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ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 10, Issue, 04, pp.9587-9591, April, 2019

RESEARCH ARTICLE

CASE SERIES OF RHINOCEREBRAL MUCORMYCOSIS: MORTALITY OR SURVIVAL REAL FACTORS

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ARTICLE INFO

Article History:
Received 20th January, 2019
Received in revised form
16th February, 2019
Accepted 24th March, 2019
Published online 30th April, 2019

Key words:
Rhinocerebral mucormycosis,
Diabetes Mellitus, Antifungal therapy.

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ABSTRACT

Background: Rhinocerebral mucormycosis is a complex and fatal infection typically affecting diabetic or immunocompromised patients. In most cases, infection is caused by inhalation of fungal spores. ***Material and methods:*** Survival rate of patients is moderately high 75% and Mortality rate is 25% in our series due to early diagnosis and treatment with aggressive sugar control, repeated debridement and antifungal therapy. ***Results:*** In this case series, 32 cases with rhinocerebral mucormycosis were presented. The etiologic agents and other survival and Mortality factors of mucormycosis in 32 Patients were isolated and identified by sequence analysis and data were registered and presented. Conclusion: In patients with mucormycosis, early detection, surgical excision and appropriate debridement, suitable antifungal therapy, and control of risk factors like diabetes mellitus are the main parameters of successful management of this lethal infection.

***Citation: Sunil Kumar Sharma, Jigar Mehta and Vimal Ranka,* 2019.** "Case series of rhinocerebral mucormycosis: mortality or survival real factors", *Asian Journal of Science and Technology*, 10, (04), 9587-9591.

INTRODUCTION

Rhinocerebral mucormycosis is an acute and often lethal opportunistic fungal infection typically affecting diabetic (85% of the cases) or immunocompromised patients caused by fungi of the class zygomycetes. Our case series have described the mortality of approximately 25% in rhinocerebral mucormycosis. The infection has high incidence in diabetic patients due to the greater availability of glucose to the pathogen, lower response of T-cells, reduced serum inhibitory activity against the Rhizopus in lower pH, and increased expression of some host receptors that mediate the invasion of human epithelial cells through microorganism. The aim of this case series was to present patients with rhinocerebral mucormycosis who were successfully treated due to well-timed diagnosis of infection, and identification of etiologic agent by KOH fungal Preparation, fungal culture and histopathology examination of nasal tissues.

Pathogenesis: The infection usually presents as DM with ketoacidosis. acute sinusitis with fever, nasal congestion, discharge, and headache and sinus pain. All of the sinuses become involved and spread to the contiguous structures, such as the palate orbit and brain, usually progress rapidly. The hallmark of spread beyond the sinuses are tissue necrosis of the palate, resulting in palatal eschars, destruction of the turbinates, perinasal swelling, erythema, cyanosis of the facial skin and overlying tissues. Signs of orbital involvement include periorbital edema, proptosis and blindness. Facial numbness are frequent and result from infarction of sensory branches of the fifth cranial nerve.

The common underlying diseases

- DM with ketoacidosis,
- Patients On Steroids
- Malignancies
- Solid organ transplant
- Iron overload
- AIDS
- Treatment with deferoxamine
- Drug abuse
- Trauma/Burns
- Malnutrition

Rhizopus organism has an enzyme, ketone reductase that allows them to thrive in high glucose, acidic conditions. Necrosis and infarction of infected tissues is a hallmark of mucormycosis. Mucorales hyphae are broad 2 to 5 microns, irregularly branched and without septation.

Treatment protocol:

Our protocol to treat mucormycosis management include

1. Control of underlying pathology like sugar control, diabetic care and addressing other Haematological factors.
2. Better rehydration, Infused normal saline 60 ml per hour to prevent Renal shutdown due to amphotericin.

3. Assessment of the fungal extension and staging and planning of debridement and surgery.
4. Antifungal Therapy: In current practice, amphotericin is the sole antifungal agent licensed by the US Food and Drug Administration. Antifungal treatment options consist of lipid formulations of amphotericin B, amphotericin B deoxycholate, or posaconazole. First-line treatment is with an amphotericin derivative, preferably with Liposomal Amphotericin B. Liposomal Amphotericin B has proven efficacy in the treatment of mucormycosis. At the present time, the liposomal formulation (e.g., ambisome) is the drug of choice based on efficacy and safety data. Lipid preparations of amphotericin B are used at 5mg /kg/d. Some have used doses of up to 7.5-10 mg/kg/d to treat mucormycosis, especially CNS disease; however, the benefit of higher doses is unknown and these doses have a higher risk for nephrotoxicity. Amphotericin B deoxycholate can also be used for the treatment of Mucormycosis, especially in settings of cost restraints. The typical dose is 1 -1.5 mg/kg/d. The total dose given over the course of therapy is usually 2.5-3 g. High doses of this drug are required, and nephrotoxicity may result. This is of particular concern since many patients who develop mucormycosis have pre existing renal disease. Monitor the renal function of patients taking amphotericin B doubling of serum creatinine over the baseline levels is an indication for changing to liposomal amphotericin B In addition, careful monitoring and repletion of serum electrolytes (e.g phosphorus, potassium and magnesium) should be performed when administering any formulation of amphotericin B. Posaconazole Posaconazole, a triazole, is currently considered a second-line drug for treatment of mucormycosis and the typical dose is 5-6 ml qid in oral syrup as available in India (total of 800 mg/d).Administration with a high-fat meal/food and acidic beverages enhances absorption of the drug Patients on posaconazole should avoid antacids, especially proton pump inhibitors. In Addition, therapeutic drug monitoring of posaconazole levels should be considered in patients at high risk.
5. Aggressive surgical debridement of necrotic tissue in combination with medical therapy is mandatory for patient survival. In rhino cerebral disease, surgical care include sinus, nasal surgery and may require excision of the orbital contents and involved brain. Repeated surgery may be required.

MATERIALS AND METHODS

We are presenting details of our patients which were treated in our rajasthan hospital, The Gujarat Research and Medical Institute during the period of 2011 to 2018.we included several factors and recorded all details of our patients.

Total patients: 32.
Male : female = 18:14,
Age groups > 50Yrs = 28 <50 yrs=4

A: Immunocompromised :- 30 - diabetic 28,
-Haematological malignancy 1,
- Renal transplant 1

B: Immunocompetent- 2
Total survival= 24
Total death= 8

Intervention within 72 hours	Survival >90%
Intervention after 72 hours	Mortality>80%

So factors affecting the survival are

1. Timing of presentation <72 hours
2. Timing of intervention within 6 hours of admission
3. Severity of diabetic ketoacidosis
4. Status of immunity immunocompetent
5. Debridement extension
6. Extension of fungal involvement
7. CNS involvement
8. Age of presentation younger recover early
9. Antifungal therapy and monitoring

We found that patient who diagnosed and treated early mortality was very less even in severe cases. Definitive diagnosis should be made by clinical manifestation of the disease, histopathological examination of infected tissues, culture (culture studies are usually unsuccessful), and radiographic features. In most of cases CT scan of the paranasal sinuses (PNS) was performed. There was evidence of air fluid level in both maxillary sinuses compatible with acute sinusitis. Mucosal thickening was also seen in ethmoidal and sphenoid sinuses. In 2 cases we did In MRI study, there is evidence of enhanceable soft tissues density in right ethmoidal air cell with bone destruction and extension to right and retro orbital and intracranial area. Opacification of right sphenoidal and ethmoidal sinus also is seen. Histopathological findings and the results of culture confirmed our diagnosis. The isolate was identified as Mucor, Rhizopus, Rhizomucor, Absidia and cunninghamella.

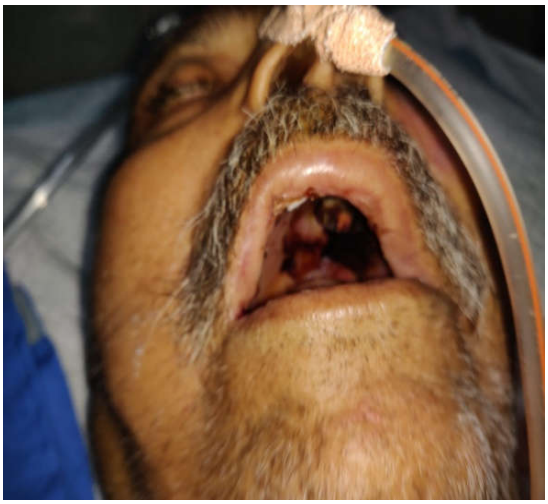


Fig. 1. Typical palatal eschar

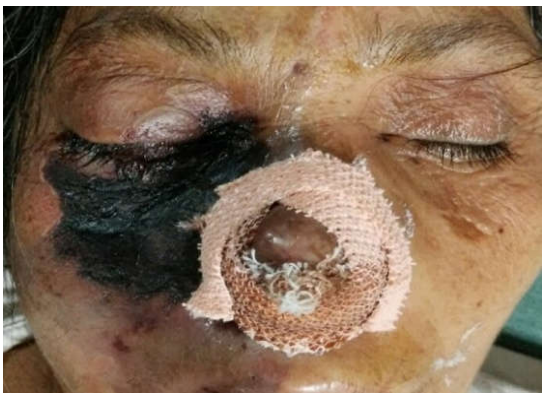


Fig. 2. Extensive disease

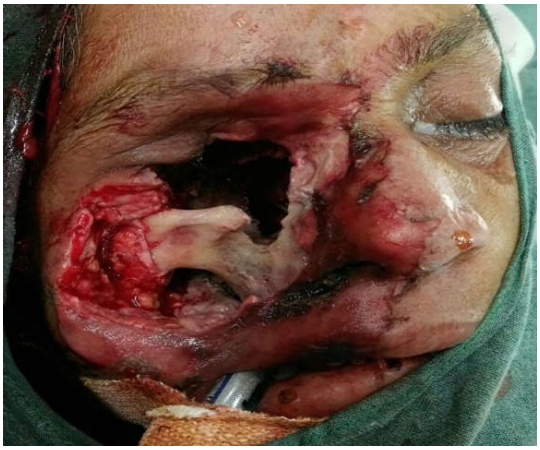


Fig. 3. Extensive tissue debridement with orbital Exenteration

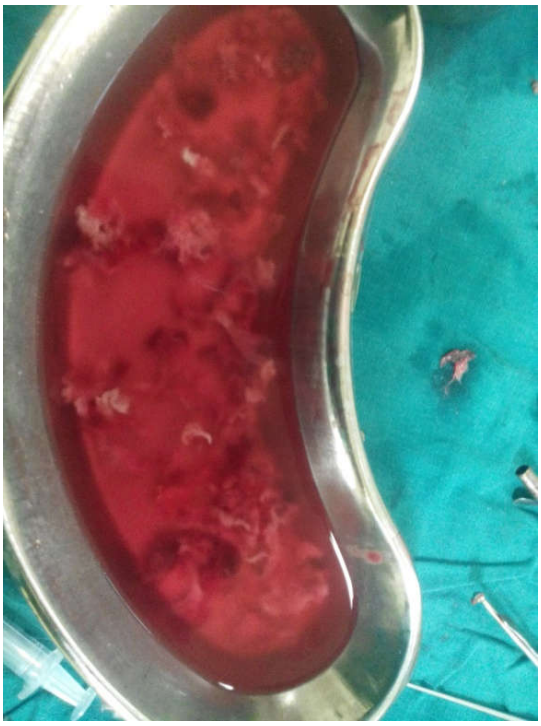


Fig. 4. Extensive fungal gross tissue

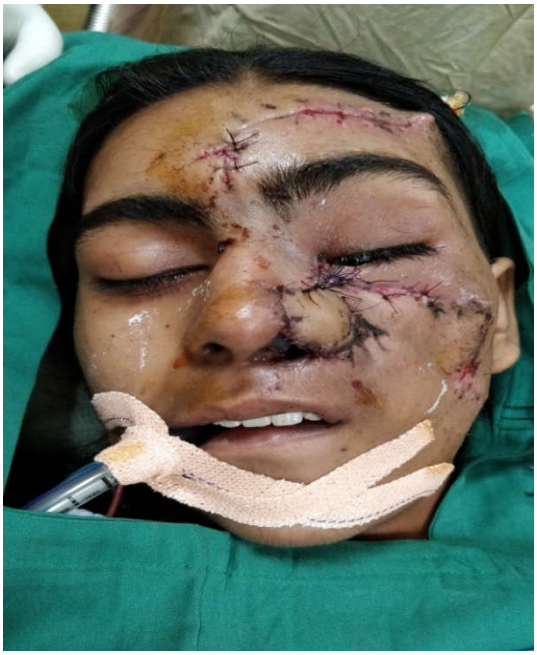


Fig. 5. Post of Reconstruction of nose with local forehead flap

Fig. 6. Post left Exenteration Patient sitting

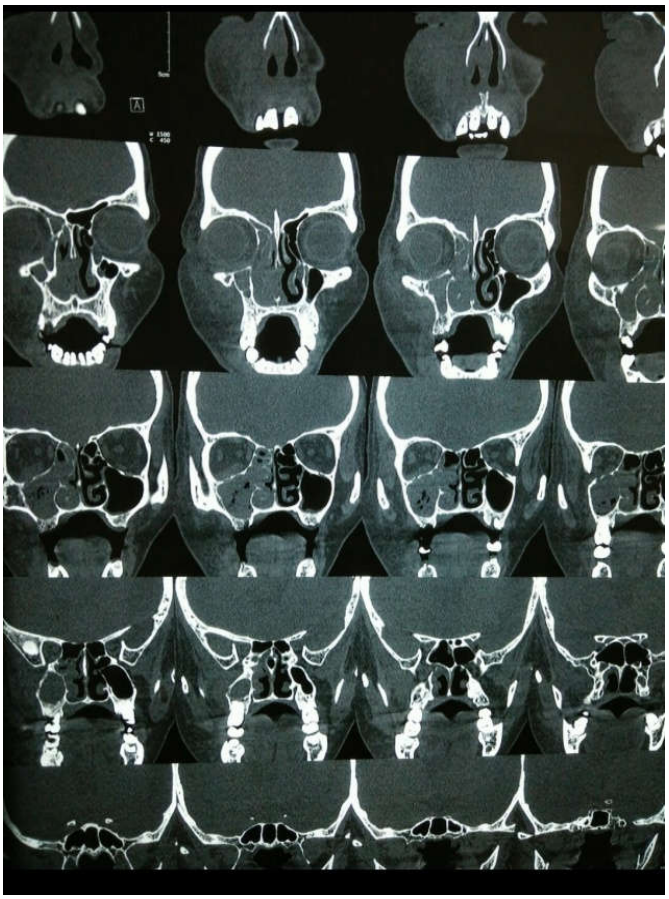
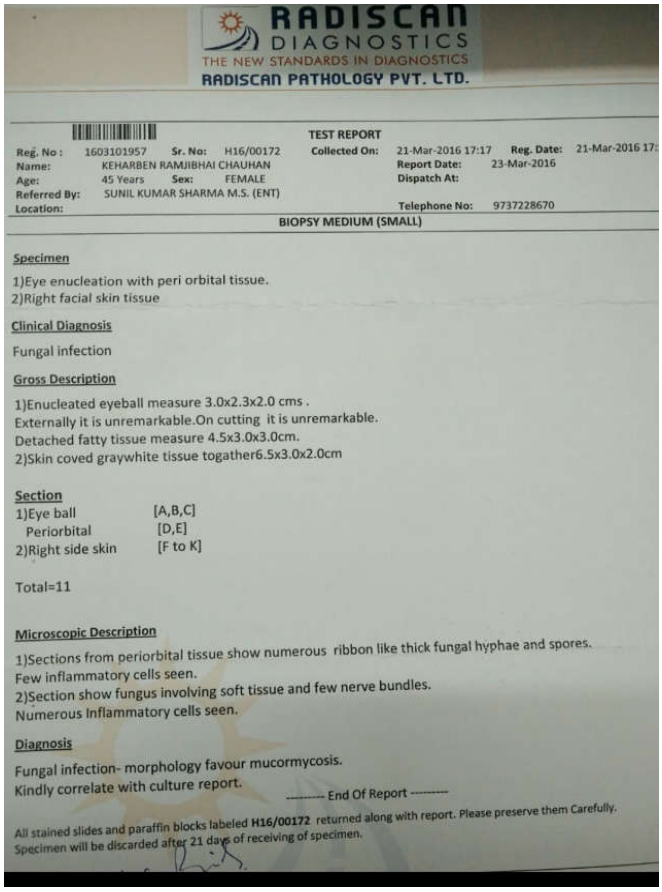


Fig. 7. Extensive unilateral fungal sinusitis

RESULTS

Mortality rate of mucormycosis is less in our series due to early intervention, repeated debridement and aggressive antifungal therapy. In most of cases we did 3 repeated and regular debridement and aggressive diabetic control with 24 hour hydration. In most of cases we used conventional amphotericin -B for 30 to 40 days during 2011 to 2015 in initial 15 cases, outcome was very nice, no Patient develop Renal shutdown. We were monitoring therapy with daily serum potassium and serum creatinine. Most of the patients died due to brain infarct due to fungal vascular invasion and



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TEST REPORT

Reg. No : 1603101957 Sr. No: H16/00172 Collected On: 21-Mar-2016 17:17 Reg. Date: 21-Mar-2016 17:
Name: KEHARBEN RAMJIBHAI CHAUHAN Report Date: 23-Mar-2016
Age: 45 Years Sex: FEMALE Dispatch At:
Referred By: SUNIL KUMAR SHARMA M.S. (ENT)
Location: Telephone No: 9737228670

BIOPSY MEDIUM (SMALL)

Specimen

1)Eye enucleation with peri orbital tissue.
2)Right facial skin tissue

Clinical Diagnosis

Fungal infection

Gross Description

1)Enucleated eyeball measure 3.0x2.3x2.0 cms .
Externally it is unremarkable.On cutting it is unremarkable.
Detached fatty tissue measure 4.5x3.0x3.0cm.
2)Skin coved graywhite tissue togather6.5x3.0x2.0cm

Section

1)Eye ball [A,B,C]
Periorbital [D,E]
2)Right side skin [F to K]

Total=11

Microscopic Description

1)Sections from periorbital tissue show numerous ribbon like thick fungal hyphae and spores.
Few inflammatory cells seen.
2)Section show fungus involving soft tissue and few nerve bundles.
Numerous Inflammatory cells seen.

Diagnosis

Fungal infection- morphology favour mucormycosis.
Kindly correlate with culture report.

-------- End Of Report --------

All stained slides and paraffin blocks labeled **H16/00172** returned along with report. Please preserve them Carefully.
Specimen will be discarded after 21 days of receiving of specimen.

Fig. 8. Histopathology report

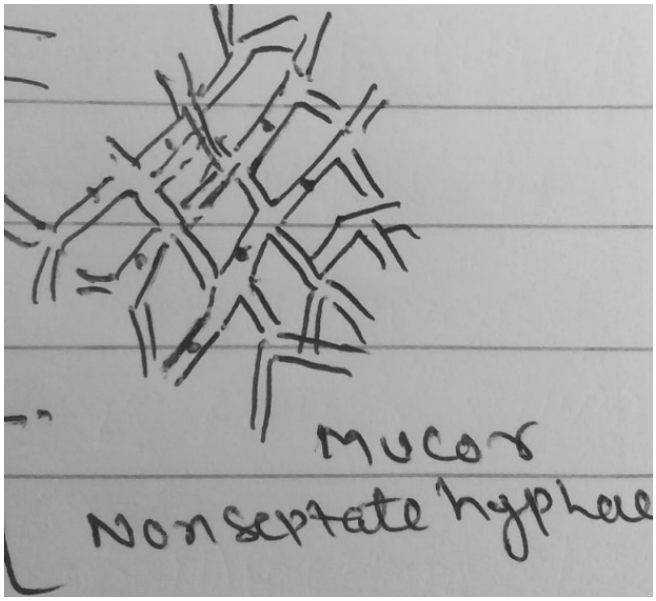

Fig. 9. Mucor typical hyphae drawing

direct brain tissue involvement, these all Patients were delayed present to us. After 2015 we used initial 15 days conventional amphotericin -B after that we used syrup posaconazole, no difference in outcome. In one patient who had Renal transplant we used liposomal amphotericin -B, then posaconazole.

2011-2015 in 15 cases	Amphotericin -B for 30-40 days
2015-2018 in 17 cases	Amphotericin -B /liposomal for 15 days then syrup posaconazole

Most patients were above 50 yrs of the age and male were more affected. Most of our patients are diabetic about 87.50 %.we had 2 patients who are immunocompetent. Most patients with mucor present with high sugar levels and high total counts. We did early endoscopic debridement, partial maxillectomy, orbital decompression and orbital exenteration according to the stage of presentation. We did reconstruction after 1 month of disease control, in 3 cases we did local flap reconstruction in eye Exenteration cases and partial maxillectomy cases.

CNS involvement with frontal lobe and cavernous sinus: 2
Orbital involvement with vision loss: 10
Orbital involvement with normal vision: 2
Without any orbital involvement//pure pansinusitis: 18 Case

We staged our cases and suggested this classification by. Dr. Sunil kumar sharma, consultant Department of otorhinolaryngology and head and neck surgery at The Gujarat Research and Medical Institute.

Stage	Subtype and details	Surgeries	Mortality
1	A-Unilateral sinusitis, B-Bilateral sinusitis	Endoscopic debridement	20%
2	A-Palatal involvement<2 cm B-Palatal involvement>2 cm	A:-Endoscopic debridement with palate debridement B:-Endoscopic debridement with Partial maxillectomy	30-35%
3	A-orbital involvement with normal vision B-orbital involvement with vision loss	A:-Endoscopic debridement with orbital decompression B:-Endoscopic debridement with orbital Exenteration	60-75%
4	A-CNS involvement with consciousness B-CNS involvement with loss of consciousness C-facial skin involvement	Endoscopic Resection with involvement brain tissue and external skin resection	90-100%

DISCUSSION

Mucormycosis is a fungal infection caused by a member of the family Mucoraceae. Rhizopus, Mucor, Absidia are the most common isolated from patients with mucormycosis. Rhizopus is responsible for 60% of all cases of mucormycosis, and 90% of rhinocerebral mucormycosis. The fungi are found in soil, bread, mold, rotten fruits and vegetables. The most common and fatal is rhinocerebral involvement. Though mucormycosis is ubiquitous and grows rapidly, it seldom strikes in immunologically competent patients. Therefore, if an infection with mucormycosis occurs, it usually indicates a serious underlying medical condition. Because the disease provokes diffuse tissue necrosis, the fungi can easily invade the wall of blood vessels, leading to thrombosis and tissue ischemia. Therefore, it is not uncommon to find the infection spreading to the cavernous sinus or the central nervous system. The deterioration in mental status is an ominous sign, often heralding intracerebral extension of the disease process. All of these symptoms may develop over a period of several days or may occur as a fulminating process within hours. Imaging studies are important to evaluate the extent of the disease. CT of patients with rhinocerebral mucormycosis shows opacification of the paranasal sinus and thickening of the sinus mucosa and bone destruction without an air-fluid level. In addition, when the orbit is invaded, increased density of the orbital fat and venous engorgement may be seen. Magnetic resonance imaging (MRI) can demonstrate soft tissue lesions better, especially in diagnosis of cavernous sinus thrombosis.. Biopsy of the affected tissue is required to confirm the infection. On histologic section, these organisms are characterized by wide, non-septate hyphae with right-angled branching. Cultures are still the standard means of diagnosis.

But even positive histologic findings, routine sinus cultures and blood cultures are rarely positive. Treatment of rhinocerebral mucormycosis should consist of prompt control of hyperglycemia and ketoacidosis, aggressive surgical debridement of involved tissue, and administration of parenteral amphotericin B.The importance of surgery is pronounced when no surgical treatment or only biopsy was performed the mortality rate is very high, which seen in Patient who refused to operate.

Conclusion

Rhinocerebral mucormycosis is an acute opportunistic mycosis that predominantly occurs in the patients with diabetes. The clinic physician may see patients with RCM in its earliest stages masquerading as other less serious diseases. Early diagnosis aggressive surgical debridement, high dose amphotericin B and good control of blood sugar are the most important factors to decrease the morbidity and mortality from this fungal disease. Early detection, surgical excision and appropriate debridement, suitable antifungal therapy, and control of risk factors like diabetes mellitus are the main parameters of successful management of this lethal infection among diabetic patients.

Acknowledgments*:* The authors express their appreciation to The Gujarat Research & Medical Institute Rajasthan Hospital personnel. Conflict of interest: The authors express no conflict of interest.

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