A Case of Rhino-Orbital Cerebral Mucormycosis presenting with spontaneous Cerebrospinal fluid Rhinorrhoea

Rajesh Verma (drrajeshverma32@yahoo.com)
King George's Medical University https://orcid.org/0000-0001-7016-2361
Rajarshi Chakraborty
King George Medical University: King George's Medical University
Keerthiraj DB
King George Medical College: King George's Medical University

Research Article

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Abstract

Rhino-orbital cerebral mucormycosis has increased in the recent second wave of post-Covid-19 illness, mainly in tropical countries like India. The burden of diabetes mellitus and rampant use of corticosteroid, environmental factors, post-covid-19 immunological derangement might be contributory factors to the development of extensive outbreak of ROCM. Cerebrospinal fluid rhinorrhea is rarely documented with such fungal infection in literature. This case report described a 45-year diabetic woman in the post-Covid-19 phase,who developed rhino-orbital cerebral mucormycosis, presenting with spontaneous cerebrospinal fluid rhinorrhea.

Introduction

Rhinorbital cerebral mucormycosis is an invasive fungal infection of the paranasal sinuses, orbits, and brain. Rhino-orbital cerebral mucormycosis has increased in the recent second wave of post-Covid-19 illness mainly in tropical countries like India [1, 2, 3, 4]. The burden of diabetes mellitus and indiscriminate use of corticosteroid, environmental factors, post-covid-19 immunological derangement might supposedly contribute to the development of extensive outbreak of ROCM [5, 6, 7]. Cerebrospinal fluid (CSF) rhinorrhoea is the leakage of CSF from the subarachnoid space into the nasal cavity. Cerebrospinal fluid rhinorrhea is rarely documented with such fungal infection in literature. There are only a few case reports of iatrogenic CSF rhinorrhea in ROCM during orbital exenteration and sinus surgery [8, 9, 10].

Case Description

A 45 year female with a background history of recent severe Covid-19 pneumonia, diabetes mellitus for five years, hypertension for one year, and hypothyroidism for six months presented to the tertiary care hospital of northern India with discharge per nose for 20 days. The discharge was clear, colorless, watery, non-blood stained, odorless, and increased on bending the head forward. It was associated with painful swelling over the left cheek with low-grade fever. After 12 days, there was painful, non-itchy swelling of the left eye, which was acute in onset and gradually progressive with redness of the eye and foul-smelling ocular discharge. There was no associated impairment in the sensorium, headache, convulsions, vomiting, yellowish coloration of urine, diminution of vision, or facial weakness. The patient denied an impaired hearing, difficulty in chewing, swallowing, change in voice, nasal regurgitation of liquid, neck pain, limb weakness, paresthesia, and bowel/bladder disturbances. There is no history of rash, joint pain, diarrhea, pain abdomen, or significant weight loss. She had a recent fever, cough, and dyspnoea for 15 days before the nasal discharge. She was diagnosed with Covid-19 pneumonia, for which she required hospitalization. The patient was administered remdesivir, methylprednisolone, short-course dabigatran, regular insulin therapy, and oxygen supplementation. She has been a known diabetic for five years and was on regular oral antidiabetic medication (metformin 1000mg and glimepiride 2 mg daily dosage), hypertensive for one year receiving telmisartan 40 mg daily, and hypothyroidism for six months on thyroxine replacement (regular 75 mcg oral levo-thyroxine). Her general examination revealed a pulse of 88/min, regular, blood pressure 136/70 mm Hg, respiratory rate 17/min, temperature 98.8F, sPO2 97% in

room air, presence of pallor, with absent icterus, edema, cyanosis, clubbing, significant lymphadenopathy, thyroid swelling, rash, joint tenderness or generalized swelling. Her local examination showed clear, colorless watery discharge from the left nostril, tenderness in the left frontal, ethmoidal and maxillary sinuses with induration over the left maxillary area. The left eye showed chemosis and conjunctival injection. The neurological examination showed normal higher mental function, normal cranial nerve examination including fundus except that olfaction could not be tested, while there was external ophthalmoplegia in the left eye. The rest of the nervous system examination was unremarkable. Her respiratory, cardiovascular, gastrointestinal, and gynecological examinations were normal. Her investigations showed hemoglobin of 10.7 g/dL, leucocyte count of 14600 cells/cumm, neutrophil 76%,lymphocyte 20%, eosinophil 2%, monocyte2%, platelet count 2.80 lac cells/cumm, microcytic hypochromic picture, bilirubin 0.55 mg/dL, random blood glucose 461 mg/dL aspartate transaminase 28 IU/L, alanine transaminase 27.6 IU/L, alkaline phosphatase 202.9 IU/L, protein 6.80 g/dL, albumin 3.7 g/dL, urea 2.8 mg/dL, creatinine 0.71 mg/dL, C Reactive protein 26.9 mg/L, prothrombin time 20.8, INR 1.23, sodium -134.1 mmol/L, potassium -3 mmol/L, ionic calcium 3.44 mg/dL, Interleukin-6 (3.9 pg/mL), lactate dehydrogenase -586.4 IU/L, HbA1C 11.3% with normal thyroid assay. The serology was negative for HBsAg, Anti HCV, HIV, and COVID-19 RT PCR was non significant. Her cerebrospinal fluid examination was normal, including gram stain, fungal stain, and culture/ sensitivity. The nasal discharge was positive for beta-2 transferrin. Her electrocardiogram and chest X-ray were normal. The urine and blood cultures were sterile. Her computerized tomography of paranasal sinuses showed mucosal thickening in the left maxillary, ethmoidal and frontal sinuses, obliteration of osteomeatal complexes, with a defect in left-sided cribriform plate. The magnetic resonance imaging of paranasal sinus and orbit revealed left maxillary, sphenoid, frontal, and bilateral ethmoidal sinusitis, erosion of left inferior orbital wall with focal erosion of medial wall, involvement of extraconal fat, thickening of inferior rectus, involvement of premaxillary soft tissue and masticatory spaces with focal erosion of cribriform plate with right-sided mastoiditis. Her brain MRI showed focal erosion of the left cribriform plate(Figure-1). Functional endoscopic sinus surgery was done, which showed left-sided greyish-brown crusts with congestion suggesting maxillary sinusitis(Figure 2a). The samples were sent for a routine examination, including fungal stain and culture sensitivity. The histopathological examination of nasal tissue was positive for broad-based aseptate fungal hyphae branching at an acute angle resembling mucormycosis along with moderate lymphoplasmacytic inflammatory infiltrates and extensive necrosis(Figure-2b). She was diagnosed as stage 3 rhino-orbital cerebral mucormycosis (ROCM) and treated with liposomal amphotericin B therapy (daily intravenous and single intra-vitreous injection) for six weeks, followed by oral posaconazole therapy for three months. Euglycaemia was maintained with oral antidiabetic medication. The cerebrospinal fluid rhinorrhea resolved with seven days of amphotericin B and the orbital swelling resolved after 14 days of amphotericin B intra-vitreous injection. The sinusitis resolved over three months clinically and radiologically.

Discussion

This case report describes the clinical course of a 45-year-old diabetic female with the post-Covid-19 state suffering from rhino-orbital cerebral mucormycosis presenting with spontaneous cerebrospinal fluid rhinorrhea.

Mucormycosis is referred to as a diabetes-defining illness. COVID-19 has proven to contain diabetogenic effects via pro-inflammatory cytokine-mediated damage of the pancreatic beta cells, insulin receptor signaling impairment, and peripheral insulin resistance [7, 11]. COVID-19 disease and corticosteroid therapy used for the same can cause immunosuppression by impairment of CD4+/CD8+ T-cells and antigen-presenting dendritic cells, thus favoring the development of secondary fungal infection [12]. Mucormycosis is an angio-invasive disease caused by saprophytic fungi belonging to the Mucorales order of fungus. They are ubiquitous present in nature. India accounts for the highest number of mucormycosis cases globally, with a prevalence of 0.14 cases per 1000 population (nearly 80 times higher than developed countries) [13]. Mucormycosis can manifest in different clinical forms based on site of involvement: ROCM is the most familiar type in India (45–74%), followed by cutaneous (10–31%), pulmonary (3–22%), renal (0.5–9%), gastrointestinal (2–8%), and disseminated infections (0.5–9%) [14, 15]. Diabetes mellitus is the most important predisposing factor for ROCM [16, 17]. Brain involvement occurs primarily by direct contiguous spread (70%) from the paranasal sinuses and 30% via hematogenous route. [18]. It has been seen that the infection of sphenoid and ethmoid sinuses has a higher risk of cavernous sinus thrombosis and carotid artery invasion with embolization to frontal and parietal lobes. Fungal hyphae can invade the lumen of arteries and cause occlusion, thrombosis, and infarction with resultant hypoxia and more tissue necrosis. The ROCM has four stages- Stage 1: involvement of nasal mucosa, Stage 2: involvement of paranasal sinuses, Stage 3: orbital involvement, and Stage 4: involvement of central nervous system [19].

Cerebrospinal fluid(CSF) rhinorrhoea or ‘liquorrhoea’ is the leakage of CSF from the subarachnoid space into the nasal cavity. CSF rhinorrhoea can be congenital, or it can be acquired by trauma (iatrogenic or non-iatrogenic), neoplastic, or spontaneously. Spontaneous fistula can be further subdivided into primary cases, where no underlying cause can be found, or they can be secondary to intracranial pathology (normal or high intracranial pressure). Normal-pressure leaks are caused by tumors, congenital defects, infection, arachnoid granulations, meningoencephaloceles, and idiopathic conditions. It is found that 80-90% of CSF leaks are traumatic, 10% postoperative, and only 3–4% of leaks are spontaneous[20, 21]. A cerebrospinal fluid leak from an intracranial cavity to nasal respiratory tract can produce fulminant meningitis because of the risk of ascending infection. Spontaneous cerebrospinal fluid rhinorrhea is a rarely reported phenomenon in the progress of ROCM with sparse literature till date [8.9.10]. The exact incidence of CSF rhinorrhea in ROCM is yet to be known. The pathogenesis of such presentation might be due to direct osteodural invasion of fungus to cause trickling out of cerebrospinal fluid from the defect. In addition, many cases can go unrecognized because of concurrent sinusitis during ROCM. These defects, if undetected, can lead to life-threatening severe ascending infections of the brain.

ROCM is associated with very high morbidity and mortality if untreated [14, 16, 18]. An early aggressive surgical debridement of infected tissues, early initiation of appropriate antifungal therapy, and adequate glycemic control are the main pillars for managing mucormycosis. Liposomal amphotericin B constitutes the first-line treatment for CNS mucormycosis followed by alternative medication like posaconazole and isavuconazole [22]. Intraocular (retrobulbar) amphotericin B injection has emerged as a promising non-surgical therapy in ROCM patients by halting orbital disease progression and preserving the globe [23]. Improving the survival rate requires rapid diagnosis and early therapeutic interventions with a multi-disciplinary holistic team effort.

Conclusion

Rhino-orbital-cerebral mucormycosis has increased in a recent second wave of post-Covid-19 illness esp in tropical countries like India. The burden of diabetes mellitus, indiscriminate use of corticosteroids, environmental factors, post-covid-19 immunological derangement contributed to a recent outbreak of ROCM. The development of CSF rhinorrhea might be due to the fungal invasive destruction of the cribriform plate. Aggressive management with early introduction of liposomal amphotericin B therapy gives a better outcome in ROCM. Euglycaemia and judicious use of corticosteroids should be advocated to prevent such outbreaks in the future. There needs to be a high degree of suspicion of CSF rhinorrhea in patients suffering from invasive sinusitis for early detection and better outcome.

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Declarations

Consent: The patient has given the consent to participate and publish their clinical data and images
Competing Interest: The authors declare no competing interests.

Figures

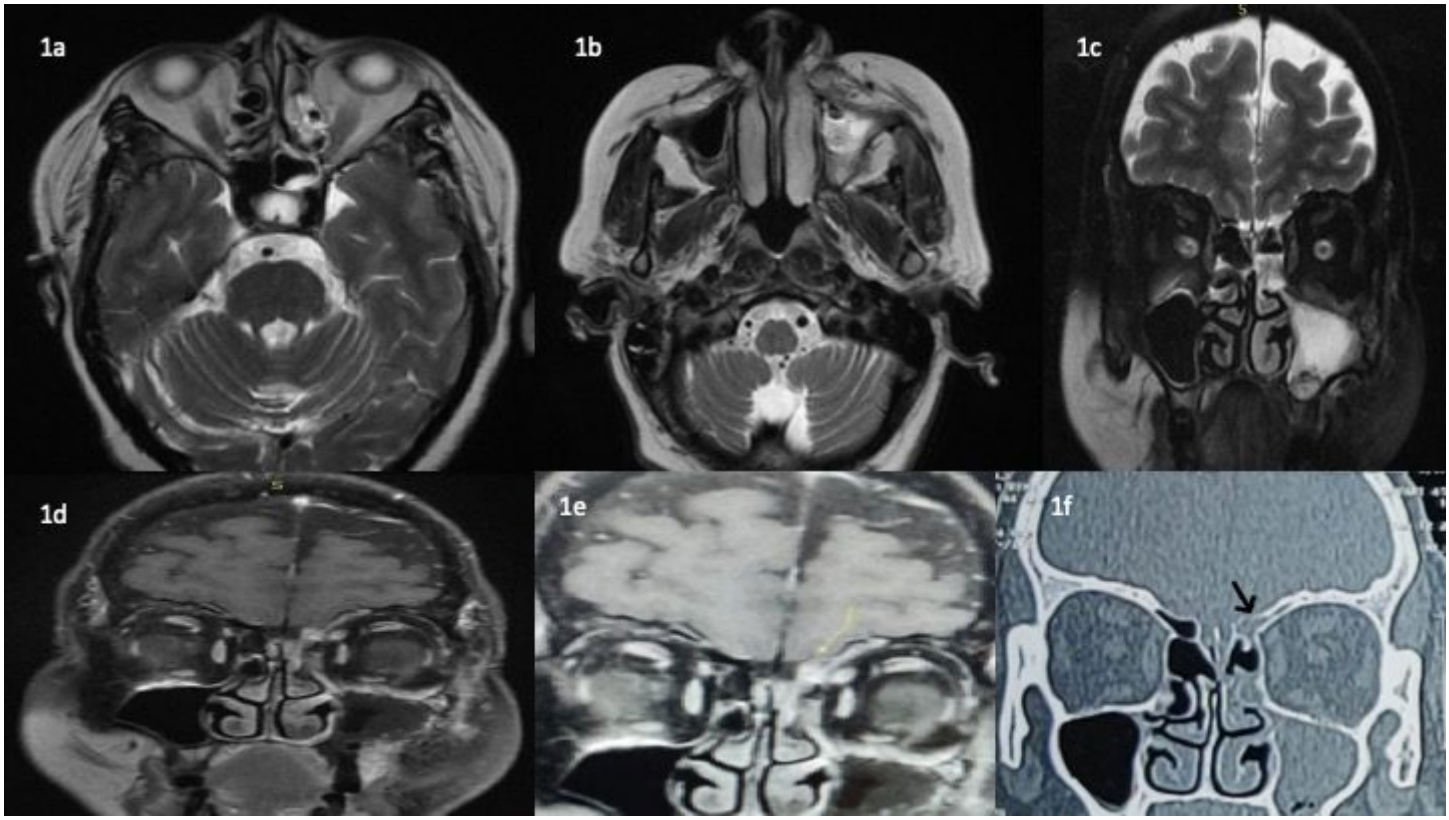

Figure 1

(a) Axial T2 hyperintensities in left ethmoidal and sphenoid sinuses and (b) left maxillary sinus, (c) Coronal T2 hyperintensities in bilateral ethmoidal and left maxillary sinus, (d) Coronal gadolinium contrast showing enhancement in left frontal, maxillary and bilateral ethmoidal sinuses, (e) focal erosion of left cribriform plate with enhancement of bilateral frontal sinus, ethmoidal and left maxillary sinuses, (f) CT paranasal sinus showing defect of left sided cribriform plate.

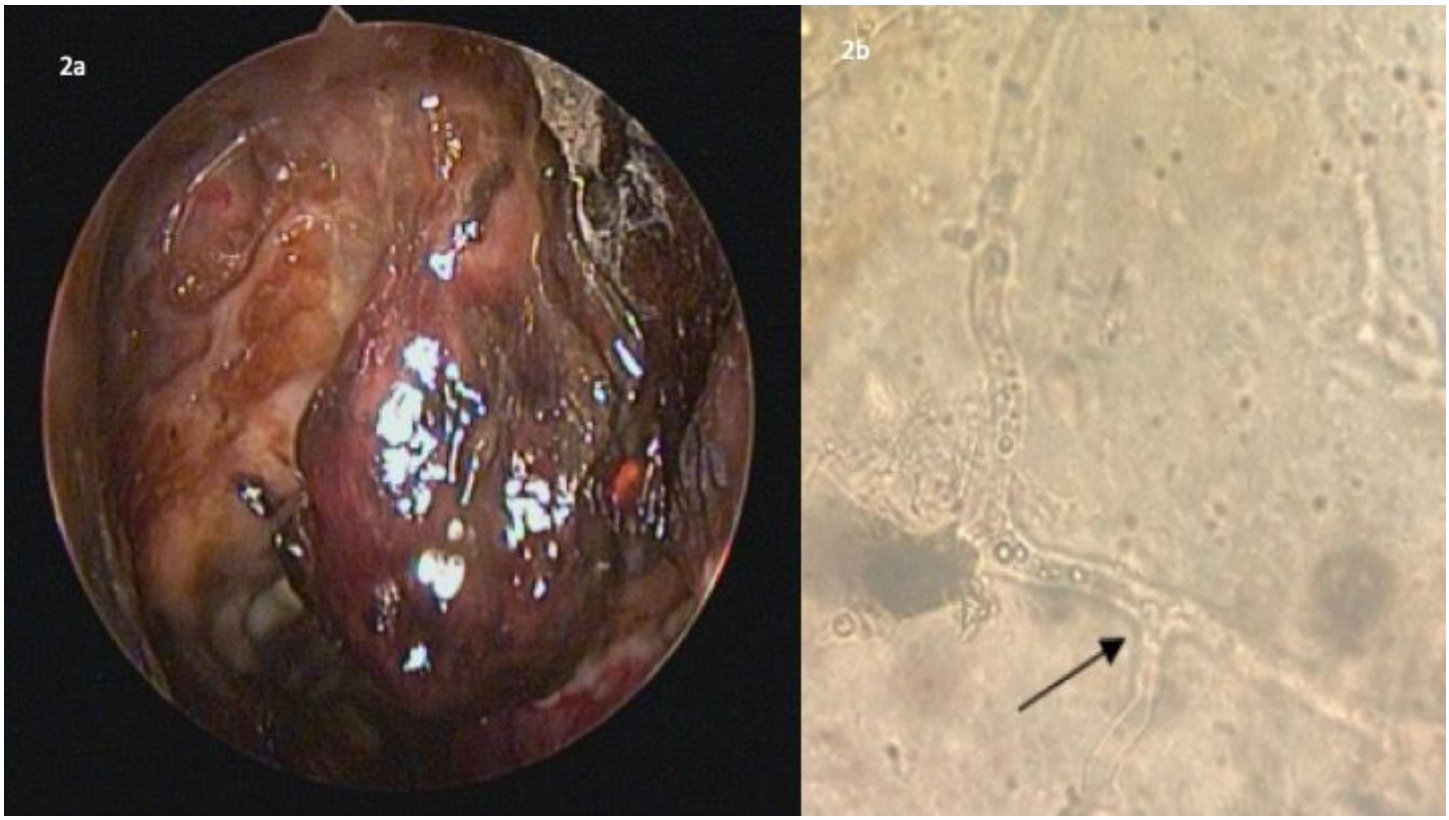

Figure 2

(a) Nasal endoscopic view showing necrotic tissue over middle turbinate and cribriform area, (b) KOH mount showing broad aseptate right angle branching (Black arrow) fungal hyphae of Mucormycetes