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Novel grading system for rhinocerebral mucormycosis

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Abstract

Introduction: Rhinocerebral Mucormycosis (RCM) has been challenging infection specially occurring in diabetic and immunocompromised patients. Its clinical manifestation varies from mild cases to very severe fatal infection with toxemia and septicemia. Especially in the background of covid 19 RCM infections has increased drastically.

Aims and objectives: We are proposing novel grading system for RCM which can help to categorize these patients and provide systemic treatment guidelines as per their stage

Patients and methods: From the patients that have attended GCS medical college and hospital with diagnosis of RCM we have classified them in to grade I to grade IV according to their clinical and radiological findings and as per their local or systemic symptoms.

Results: We could classify the patients and accordingly the treatment and approach could be planned. Prognosis can also be explained from their grades.

Keywords: Rhinocerebral Mucormycosis (RCM); Diabetes; Immunocompromised; Covid 19; Grading system.

Introduction

Rhinocerebral Mucormycosis (RCM) is rare opportunistic infection causing morbidity as well mortality in immunocompromised patients. It is also known as zygomycosis. It spreads rapidly in immunocompromised host and involves paranasal sinuses, midface bones as well orbit and brain. It is an acute fungal infection but it may also present as chronic occurrence that is indolent slowly progressing over several weeks [1].

It is commonly found in patients with uncontrolled diabetes mellitus, HIV infection, steroid therapy burns, organ transplant, hemochromatosis, neutropenia, hematological malignancies. But the occurrence can also be there in absence of predisposing factors [2]. Recent pandemic of COVID 19 is found to be the major risk factor for RCM infection. As the triad of viral infection, steroid therapy and diabetes predisposes host for such opportunistic infection.

There are no current grading systems available that can classify RCM into various stages. In medical science grading systems are available for various diseases that help for management of condition as well to judge prognosis as per severity. It is at times confusing to decide whether transnasal conservative approach is indicated or need radical open debridement. So we are proposing to classify the RCM infection as per severity and to guide for surgical and medical therapy.

Classification

From the patients diagnosed with RCM on clinical and microbiological findings we have run radiological examinations.

From overall evaluation we had observed that all patients do not require radical approach while some must go for radical sequestrectomy to stop progression of disease. We hereby propose a grading system which helps to evaluate severity of

disease so that we may plan treatment. This also helps to explain severity of the disease and know prognosis i.e., higher the grade worse the prognosis. To add presence of B symptoms add to worse prognosis.

Local symptoms

Grade I: Mild cases, no bone involvement, restricted only to mucosa.

Grade II: Moderate, small area of bone involved. Maxilla unilateral without involvement of orbital floor.

Grade III: Severe cases with extensive involvement of uni/bilateral maxilla, and pan sinuses, extending to orbit with or without necrosis of orbital contents.

Grade IV: Very severe cases infection extending beyond orbit and skull base to cranial cavity.

Systemic symptoms

Presence of systemic symptoms like fever, raised total leukocyte counts, irritability, dyspnea, loss of consciousness

Management guidelines

Presence of B symptoms should be taken as priority and considered immediate admission and vital monitoring. All routine investigations should be carried out including hemogram, liver function tests, renal function tests, HIV, HbsAg, HCV antibodies. History of Covid 19 infection and severity should be taken including dose and duration of steroid therapy. Blood sugar monitoring must be done frequently and insulin should be started as per sliding scale. Ketoacidosis should be ruled out. Intravenous fluids should be administered as per requirements. Supportive antibiotic therapy should be started as per culture and sensitivity report. All other supportive therapy should be started.

Multispecialty team approach is needed for better care including physician, critical care physician, infectious disease specialist, maxillofacial surgeon, ENT surgeon, dentist, ophthalmologist, and neurosurgeon.

Nasal or palatal swabs should be collected for KOH smear to diagnose and confirm RCM. Imaging should be done in stable cases to know extent and spread of infection.

Intravenous amphotericin B should be started on early basis with strict monitoring of vital parameters.

Once patient is vitally stable a symptoms should be addressed. Patient should be assessed for general anesthesia per ASA grading. High-risk consent should be obtained from all. Oral intubation and less use of IPPV are recommended to prevent spread to lower airway. Early surgery is recommended on priority basis to reduce fungal load and remove necrosed contents so that antifungal can penetrate better.

Grade I: Transnasal endoscopic approach should be selected.

Grade II: Transnasal endoscopic approach with correlation to endoscopic findings sequestrectomy may be considered.

Grade III: Most of these patients present with exposed bone or pus discharge. Open per oral approach should be done, mucosal flaps should be raised to expose necrotic bone and all necrotic bone should be sacrificed along with curettage of sinus contents. Frontal and sphenoid sinus may be approached by endoscope.

Grade IV: After these patients become stable and few days of amphotericin B therapy early radical surgery is recommended. Per oral maxillectomy and removal of all necrosed contents is recommended. Exenteration of necrosed orbital contents should be considered.

Final reconstruction must be delayed to assess outcomes. Primary mucosal suturing is always preferred whenever possible. In cases with mucosal defects palatal plates should be designed to prevent nasal regurgitation. Removal of naso-gastric tube should be done on earlier bases to avoid colonization around it. Temporalis flap is also being recommended by some authors; still we do not prefer to do primary reconstruction in RCM cases.

RCM presents to us in 2 ways: One is rapid fulminant way with severe systemic symptoms and second is chronic presentation with only local symptoms. So main aim of this grading is to judge severity of disease and explain about survival probabilities. This also explains whether to start with medical therapy or upfront surgery followed by antifungal therapy.

Discussion

RCM is invasive fungal infection caused by group of septate and aseptate filamentous fungi Mucoraceae family [1]. Mucormycosis is a general term for infections caused by a group of filamentous fungi belongs to the class Glomeromycetes, which has replaced the former class name Zygomycetes. In a review of more than 900 reported human cases of mucormycosis, Roden and colleagues found the majority of human mucormycosis cases were caused by fungi classified under the following genera [2]:

- Rhizopus (47%)
- Mucor (18%)
- Cunninghamella (7%)
- Apophysomyces (5%)
- Absidia species (5%)
- Saksenaea species (5%)
- Rhizomucor pusillus (4%)

Other genera belonging to Mucorales represented less than 3% of culture confirmed cases.

The first case of mucormycosis was described in 1885 by Paltauf, who created the term mycosis mucorina and ater coined as Mucormycosis in 1957 by Baker [3].

Mucormycosis is primarily a disease of subjects with altered host defenses associated with the underlying conditions and predisposing factors such as diabetes mellitus, hematologic malignancies, chemotherapy, corticosteroid therapy, organ transplantation, and so on. Diabetic patients are predisposed to mucormycosis because of the decreased ability of their neutrophils to phagocytize and adhere to endothelial walls. High blood sugar level may also alter the ability of macrophages [4].

Infection occurs following inhalation of spores of mucorales into the oral and nasal mucosa. Their germination is preferred by low oxygen, high glucose, acidic medium and high iron levels [5].

Importantly, DM has been the most common risk factor linked with mucormycosis in India, although hematological malignancies and organ transplant takes the lead in Europe and the USA [6].

From the recent studies it has been observed that uncontrolled blood sugar levels are most common factor associated with RCM, other factors seen along with covid 19 infections were steroid therapy, ramdesivir, tocilizumab, oxygen therapy in decreasing order [7].

Although mucormycosis is an extremely rare in healthy individuals but several immunocompromised conditions predispose it. This includes uncontrolled DM with or without DKA, hematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxamine or desferrioxamine therapy, voriconazole prophylaxis for transplant recipients, severe burns, Acquired Immunodeficiency Syndrome (AIDS), intravenous drug abusers, malnutrition and open wound following trauma [8].

Patients usually present with symptoms like one sided headache, rhinorrhea, nasal congestion hypoesthesia, epistaxis, facial pain, nasal discharge. Systemic symptoms like fever, lethargy, nausea may also be seen. Orbital symptoms include retro orbital pain, diplopia, blurring of vision. CNS involvement usually presents with convulsions, dizziness, altered mental status, and gait. Respiratory symptoms include difficulty in breathing, cough and hymoptysis [9].

High index of suspicion should be made in the existence of risk factors as clinical signs are nonspecific.

On examination signs of erythema on paranasal areas are evident and may be with swelling of cheek. Extra oral sinus may also be present with pus discharge. In severe cases blackening of skin of nose or cheek may also be present. On nasal examination black Escher may be visible with or without bleeding and blocked nose. All signs of sinusitis will be present. On oral examination foul smell with inflamed mucosa and discharge may be present. Loose teeth or mobile segment of bone may be seen. In chronic cases exposed necrotic bone may be evident. Orbital signs include proptosis with conjuctival chemosis. Altered or lost vision and ophthalmoplagia may also be present. Patients with neurological involvement may show neurological signs.

Imaging of choice is MRI for better soft tissue delineation and should be combined with plain CT cuts for better bony visualization. Orbit may be evaluated better by MRI. CT will show signs of sinusitis with present of sequestrum and fungal balls. MRI can show muscle edema and extension to skull base with neural involvement. Orbital collection and amount of necrosis in orbital cavity can also be evaluated. MRI at times may also show false positive results [10].

As the disease is aggressive, definitive therapy and a sequential plan of management is needed. Yet comprehensive clinical trial is required to confirm the unambiguous therapy and define optimal management strategies.

Primary first line antifungal monotherapy for mucormycosis should be based in polyenes. Amphotericin B, B deoxycholate (AmB) was the cornerstone of mucormycosis therapy for decades [11]; yet the use is now restricted due to availability of better molecules. Recent studies have shown that amphotericin B Lipid formulations (ABLC) are relatively less nephrotoxic and can be administered for a longer duration [12]. As per recent guidelines, treatment of mucormycosis with liposomal amphotericin B (LAmB) was associated with a 67% survival rate, compared to 39% survival when patients were treated with AmB (p=0.02) so it is now preferred as initial therapy for RCM [13,14]. Studies have shown advantages of LAmB over ABLC for the treatment of CNS mucormycosis while ABCL has better penetration in lung [15]. There is no definitive data on doses of polyene but 5-7.5 mg/kg/d of lipid polyenes are reasonable for most cases of mucormycosis. There is advantage of higher doses up to 10 mg/kg/d for LAmB in CNS involvement. LAmB can be safely given up to higher doses without significant nephrotoxicity [16]. Duration of antifungal therapy is also debatable from 21 days to 50 days but for cases with CNS involvement need longer therapy with LamB.

Fluconazole, voriconazole, and itraconazole do not have reliable activity against mucormycosis. Posaconazole is also failed to show significant results as a first line therapy for RCM. Still, it may be used as salvage therapy for resistant cases or as step-down therapy [16-19].

There are many studies showing improved outcomes from combination therapy [20]. But if used in combination therapy then dose escalation is not recommended due to paradoxical loss of efficacy [21,22]. Combination therapies of deferasirox and LAmB have shown 100 fold decreases in brain fugal burden and significantly superior outcomes [23]. The main problem associated with deferasirox therapy are nephrotoxicity yet exact pathogenesis is not clear [24]. Combination of posaconazole with polyenes has not shown any significant benefit in recent studies [25]. Role of colistin as antifungal agent was also studied but had failed to show any benefit in combination therapy [26].

Proinflammatory cytokines, such as interferon (IFN)-γ and G-CSF was also used effectively in combination therapy; they enhance the ability of granulocytes to damage the fungus. Still their role in primary therapy is debatable yet for resistant cases and in neutropenic host they may be used as life saving agents [27,28].

Hyperbaric oxygen therapy was also proposed and used for RCM [29].

Posaconazole, deferasirox and G-CSF may be used as salvage therapy in refractory cases with some benefits [19,23,28].

The surgical management of RCM is either endoscopic debridement or open sequestrectomy. If there is presence exposed maxillary alveolus in oral cavity open approach is always preferred which saves time of anesthesia. After maxillary alveolus had been removed all the sinuses can be approached. If require endoscopic debridement may be combined with open sequestrectomy. All the bones should be removed till active bleeding is seen from fresh margins. After thorough wash cavity should be packed with antral pack that should be removed within 48 hours [1,3,7].

There are classifications of site specific mucormycosis existing but grading of RCM has not been given. Richard et al. in 1997 classified fungal sinusitis into 3 types according to duration: granulomatous, acute fulminant and chronic invasive sinusitis [30]. Muley Chitguppi and Jambure proposed grading

system of Rhino maxillary mucormycosis in to 3 grades as per severity: mild, moderate and severe based on 30 patients [31]. Slonimsky et al. has proposed model for classification of Acute Invasive Fungal Rhino sinusitis (AIFR) caused by Mucor versus Aspergillus species by evaluating computed tomography radiological findings [32]. Egyptian group has classified RCM in to 3 stages based on radiological findings according to extension to paranasal sinuses, extension to orbit and oral cavity and extension to intracranial compartment [33]. Wali et al group has classified classical clinical progression of Cerebro Rhino Orbital Mucormycosis (CROM) into three stages: as per nasal, orbital and cerebral involvement [34]. European confederation of medical mycology has provided global guidelines for management of mucormycosis but stage wise management guidelines are missing [35].

Conclusion

In present study the purpose of grading system is depending upon symptoms and severity local or systemic and management guidelines as per the stage of involvement; which is quite simple for Indian subcontinent as well may be used globally.

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