus surgery: Uncinectomy with middle meatal antrostomy could not expose the area infested with mucormycosis. Endoscopic medial maxillectomy was performed to reach the lateral most part of sinus and complete clearance of disease was achieved. Medical treatment started after confirmation of aseptate broad hyphae on KOH mount.

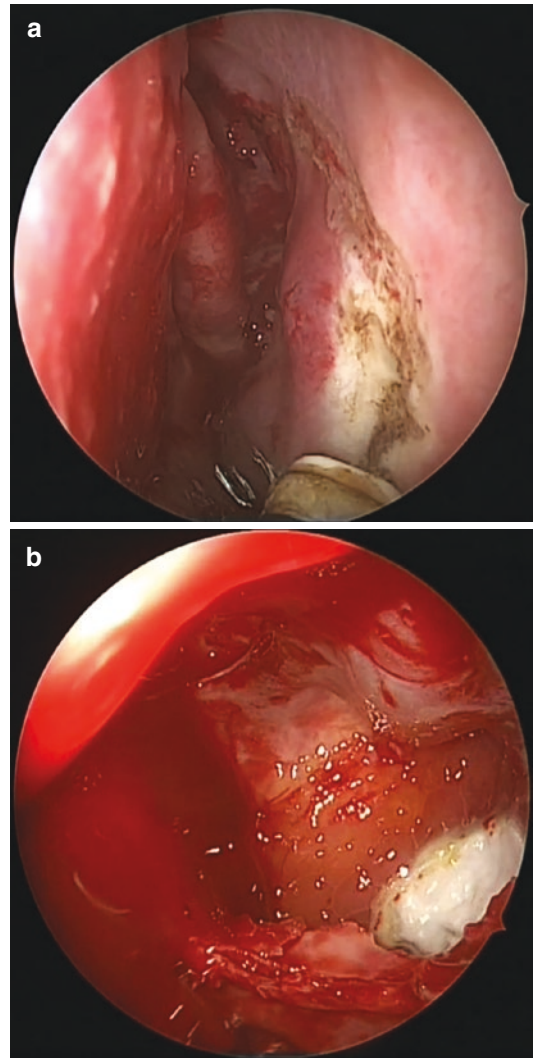

Fig. 17.29 (**a**) Left nostril: A showing medial maxillectomy in progress. (**b**) Location of disease far more laterally in maxillary sinus

The two cases described above, show how the treatment is to be customized according to the location and extent of disease.

17.9.5 Case 5: Involvement of the Sinuses, Pterygopalatine Fossa and Orbit

A Thirty-eight year-old male came to emergency department on tenth day of COVID illness with complaints of left-sided facial pain, pain over left

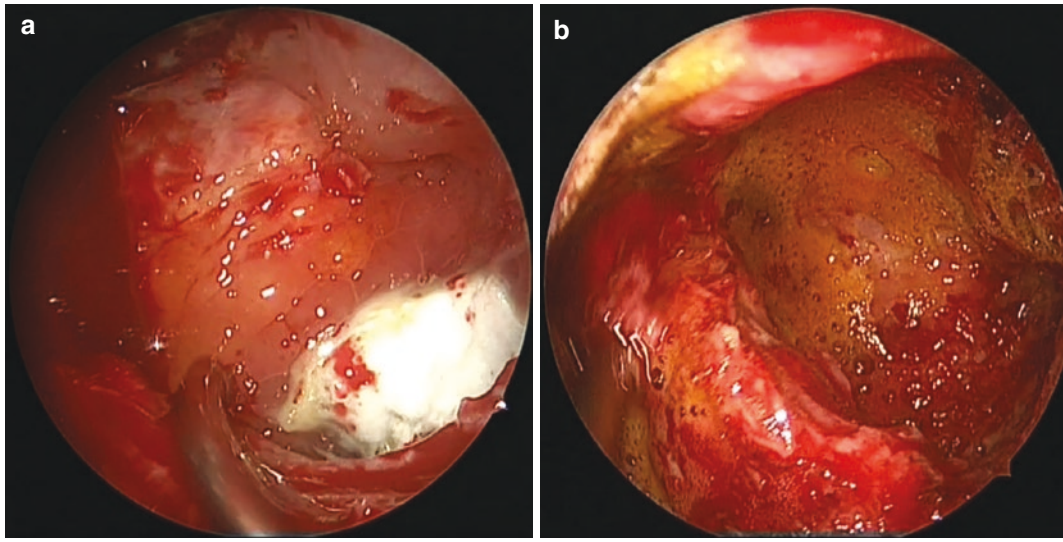

Fig. 17.30 (**a**) After medial maxillectomy the complete extent of disease is visualized. (**b**) Complete clearance of disease

upper jaw, fever and breathlessness. The patient was a known case of poliomyelitis.

17.9.5.1 Clinical Features

Patient presented with a history of drooping of the left upper eyelid and facial swelling. On examination he was afebrile, but had proptosis left eye with oedema over the left side of the face. He underwent a complete systemic and laboratory evaluation.

A multidisciplinary team including otorhinolaryngologist, radiologist, physician, neurosurgeon and ophthalmologist carried out a comprehensive evaluation of the patient and a diagnosis of COVID-associated mucormycosis was made.

17.9.5.2 Investigations

The investigation performed were CT PNS, orbit and brain (Fig. 17.31), MRI PNS with contrast (Figs. 17.31 and 17.32) and X-ray Chest PA view followed by HRCT chest.

The baseline blood investigations showed raised blood sugar levels and patient was found to be suffering from undetected diabetes mellitus.

Nasal crusting was sent for KOH wet mount examination and revealed broad aseptate acute angle branching hyphae suggestive of mucormycosis.

17.9.5.3 Blood Screening

The team sent routine blood investigations, including complete blood count, kidney function test, liver function test, random blood sugar, glycosylated haemoglobin and arterial blood gas analysis. All the levels were deranged, including a high total leukocyte count that kept rising for 5–6 days. Twice daily evaluation was performed, as per mucor checklist for further disease progression and following treatment started.

17.9.5.4 Treatment for COVID

The exact onset date was noted, and the physician started the treatment taking care to avoid the use of steroids and immunosuppressant drugs like tocilizumab as the patient was already immunocompromised. He was started on low-molecular weight heparin in the dose of 0.4 unit subcutaneous once a day, as his D-dimer levels were raised.

17.9.5.5 Evaluation and Management of Hyperglycaemia

He was a case of undetected diabetes, so his blood sugar levels were monitored every 4 h and the physician started subcutaneous insulin. Later he switched the patient on oral hypoglycaemic agents.

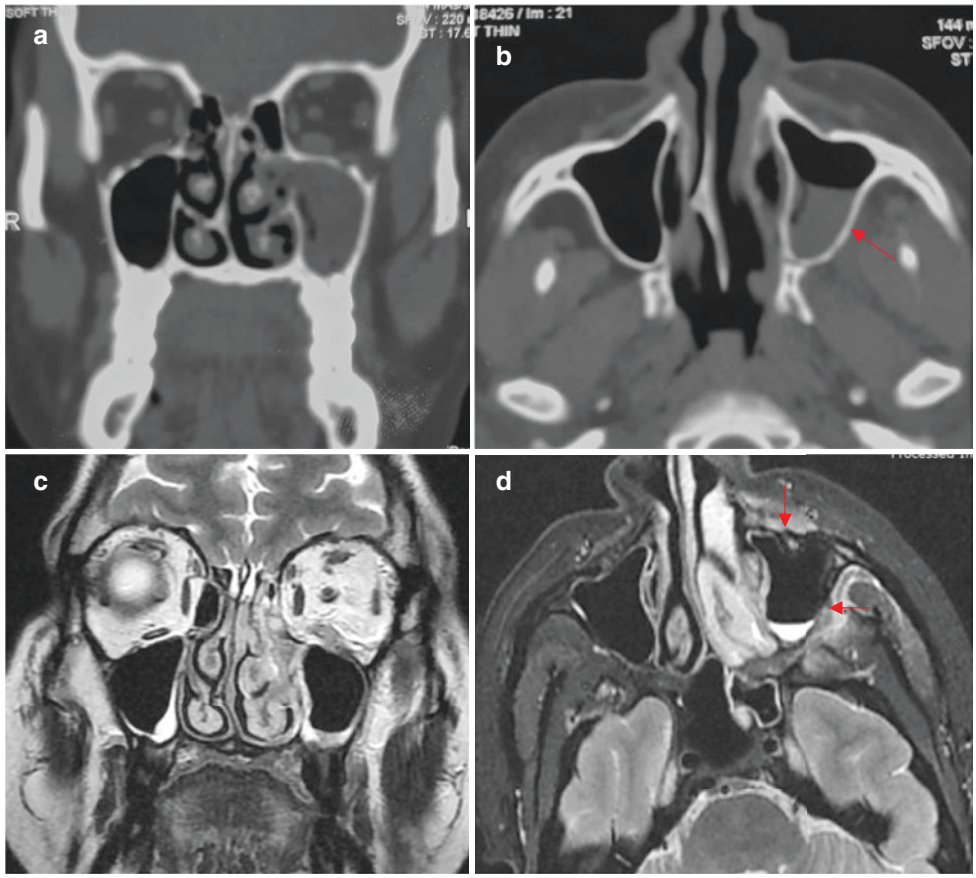

Fig. 17.31 (**a**) CT PNS showing opacification of left maxillary sinus. (**b**) Left maxillary sinus opacification with soft tissue density and thickening of left retroantral soft tissue (red arrow). (**c**, **d**) T2W image of MRI PNS in coronal and axial plane shows mucosal hypertrophy of left middle and inferior turbinates with soft tissue infiltration of preantral and retroantral area suggesting involvement of pterygopalatine area (red arrows)

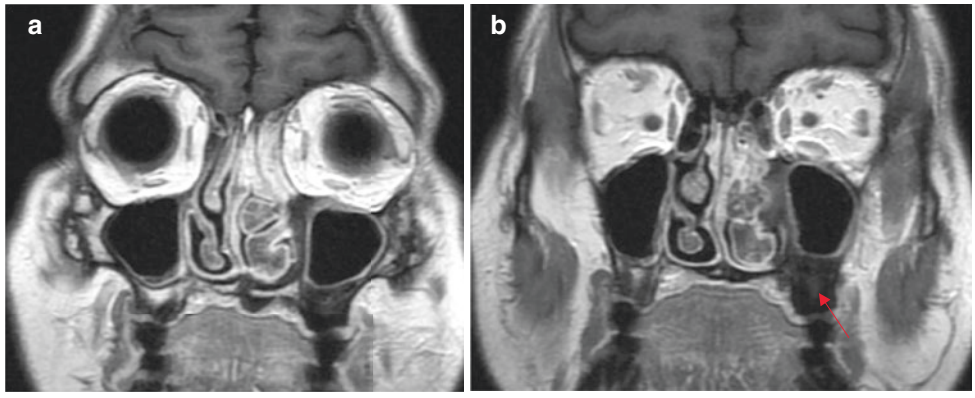

Fig. 17.32 Contrast-enhanced T1W images of MRI PNS in coronal plane (**a**) and (**b**) show non-enhancing areas in left middle and inferior nasal turbinates and also in lateral and inferior wall of left nasal cavity (red arrow)

17.9.5.6 Treatment of Respiratory System

The physician reviewed HRCT chest, and as the patient was maintaining SpO_2 on room air, no active management was needed for his respiratory system.

17.9.5.7 Treatment of Mucormycosis

Once the KOH was suggestive of mucormycosis first-line antifungal treatment with Inj. Liposomal amphotericin-B was started (5 mg/kg/day, the total being 300 mg single dose i/v). Supportive therapy with intravenous injection cefoperazone with sulbactam (1.5 g BD) was also started.

17.9.5.8 Surgical Treatment

As the contrast-enhanced T1W image of MRI PNS in axial plane showed involvement of left pterygopalatine fossa, though the posterior wall of left maxillary sinus was intact, endoscopic surgical debridement in the form of left medial maxillectomy along with excision of necrotic part of middle turbinate was performed to clear disease from maxillary sinus and pterygopalatine fossa. Posterior bony wall of maxillary sinus was removed and the necrotic diseased tissue was excised from pterygopalatine fossa after clipping the sphenopalatine artery.

Debridement and regular cleaning were performed every 48 h for 14 days along with injectable antifungal in the form of liposomal amphotericin B for 10 days which then was followed by tab Posaconazole 300 mg BD for 3 weeks further followed by maintenance therapy of posaconazole 300 mg once a day for 15 days. Patient became disease free after 2 months.

The fungal culture reported from HPE sample was *Rhizopus Microsporum*.

Three months after surgery and antifungal treatment, complete clearance of disease achieved (Fig. 17.33).

17.9.6 Case 6: Mucor Involving Lateral Wall and Floor of the Right Maxillary Sinus and Hard Palate

17.9.6.1 Radiological Findings

Figures 17.34 and 17.35.

17.9.6.2 Surgical Steps and Findings

As the mucor was invading the bone in the inferior and lateral wall of the right maxillary sinus along with involvement of right-sided hard palate, subtotal (infrastructure) maxillectomy was planned.

Pre-operatively following are discussed with patients and relatives about facial incisions, potential injury to the infraorbital nerve, reconstructive options and the loss of dentition with the need to wear dentures or have dental implants and are also included in the consent.

Intraoperatively necrotic tissue was found in the right maxillary sinus and inferior and lateral bony maxillary walls were eroded.

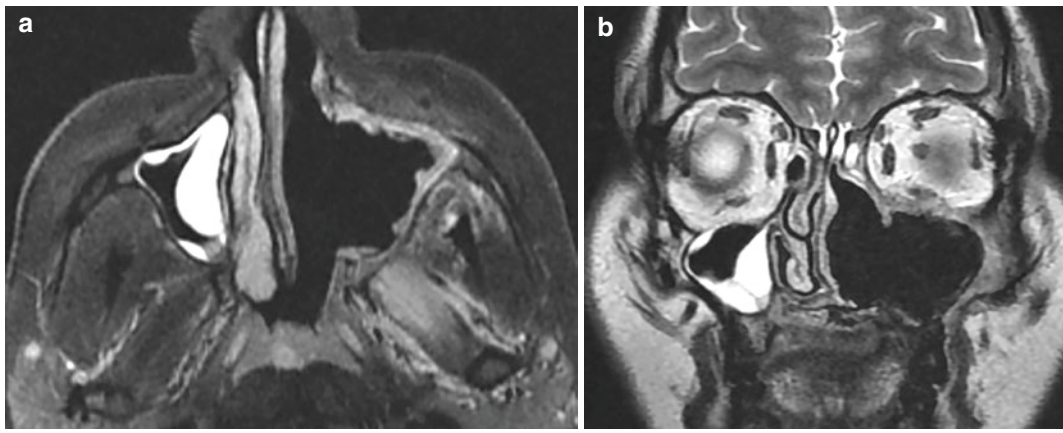

Fig. 17.33 (**a**) STIR axial and (**b**) T2W coronal images show post-operative defects in left nasal cavity and left maxillary sinus with complete clearance of disease

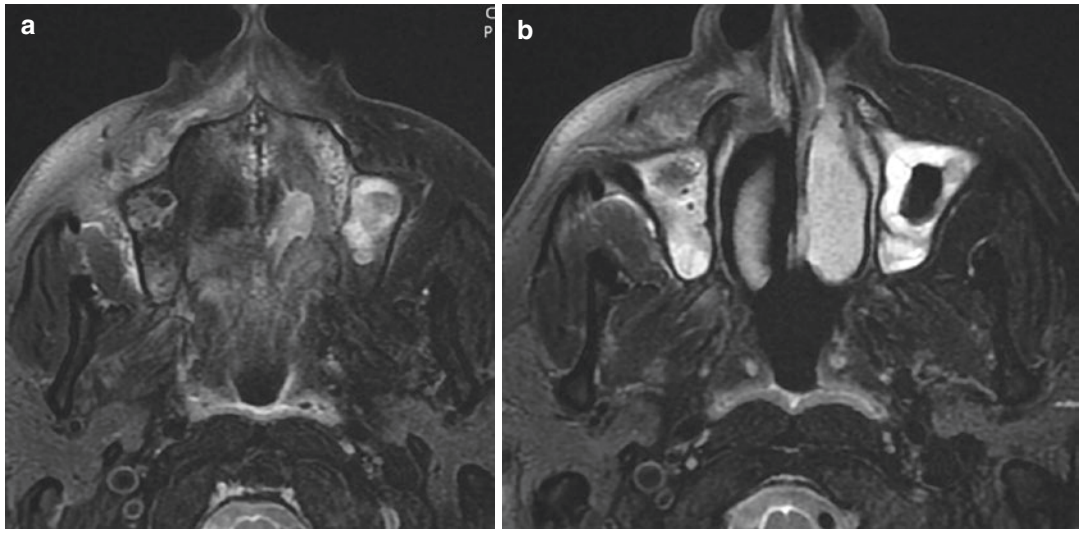

Fig. 17.34 (**a**) Axial STIR images show bilateral maxillary sinusitis along with involvement of palate. (**b**) Inflammation is seen in the right premaxillary and retroantral space

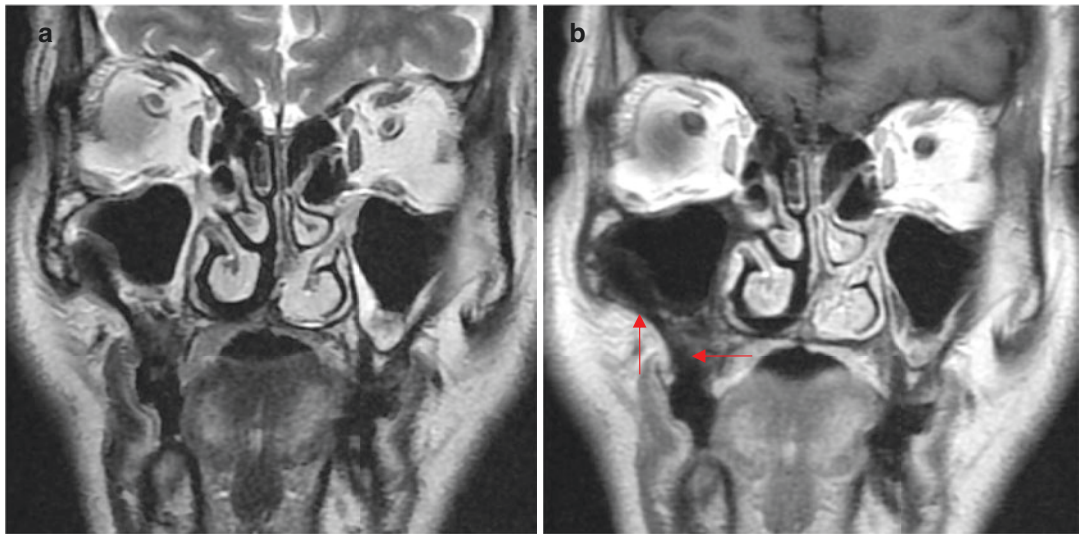

Fig. 17.35 (**a**) T2W and (**b**) contrast-enhanced T1W images in coronal plane show non-enhancement of lateral and inferior walls of right maxillary sinus and hard palate (red arrow)

Subtotal (Infrastructure) maxillectomy is performed in three stages:

1. Soft tissue dissection and bone exposure
2. Bone resection
3. Closure and reconstruction

In subtotal (infra structure) maxillectomy, the upper one-third consisting of the orbital floor formed by the roof of the maxillary sinus and the zygomatic arch is disconnected from lower two-thirds, including the hard palate and alveolar ridge. This is done by an osteotomy just beneath the infraorbital foramen.

Classical Weber Ferguson sub-ciliary incision was given and skin and subcutaneous flap elevated off the surface of maxilla. Next, a full-thickness incision was given on upper lip and divided up to the gingivolabial sulcus. The upper cheek flap was elevated completely by taking an

incision in upper gingivobuccal sulcus remaining close to the gingiva and extended up to the maxillary tuberosity. The key to elevating cheek flap completely is to remain right over the periosteum of the maxilla until its posterolateral aspect is exposed. While elevating this flap we encounter the infraorbital nerve exiting from the infraorbital foramen and entering into soft tissue of cheek. The nerve was preserved in this case. Then the soft tissue along the ala of the nose was divided and through the mucosa of lateral wall of the nasal cavity entry was made into the nasal cavity.

Osteotomies were performed in the following sequence:

Lateral wall of the maxillary sinus.

Anterior wall up to nasal vestibule.

Parallel to the orbital floor. Markings for bony cuts were made in a way that a rim of bone around the infraorbital foramen was preserved.

Posteriorly pterygoid plates are made free from the maxillary tuberosity.

The hard palate osteotomy began with a vertical cut in between the central and lateral incisors on the alveolar ridge, then continued backward in a parasagittal plane on the ipsilateral side of the nasal septum, parallel to the intermaxillary and interpalatine sutures to reach the posterior edge of the hard palate. The hard palate was then separated from soft palate.

To complete the osteotomy a horizontal cut was made through the lateral maxillary wall and a vertical cut extending across the front of the posterior maxillary wall and through the retromolar region, reaching the medial maxillary wall and the perpendicular plate of the palatine bone, which is wedged into the lateral nasal wall between the maxilla and the sphenoid pterygoid process. The next bone cut is continued done keeping in mind, if possible to leave a ledge of the posterior maxillary wall attached to the pterygoid process. This cut is made through the inferior or middle nasal meatus to the pyriform aperture. Initially, all bone cuts are made using a power saw or drill, then sharp osteotome is used to connect the cuts or holes made by drill, and the surgical specimen is removed by clearing all soft tissue connections using electrocautery (Figs. 17.36, 17.37, 17.38, and 17.39).

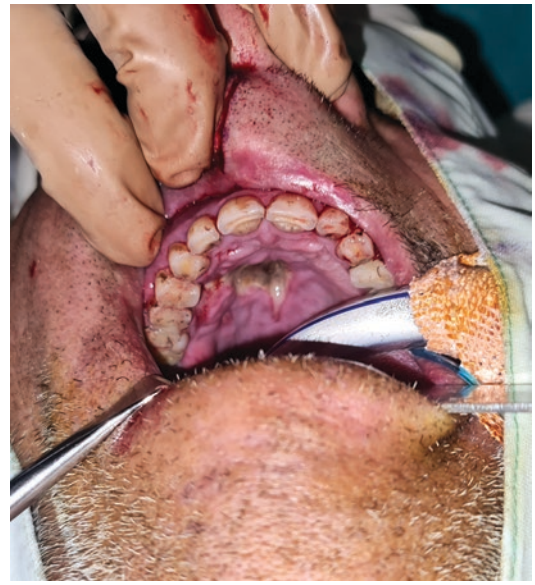

Fig. 17.36 Erosion of right-sided palate (bone and mucosa) by the disease

Fig. 17.37 Weber-Ferguson incision left side

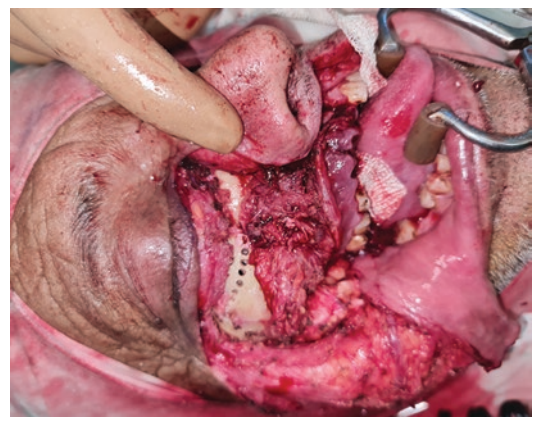

Fig. 17.38 After lifting the skin flap, the soft tissues of the face are elevated off the face of the maxilla. Markings on maxilla for bone cuts are visible

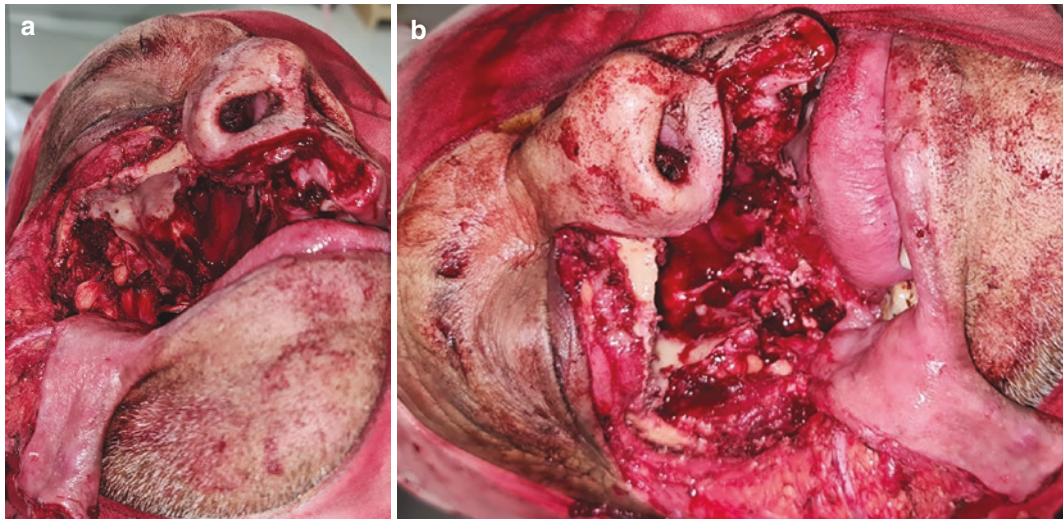

Fig. 17.39 Excision of the hard palate, lateral and medial wall along with floor of right maxilla, and teeth performed

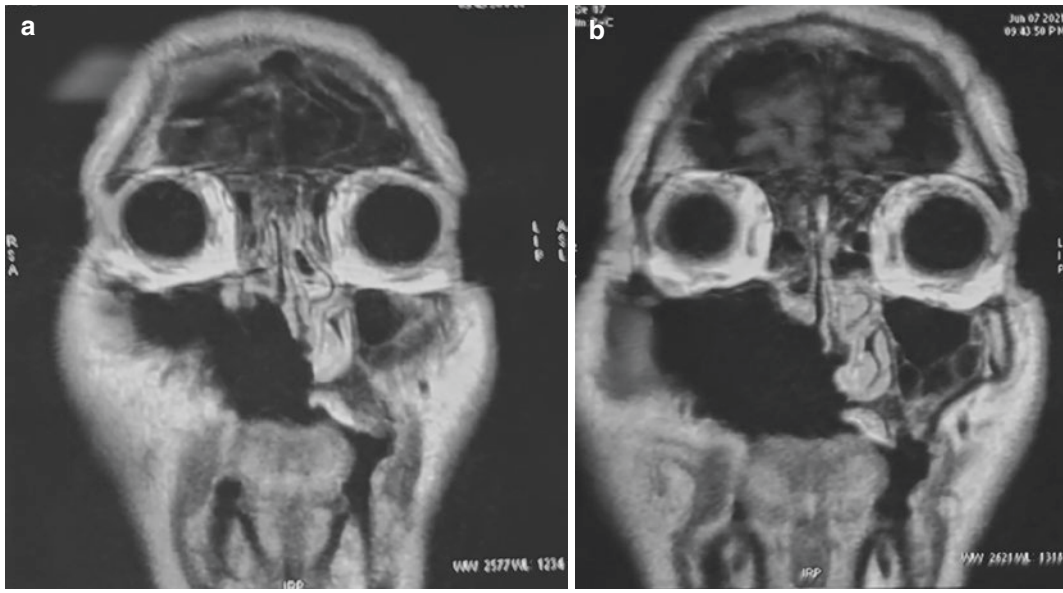

Fig. 17.40 (**a**, **b**) Post-surgical findings at the surgical site after two months showing complete clearance of disease with healthy mucosa covering all the raw areas

- *Post-surgery radiological findings* (Fig. 17.40).
- Two months after surgery and complete course of anti fungal medication, complete clearance of disease could be achieved with healthy mucosa covering all the raw areas (Fig. 17.41).
- For reconstruction of palatal defect, pedicled temporalis muscle flap surgery was performed in second stage after 3 months of primary surgery, once all the laboratory and radiological parameters showed complete clearance of disease (Figs. 17.42, 17.43, 17.44, and 17.45).

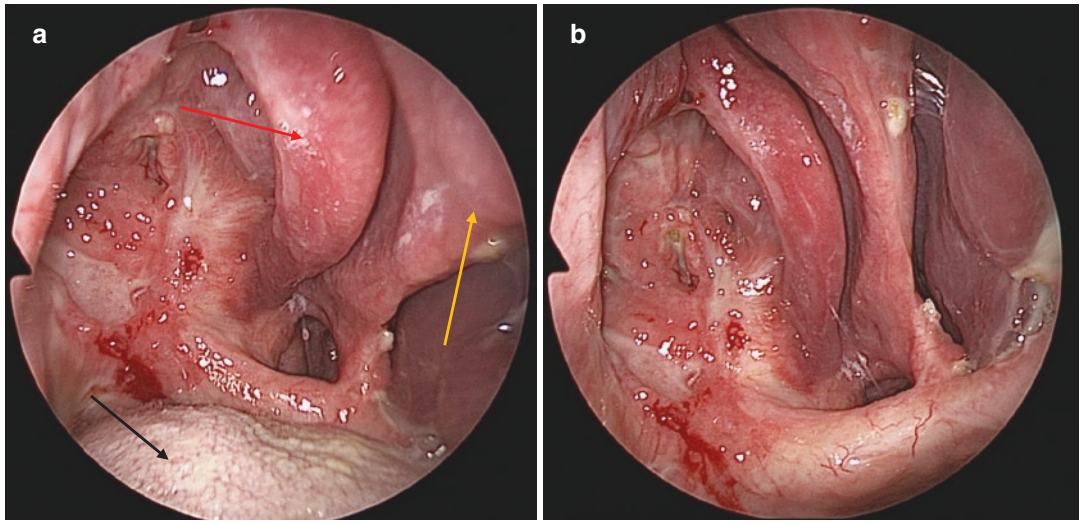

Fig. 17.41 (**a**, **b**) Post-subtotal maxillectomy right side showing complete clearance of disease with healthy mucosa covering all the raw areas. Tongue black arrow, middle turbinate red arrow, septum yellow arrow

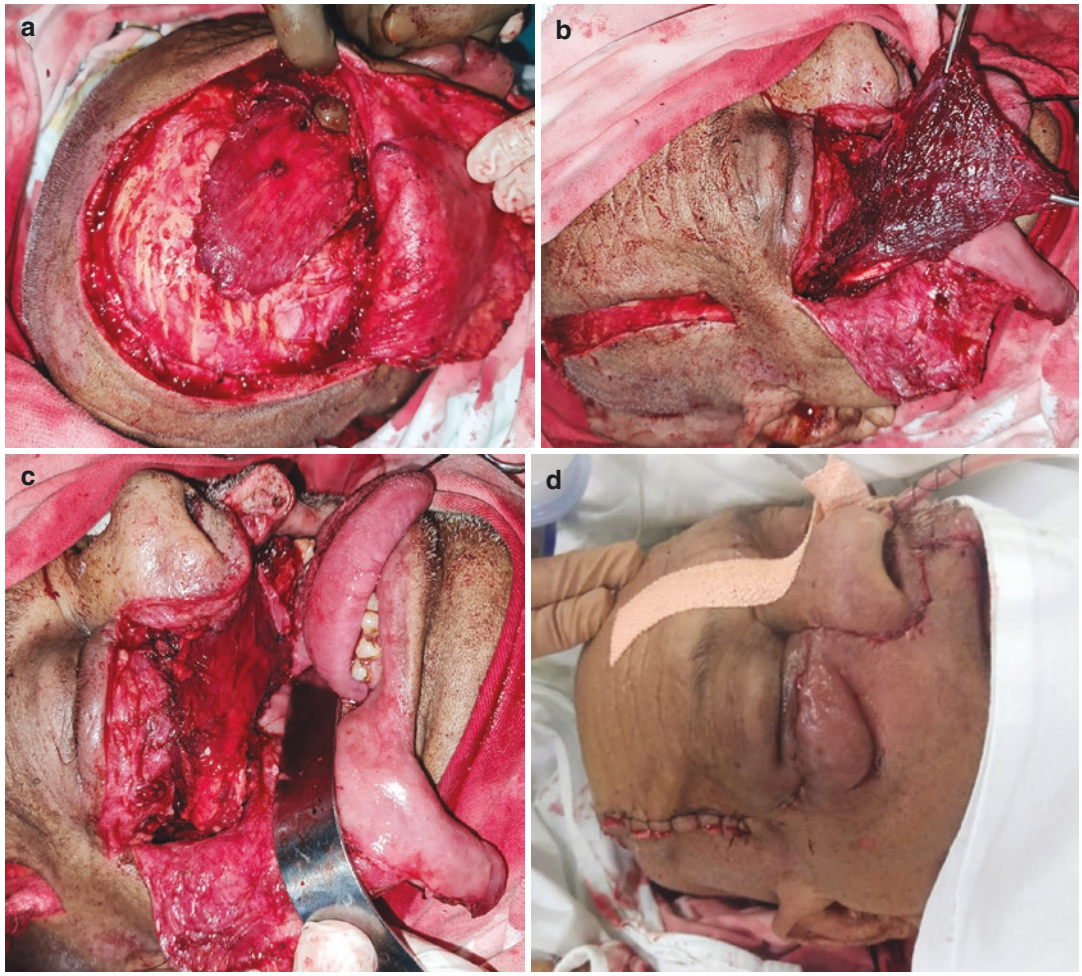

Fig. 17.42 (**a**) Temporalis muscle harvested. (**b**) Temporalis muscle transferred to face from beneath zygomatic bone. (**c**) Temporalis muscle flap sutured to surrounding soft tissue. (**d**) Final suturing of incision line

17.9.7 Cases of Orbital Involvement

17.9.7.1 Case Number 7a

17.9.7.2 Case Number 7b

17.9.7.3 Case Number 7c

17.9.7.4 Case Number 7d

A 47-year-old male presented with a history of pain in the right upper jaw, watering from his right eye, swelling around the right eye and breathlessness. He developed these symptoms a month after the COVID. He had a history of coronary artery disease and was a known case of diabetes mellitus, hypertension and hypothyroidism.

Evaluation

On admission, he was afebrile, tachypnoeic and hypoxic. He underwent a complete systemic and laboratory evaluation. A multidisciplinary team evaluated the patient as per protocol. Nasal discharge was sent for KOH wet mount that revealed broad aseptate hyphae.

Imaging

CT scan of paranasal sinuses and orbit, various sequences of MRI along with HRCT chest performed. Contrast-enhanced T1W MRI revealed a non-enhancing focus in the right inferior turbinate and right maxillary sinus with mucosal thickening in the right ethmoidal and frontal sinuses. HRCT Chest revealed multiple patchy ground glass opacities in bilateral lower lobes CT severity score 15/25.

Blood Screening

After admission, the various blood tests performed were CBC, KFT, LFT, TSH, HBA1C, RBS, CRP QUANTITATIVE, D-Dimer and S. Ferritin.

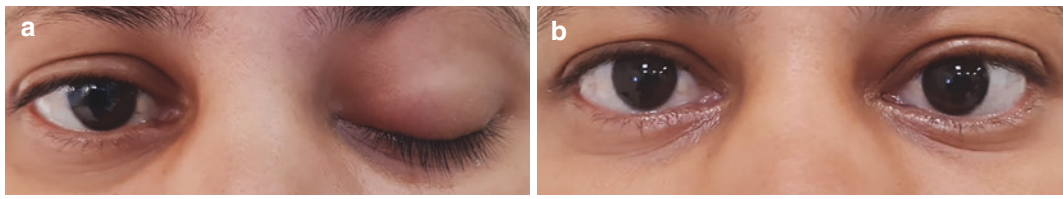

Fig. 17.43 (**a**) Left eye ptosis on the day of admission. (**b**) 30 days after surgery ptosis is resolved

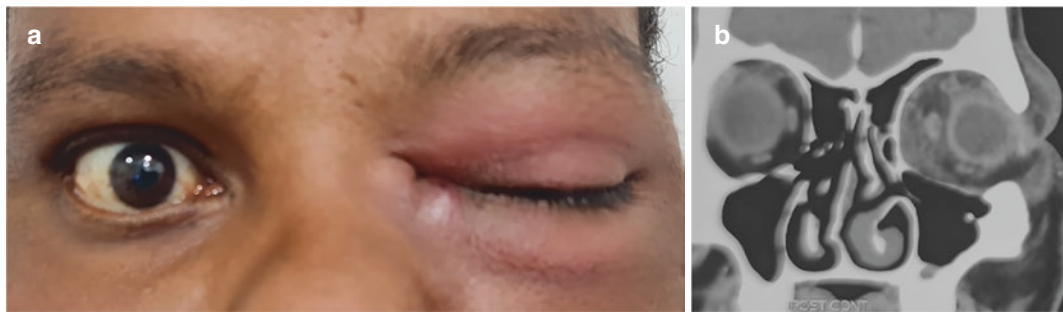

Fig. 17.44 (**a**) Patient with left periorbital swelling, ptosis. (**b**) Coronal CT-PNS of the same patient showing fat stranding in medial and superior extra conal compartment of left orbit. Medial rectus muscle is bulky

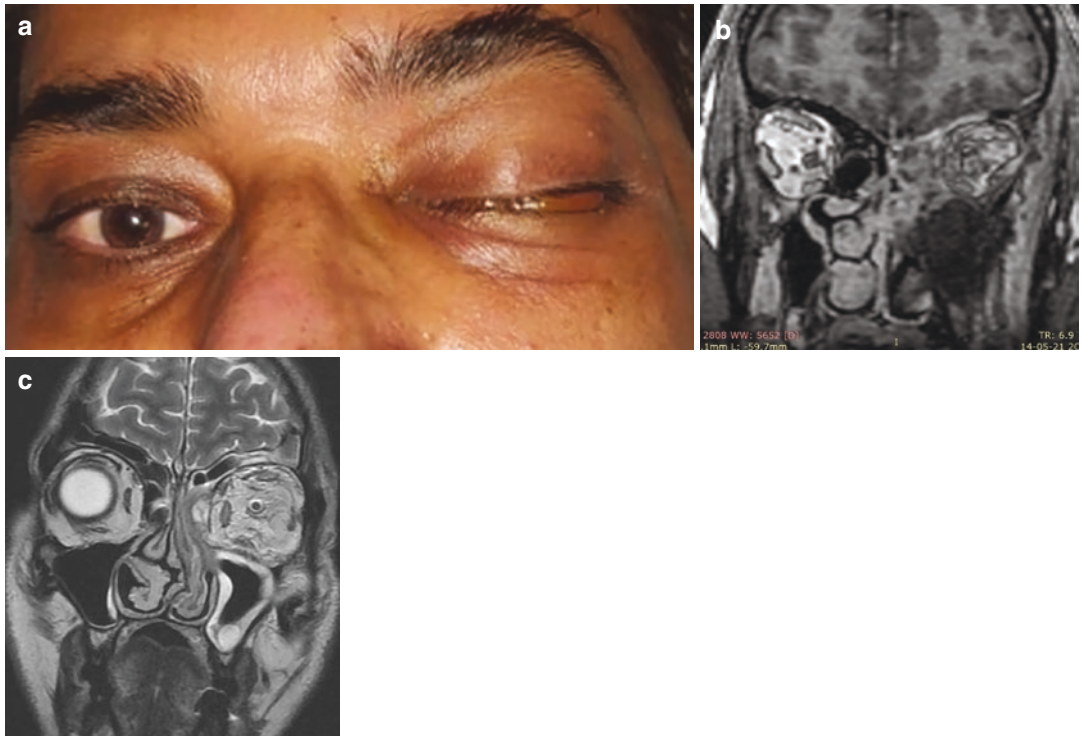

Fig. 17.45 (**a**) Left eye proptosis and ptosis, (**b**) MRI PNS contrast-enhanced T1W coronal images—hypointense and non-enhancing left inferior turbinate, part of middle turbinate, posterior part of maxillary sinus, floor of orbit and bulky extraocular muscles. (**c**) T2W coronal images show nodular mucosal thickening in left maxillary sinus and T2 hypointense areas in left middle and inferior nasal turbinates. Fat stranding is seen in left orbital space

Treatment

Evaluation and management of Diabetes Mellitus and Coronary artery disease were carried out. Since the patient was an old case of diabetes mellitus and had undergone coronary artery bypass grafting 5 years ago, a cardiologist's opinion was taken.

Simultaneous management under the intensivist and pulmonologist was continued. The patient was hypoxic, and the HRCT chest revealed signs of atypical pneumonitis. The patient was put on oxygen supplementation intermittently for a week and was then weaned off the oxygen successfully. He has continued on intravenous meropenem 1 g thrice daily along with IV moxifloxacin 100 mL twice a day.

As KOH wet mount revealed broad aseptate hyphae, he was also given an injection of Liposomal amphotericin-B (5 mg/kg/day). Regular monitoring of renal function tests was done with the period of drug holiday as and when the serum creatinine level doubled the baseline. Potassium supplementation was also given to tackle hypokalaemia.

Surgical Management

The patient was taken up for Endoscopic surgical debridement with ICU backup. Medial maxillectomy with excision of inferior and middle turbinate with clearance of necrotic fungal debris from the maxillary sinus and pterygopalatine fossa performed and tissue sent for HPE and fungal culture. Clinically patient had orbital symptoms which were correlated with per operative findings, so orbital decompression was performed, infected lamina papyracea and infected extraconal fat strands were cleared.

1. After a few days, the patient was relieved of his orbital swelling and watery discharge from the eye. Endoscopic suction and cleaning were done every 48 h. The patient was contin-

ued on Inj. Liposomal amphotericin-B for 14 days and then shifted to Tab Posaconazole 300 mg BD for 21 days followed by tab posaconazole 300 mg once a day for 1 month.

The patient is under regular follow-up and MRI 45 days after surgery confirmed clearance of disease.

- Pre-operative radiological finding (Fig. 17.46).
- Post-surgery (45 days) (Fig. 17.47): Clinical picture showing the disappearance of periorbital oedema and radiological images showing complete clearance of disease.

17.9.8 Case 8: Extensive Orbital Involvement

A 50-year-old male presented to the emergency department on the fifth day of his COVID illness with complaints of fever, left-sided facial pain, pain over the left upper jaw and ptosis, proptosis, diplopia and loss of vision in the left eye.

17.9.8.1 Examination

The patient was febrile, had conjunctival chemosis, restricted left extraocular movements, ptosis and proptosis. He was admitted, and a complete systemic and laboratory evaluation was done by a multidisciplinary team of otorhinolaryngologists, radiologists, ophthalmologists and a physician.

17.9.8.2 Investigations

All routine biochemical investigations were done, including complete blood count, random blood sugar, kidney function tests, liver function test, glycosylated haemoglobin, C-reactive protein (quantitative), Serum Ferritin and D-dimer were done.

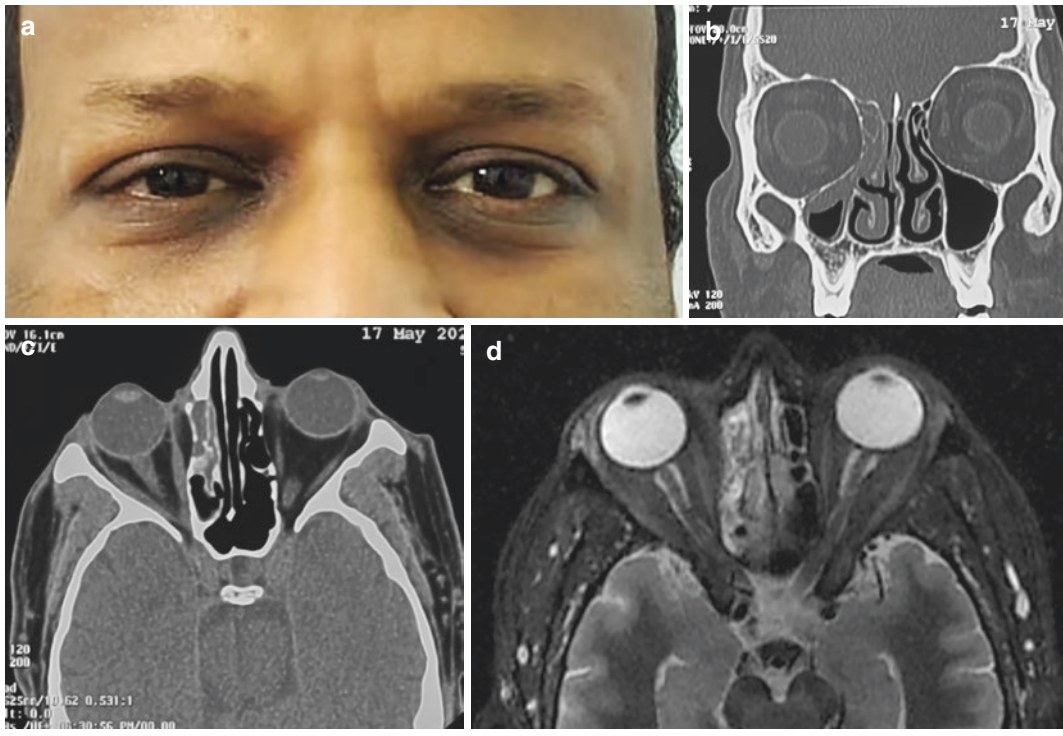

Fig. 17.46 (**a**) Mild periorbital oedema right eye. (**b**) CT-PNS coronal view; mucosal thickening in right maxillary and ethmoid sinuses and focal erosion of right lamina papyracea, (**c**) CT-PNS axial view—mucosal thickening in right ethmoid cells and erosions in lamina papyracea, (**d**) Axial STIR images through orbit show mucosal thickening in ethmoid air cells, more on the right side and mild fat stranding in the medial compartment of right orbit

Fig. 17.47 (**a**) Clinical picture of patient 45 days after surgery note periorbital swelling reduced. (**b**) MRI coronal view of the same patient 45 days after surgery; complete clearance of disease

Nasal endoscopy was done, and eschars were sent for KOH wet mount, which revealed broad aseptate hyphae.

17.9.8.3 Radiological Investigations

Radiological investigations were performed as per protocol and included CT scans of paranasal sinuses and orbit, T1W, T2W and T1W with gadolinium contrast MRI images of paranasal sinuses, orbit and brain.

CT scan of paranasal sinuses revealed opacification in the left maxillary sinus and left anterior ethmoids with air pockets. It also showed hyperdensities within the sinus cavity. T2w MRI PNS showed hyperintense shadows in the left maxillary sinus, hypointense areas in the left ethmoid sinus, medial wall of the maxillary sinus and left nasal cavity. Periorbital tissue appears bulky, which could be correlated clinically with proptosis. Premaxillary soft tissue is hyperintense suggestive of inflammation.

In STIR sequences, hyperintense areas are noted in left maxillary sinus mucosa, periorbital and premaxillary soft tissue, suggesting inflammation. Left extraocular muscles, intraconal and extraconal orbital fat appear hyperintense, which points towards extensive orbital involvement. On post-contrast T1W images, fungal invasion is suggested by hypointense non-enhancing areas in left maxillary sinus mucosa, medial wall and floor of the maxilla along with non-enhancing left inferior turbinate.

17.9.8.4 Radiological Findings

Figures 17.48, 17.49, 17.50, 17.51, 17.52, 17.53 and 17.54.

17.9.8.5 Treatment of COVID

Symptomatic treatment was started by a physician, including subcutaneous injection of low molecular weight heparin in the dose of 0.4 units once a day. No steroids and immunosuppressants were given, and the patient was reviewed regularly by the physician.

17.9.8.6 Treatment for Diabetes Mellitus

Patient had uncontrolled diabetes and was started on regular insulin with blood sugar monitoring. Strict controls were maintained to avoid Ketoacidosis.

17.9.8.7 Treatment for Mucormycosis

After the diagnosis of the mucormycosis was confirmed on KOH mount, the patient was immedi-

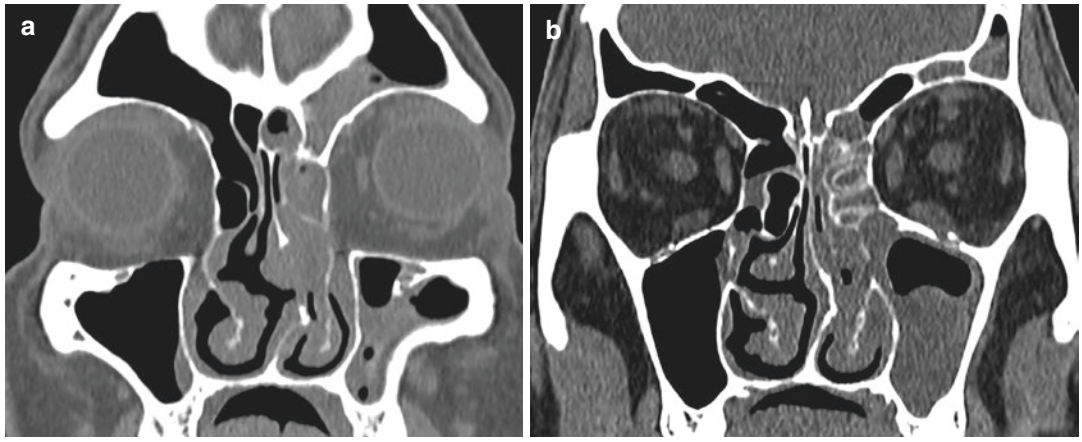

Fig. 17.48 (**a**, **b**) CT PNS images in the coronal plane show nodular mucosal thickening in the left maxillary sinus, left ethmoid air cells and left nasal cavity. Hyperdense areas are seen within the sinus cavity

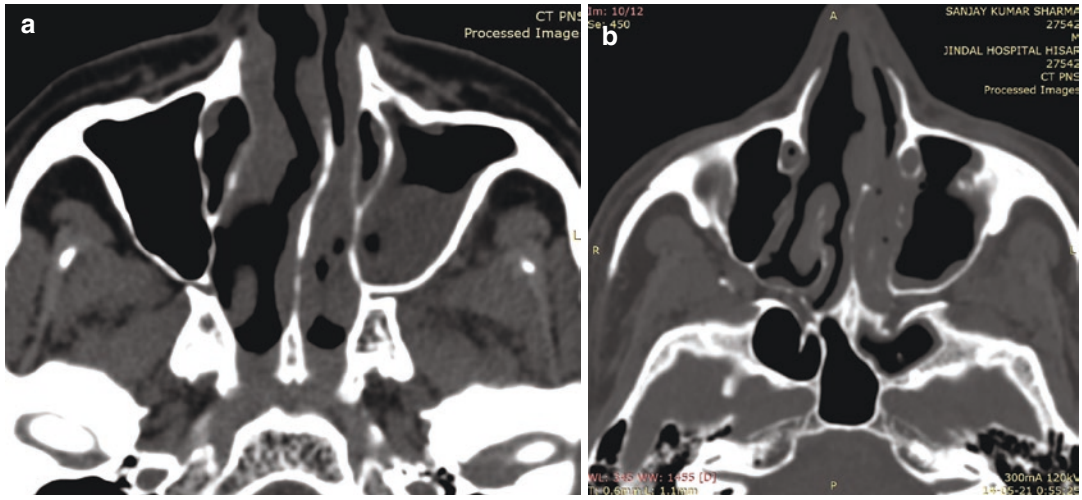

Fig. 17.49 (**a**, **b**) CT PNS images in the axial plane show nodular mucosal thickening in the left maxillary sinus, left ethmoid air cells and left nasal cavity

ately started on intravenous Liposomal Amphotericin-B (5 mg/kg/day). He tolerated antifungal drugs, and his renal functions test were maintained within normal limits during the treatment. Liposomal amphotericin-B was administered for 14 days along with tab Posaconazole 300 mg twice a day for 21 days. Later on, the patient was switched to the maintenance dose of tablet Posaconazole 300 mg once a day for a month.

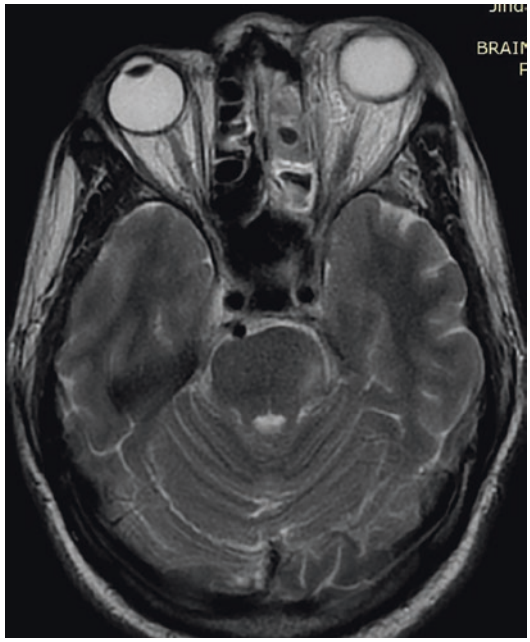

Fig. 17.50 T2W MRI PNS images in the axial plane show mucosal thickening in the left maxillary sinus and ethmoid air cells with T2 hypointense areas. Fat stranding is seen in the left orbit

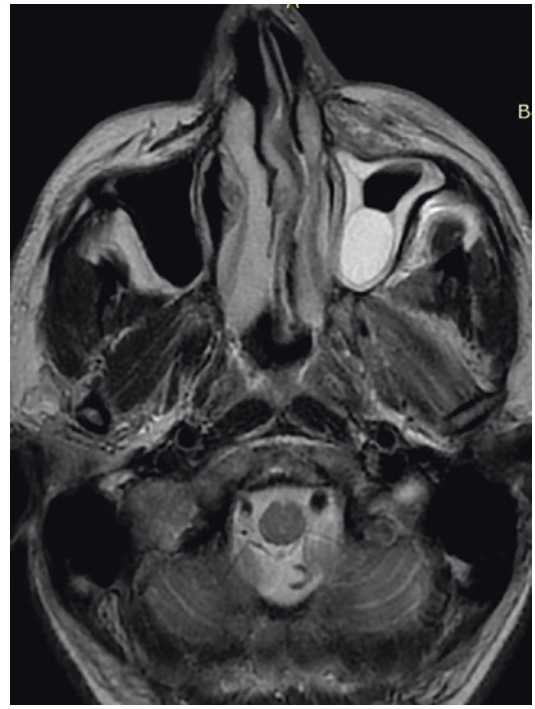

Fig. 17.51 T2W axial images show Inflammation/infiltration in left premaxillary soft tissues

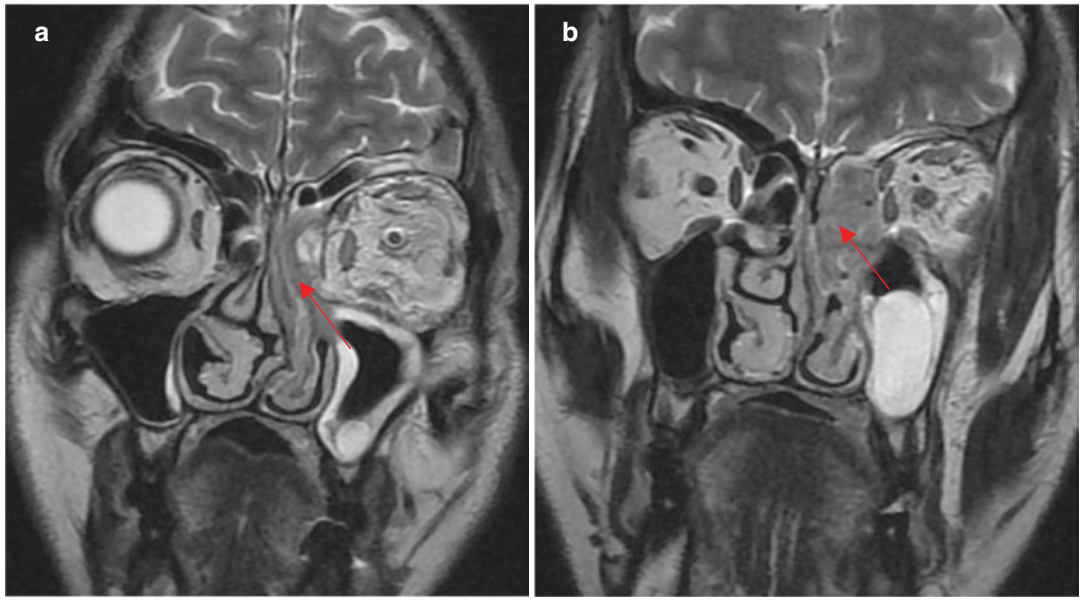

Fig. 17.52 (**a**, **b**) T2W MRI PNS images in the coronal plane show hyperintense mucosal thickening in the left maxillary sinus. T2 hypointense areas are seen in the left nasal cavity, left ethmoid air cells and along the medial wall of the left maxillary sinus suggesting fungal infection (red arrow)

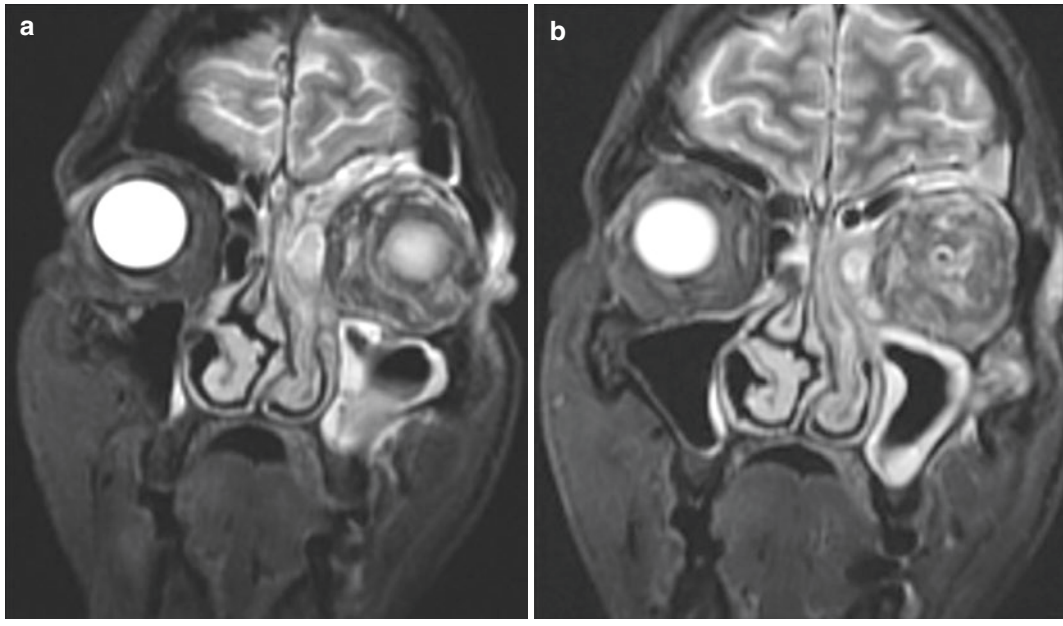

Fig. 17.53 (**a**, **b**) STIR images in MRI PNS in coronal plane show hyperintense mucosal thickening in left maxillary sinus, left nasal cavity and left fronto-ethmoid air cells. There is inflammation of intraconal and extraconal fat in the left orbit. Left orbital muscles are bulky and hyperintense

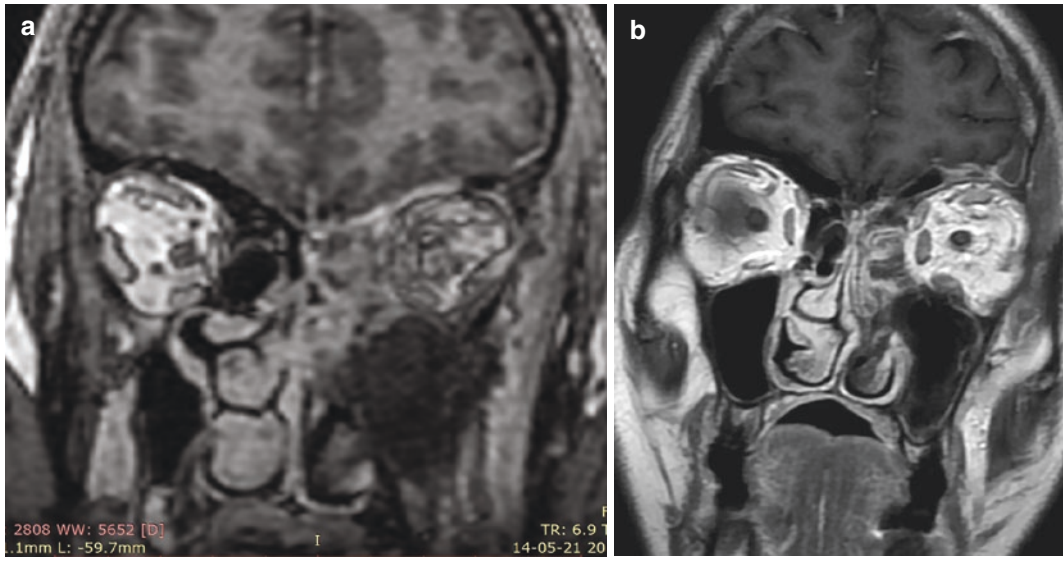

Fig. 17.54 (**a**) Contrast-enhanced T1W images in coronal plane show non-enhancing sinus mucosa in the left maxillary sinus. (**b**) Non-enhancing areas are seen in the medial wall and floor of the left maxillary sinus. Left inferior nasal turbinate is also non-enhancing

17.9.8.8 Surgical Management (Figs. 17.55, 17.56, 17.57, 17.58, 17.59, and 17.60)

Since the patient had extensive disease in the left-sided sinuses and orbit (complete involvement of the globe with total loss of vision), after discussion with the ophthalmologist, left orbital exenteration along with total left maxillectomy was planned. Orbital exenteration is a procedure performed along with total maxillectomy when a disease has extended through the bony wall, periosteum and involves all layers, including the fat, muscle or entire orbital contents, the eyelids and lacrimal apparatus.

The incision given was a modified Weber-Ferguson incision with a supraciliary extension. As the eyelid skin was lifted, the underlying soft tissue was found to be inflamed and necrosed. The upper cheek flap was elevated to expose the entire anterior and anterolateral wall of the maxilla. On subperiosteal dissection of the orbit, the medial orbital wall and the medial rectus muscle were necrosed, and the ethmoids were also full of disease. Orbital samples were sent separately for histopathology and fungal culture. All the soft tissue attachments of the maxilla, anterior, lateral, in the oral cavity and the orbit were divided. The osteotomies, in this case, included the inferior orbital rim and orbital floor and extended through the frontal process of the maxilla and the lacrimal bone, through lamina papyracea and anterior ethmoid to include the left globe in the specimen.

The rest of the osteotomies were the same as in subtotal maxillectomy explained in case number 6. After completing the osteotomies, soft tissue and muscular attachments on the posterior aspect of the maxilla were divided, and the internal maxillary artery was cauterized. The orbital rim was exposed circumferentially, and the attachment of the orbital periosteum to the orbital rim was incised in its superior half. The extraocular muscles at the apex of the orbit were divided. Optic nerve and accompanying blood vessels were clamped and divided, and the left eye with both eyelids was delivered with the maxillectomy specimen.

Unfortunately, this patient was lost to follow up.

17.9.9 Case 9: Intracranial Spread

A 49-year-old male presented to the neurology department with breathlessness and fever for the last 1 month. He had an episode of generalized tonic-clonic seizure a day before presenting to us. At the time of admission, the patient was conscious and oriented, and his vitals were stable. He was kept under the neurology department and was investigated using blood tests and imaging.

Fig. 17.55 Weber-Fergusson skin incision for maxillectomy

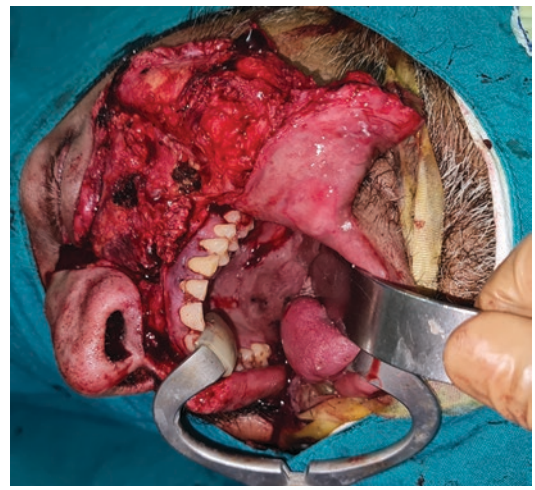

Fig. 17.57 Palatal incision

Fig. 17.56 After lifting the skin flap, the soft tissues of the face are elevated off the anterior and lateral surface of the maxilla

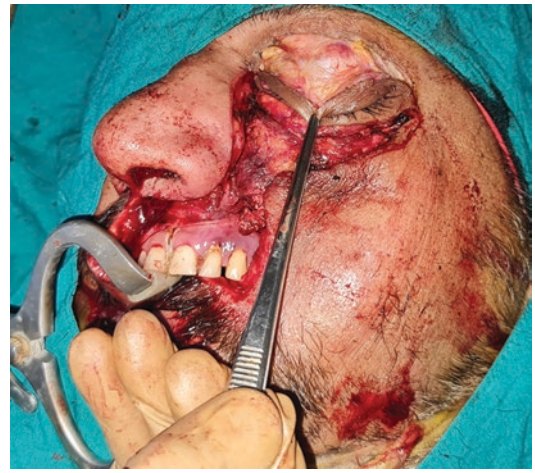

Fig. 17.58 Exenteration of left eye also performed along with maxillectomy

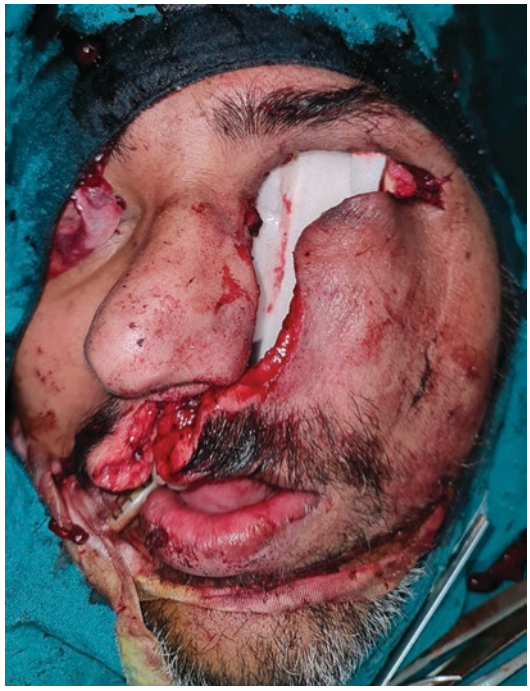

Fig. 17.59 Orbital exenteration with total maxillectomy performed. Skin and soft tissue incision to be sutured back

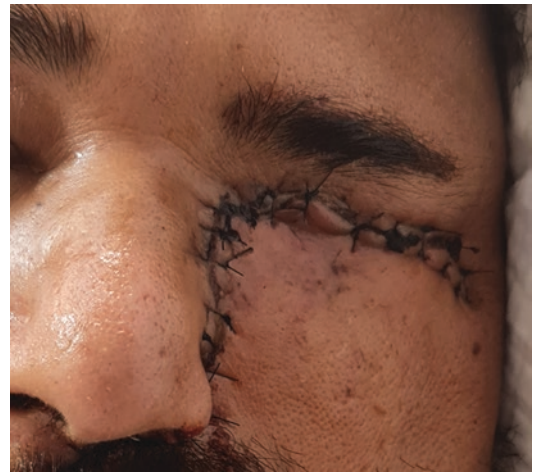

Fig. 17.60 Twenty-four hours post-surgery with sutures of incision line in place

17.9.9.1 Blood Investigations

The routine investigations revealed elevated total lymphocyte count (16.3 × 10^9/L) and CRP (97.9 mg/L), suggesting infection/inflammation.

17.9.9.2 Imaging (Fig. 17.61)

The contrast-enhanced CT scan of the head revealed an ill-defined, hypodense lesion with peripheral enhancement and surrounding oedema in the right inferior and medial temporal region, suggesting a temporal lobe abscess. A Lumbar puncture revealed lymphocytic meningitis. HRCT Chest showed signs of severe covid pneumonitis with a CT Severity Score of 18/25.

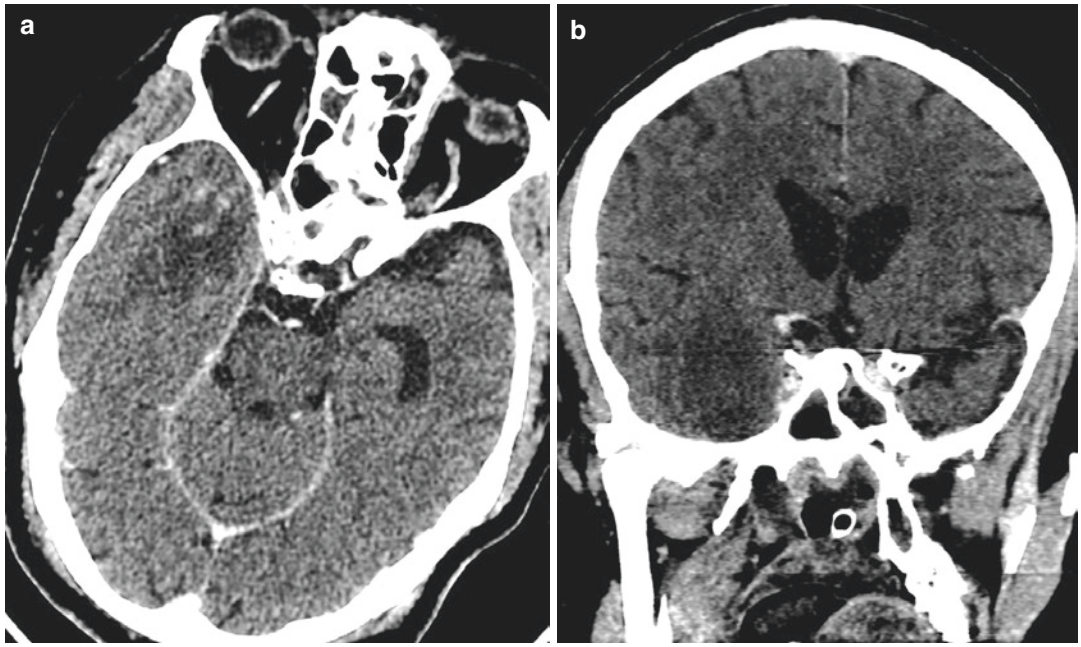

Fig. 17.61 (**a**) Contrast-enhanced CT PNS and brain (**b**) images in axial plane show hypodense lesion with mild peripheral enhancement in right temporal lobe suggestive of the abscess

17.9.9.3 Treatment of COVID

COVID symptoms related to his respiratory system were treated by the physician and an intensivist using broad-spectrum intravenous antibiotics like Cefoperazone with Sulbactam and colistin.

The treating team suspected mucormycosis, and an otorhinolaryngologist was consulted. Detailed bedside ENT examination was conducted, including nasal endoscopy, swabs were collected and sent for KOH mount. The smear showed occasional pseudohyphae. Therefore, the radiological investigations, including various sequences of MRI of paranasal sinuses, orbit and brain, were performed (Figs. 17.62, 17.63, and 17.64). The right inferior turbinate showed loss of contrast with no enhancement indicating the 'Black turbinate sign'. The patient was immediately put on intravenous amphotericin-B in a dose of 5 mg/kg/day. In the meantime, a detailed ophthalmological examination was also carried out.

17.9.9.4 Surgical Steps and Findings

A team of otorhinolaryngologist and neurosurgeon was involved in the surgical management of this patient. The drainage of the temporal abscess was carried out by a neurosurgeon (Fig. 17.65), and in the same stage, endoscopic right medial maxillectomy was performed with complete clearance of necrotic tissue filling the maxillary along with its lateral recess. The disease was also cleared from all around the orbital apex area (Fig. 17.66).

The necrotic tissue was sent for KOH wet mount and revealed aseptate broad fungal hyphae. As his general condition was not satisfactory, the patient was kept on mechanical ventilator support for 3 days. Check endoscopy and clearance were done on day three and after that, every 24 h, the patient was weaned off the ventilator support.

17.9.9.5 Further Neurological Management

To prevent a rise in intracranial pressure patient was given intravenous Mannitol

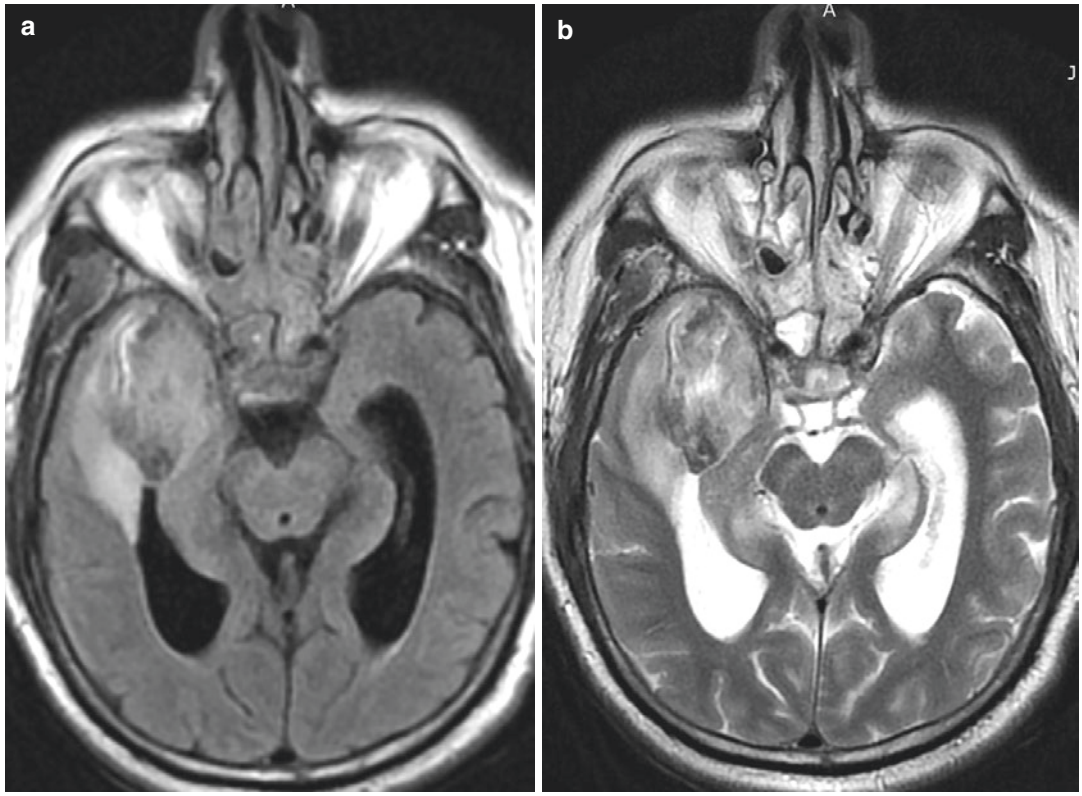

Fig. 17.62 (**a**) FLAIR and (**b**) T2W MRI images in axial plane show intra-axial altered signal intensity lesion in right temporal lobe with hydrocephalus. Sinus disease is evident in the bilateral ethmoid and sphenoid sinuses

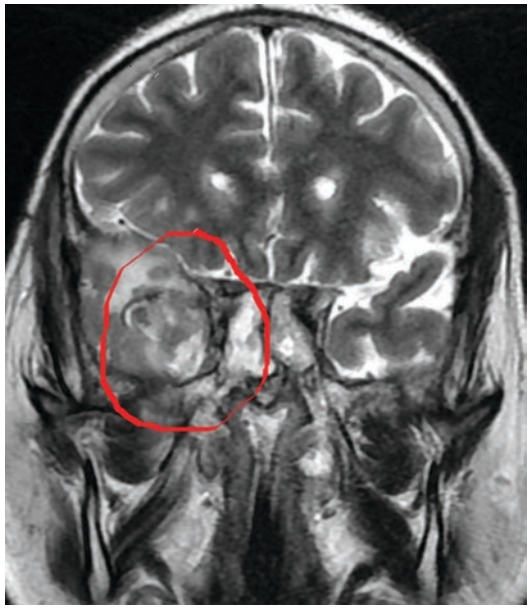

Fig. 17.63 T2W MRI image in coronal plane shows disease extending from sphenoid sinus and orbital apex to right temporal lobe in the region of orbital apex

100 mL 8 hourly and antiepileptic medication in the form of Phenytoin Sodium 100 mg 8 hourly. A post-operative NCCT head was done, and the ventricles were found to be dilated. Hence Ventriculoperitoneal shunting was done. Despite all our efforts, the patient's general condition did not improve, and the patient succumbed.

17.10 Lessons Learnt in COVID-19-Associated Mucormycosis

- The deadly triad of Ketoacidosis, low oxygen tension and hyperglycaemia in diabetics, provide the most favourable medium for the fungus to grow due to the active ketone reductase system in the organism.

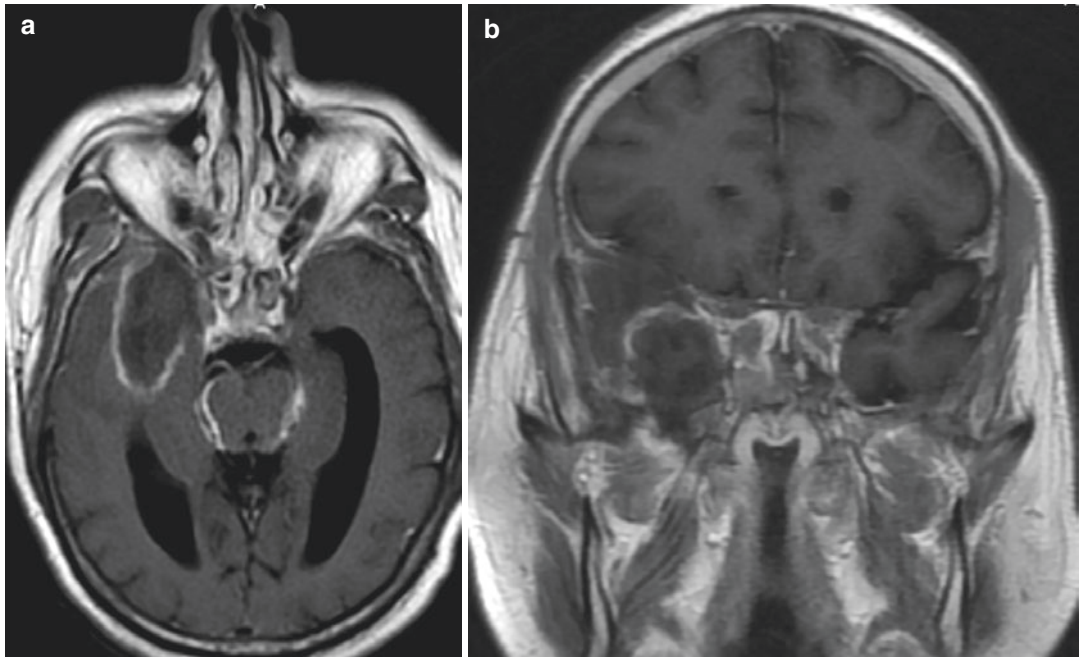

Fig. 17.64 Contrast-enhanced T1W images in (**a**) axial and (**b**) coronal plane show peripherally enhancing lesion in right temporal lobe suggestive of brain abscess. There is evidence of disease spread from the floor of the sphenoid sinus/pterygomaxillary fissure

Fig. 17.65 Craniotomy is done to drain temporal lobe abscess

- Role of a multidisciplinary team including Otorhinolaryngologist, Physician, Ophthalmologist, Neurosurgeon, Nephrologist, Pathologist and Intensivists/ICU specialists is mandatory for complete management of rhino-orbital-cerebral mucormycosis.
- Staging the disease is very important for accurate and in time treatment of different stages of ROCM.
- Multimodality imaging is helpful in prompting an early diagnosis
- Treatment primarily is medical. Surgery is to debride the infected tissue to eliminate the fungal load, to make the drug available to viable tissue and prevent further complications
- The shortage of Liposomal Amphotericin B showed us the way to newer and equally effective antifungals like Isovuconazole with lesser side effects.

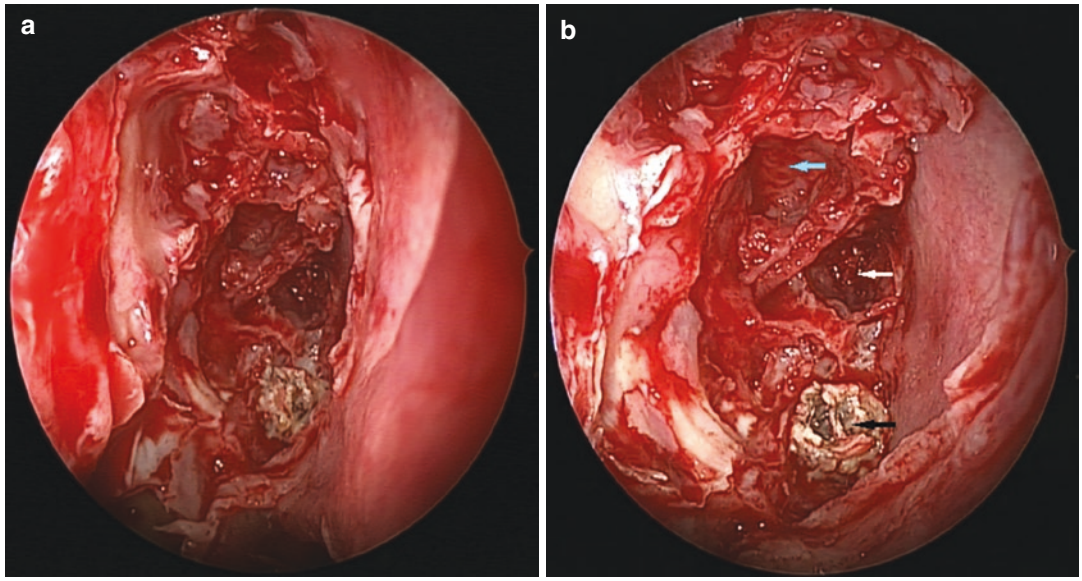

Fig. 17.66 (**a**, **b**) Localization of necrotic tissue in sphenoid sinus and orbital apex after uncinectomy, medial maxillectomy ethmoidectomy, sphenoidotomy and following the disease in orbital apex. All diseased tissue excised from a sphenoid sinus (white arrow) and orbital apex (black arrow) till fresh bleeding started. Posterior ethmoidectomy (blue arrow)

- Along with ROCM, treatment includes control of hyperglycaemia, COVID and its related complications.
- In orbital involvement, exenteration is to be avoided. Mostly endoscopic decompression and clearing the disease is good enough to save the vision and the eyeball. Intraorbital irrigation of injection Amphotericin B helps to save exenteration. Loss of vision is never an indication for exenteration of the eyeball.
- Repeated endoscopic clearance and nasal douching gives faster recovery.
- Progressive and rapid involvement of the cavernous sinus, vascular structures and intracranial contents is a sign of grave prognosis despite radical surgery and antifungals.
- It must be recognized early and treated aggressively.

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