Rhinocerebral mucormycosis (ROCM) is an uncommon, acute, and aggressive fungal infection occurring in several immunocompromised states including diabetes, which is the most common (60%–81%) predisposing factor. The disease originates in the nasal/sinus mucosa after inhalation of fungal spores and takes a rapidly progressive course extending to neighbouring tissues, including the orbit, and sometimes to the brain. Gregory et al in 1943 reported three cases of ROCM in patients with uncontrolled diabetes with unilateral orbital cellulitis, complete ophthalmoplegia, cerebral tissue invasion, and death. ROCM causes a very high residual morbidity and mortality due to the angioinvasive property of the fungus, thereby causing vascular occlusion and consequently resulting in extensive tissue necrosis. Impaired delivery of the antifungal drugs to the site of infection because of vascular thrombosis and limited aggressive surgery because of the complex anatomy of the rhino-oral region caution for early diagnosis and aggressive management in these patients.

Many case studies have highlighted the involvement of nasal/paranasal sinuses, orbit, and sometimes cerebral tissue by mucorales in patients with diabetes, especially during ketoacidosis, with high morbidity and mortality. We present the complete profile and treatment outcome of ROCM in 35 patients with diabetes seen over the last 12 years at our centre in north India.

PATIENTS AND METHODS

Medical records of 35 consecutive patients with a diagnosis of ROCM (23 men and 12 women) among the 22,316 patients with diabetes seen over the last 12 years. Five patients had type 1 diabetes mellitus, 29 had type 2 diabetes mellitus, and one had secondary diabetes. Nine patients had ROCM as the first clinical manifestation of diabetes. The mean (SD) blood glucose at presentation was 20.6 (8.3) mmol/l (range 10.0 to 53.3 mmol/l) and 17 patients had ketosis/ketoacidosis. Ophthalmic symptoms and signs were pronounced: external ophthalmoplegia (89%), proptosis (83%), visual loss (80%), chemosis (74%), and eye lid gangrene (14%). Non-ophthalmic manifestations included sinusitis (100%), nasal discharge/ulceration (74%), infranuclear VI nerve palsy (46%), palatal necrosis (29%), cerebral lobe involvement (20%), and hemiparesis (17%). Computed tomography/magnetic resonance imaging showed involvement of paranasal sinuses in all patients with ethmoid (86%) and maxillary (80%) sinuses being most frequently involved. Orbital involvement was observed in 80% of patients with cavernous sinus thrombosis in 11%, and internal carotid occlusion and hydrocephalus in 3% each. All were treated with amphotericin B (3–3.5 g) and 26 (74%) patients underwent appropriate surgery. Twenty one patients (68%) survived with a mean (SD) follow up of 39.6 (34.1) months (range 10 months to 11 years). Factors related to poor survival included delay in diagnosis and treatment (p < 0.05), facial and/or eye lid gangrene (p < 0.05), hemiplegia (p < 0.05), cerebral invasion by mucorales (p < 0.05), and treatment with amphotericin B alone (p < 0.05).

Conclusions: In patients with diabetes and ROCM, ROCM was the presenting manifestation in one fourth of the patients. Ophthalmic and extensive cerebral involvement predominated in the clinical picture. Delay in treatment due to late presentation and associated complications were major determinants of the survival outcome in these patients.

RESULTS

The overall prevalence of ROCM with diabetes was 0.15%. Thirty one patients had clinical features of ROCM at presentation, and four developed it during the hospital stay. The diagnosis of ROCM was suspected in only three (8.6%) with diabetes admitted to Nehru Hospital (attached to the Postgraduate Institute of Medical Education and Research, Chandigarh) from January 1990 to March 2002 were reviewed. Their ages ranged from 18 to 70 years with a mean (SD) of 47.3 (14.4) years. Patients having smear and/or histopathological evidence of mucormycosis only were included. The study was approved by the institute’s ethics committee.

Five patients had type 1 diabetes, 29 had type 2 diabetes, and one had secondary diabetes (fibrocalculus pancreatic diabetes). Nine patients (eight with type 2 and one with type 1 diabetes) had ROCM as the first clinical manifestation of diabetes. The mean (SD) informed duration of diabetes was 6.7 (4.6) years (range 0–22 years). Four patients with type 2 diabetes were on insulin, with 17 on oral hypoglycaemic drugs. Their clinical, biochemical, radiological (computed tomography/magnetic resonance imaging), and treatment profiles (amphotericin B and appropriate surgical intervention) were recorded in a special data sheet and analysed. Risk factors associated with poor survival rate were analysed by the logistic regression model (maximum likelihood method) and Z test for proportion. Patients who discharged themselves against medical advice were excluded from the survival factor analysis.

See end of article for authors’ affiliations.
patients before admission to our centre. The lag time between onset of symptoms referable to mucormycosis and the start of amphotericin B ranged from three to 45 days with mean (SD) of 13.8 (10.3) days. The mean (SD) blood glucose at presentation was 20.6 (8.3) mmol/l with a range of 10.0–53.3 mmol/l. Five patients had diabetic ketoacidosis (blood glucose >13.8 mmol/l, ketonuria, pH ≤7.3, and bicarbonate ≤15 mmol/l) and 12 had ketoacidosis (blood glucose >13.8 mmol/l, ketonuria, pH >7.3, bicarbonate >15 mmol/l). One patient had hyperosmolar non-ketotic coma with a serum osmolality of 326 mosmol/kg and had acidosis caused by acute renal failure. Two patients were hypertensive: one had dilated cardiomyopathy and the other had recent anterior wall myocardial infarction.

Clinical features of these patients are summarised in tables 1 and 2. Eight patients had onset of their disease with toothache with one developing submandibular abscess later, one with otitis externa and perichondritis followed by ophthalmoplegia, and one with catarrh. Eight (29%) patients had altered sensorium at presentation, while two others developed it during their hospital stay, one due to internal carotid artery occlusion, and the other due to hydrocephalus. Ophthalmoplegia (89%) was the most frequent presentation followed by proptosis (83%). Visual loss (80%) was observed in 26 patients at presentation and two patients developed it during their hospital stay. One patient had bilateral proptosis, ophthalmoplegia, and visual loss.

On computed tomography/magnetic resonance imaging, all patients had evidence of paranasal sinuses involvement. The ethmoid (86%) and maxillary sinuses (80%) were most commonly involved, followed by sphenoid and frontal sinus in six (17%) each and pansinusitis in five (14%) (fig 1A). Two patients had a gas shadow over the maxilla suggestive of necrotic tissue culture in both of them grew Staphylococcus aureus. Orbital involvement was observed in 28 (80%) patients (fig 1B) and the cavernous sinus thrombosis in four (11%). Intracranial extension with cerebral lobe involvement presenting as hypodense/hypointense area with or without rim enhancement (fig 1C and D) was observed in seven (20%) patients. One of these patients had a massive cerebral infarct with marked perilesional oedema resulting in hydrocephalus, which required ventriculoperitoneal shunt placement, and the other had internal carotid artery occlusion.

The diagnosis of mucormycosis was based on direct microscopy of aspirate/crusts from the nasal/sinus mucosa in 14 (40%), on histopathology in 11 (31%), and on both in 10 (29%). The finding of aseptate hyphae with right angled branching was considered pathognomonic for determining the morphology of the mucor. Culture on Sabroud’s media was performed in 28 patients and was reported positive in seven: Rhizopus spp, 1; Rhizopus rhizopodoformis, 1; Rhizopus arrhizus, 4; Mucor spp, 1.

All these were treated with amphotericin B, with total doses varying from 3.0–3.5 g, and 26 patients were subjected to appropriate surgery including lateral rhinotomy, sinusectomy, orbital exenteration (11/26), and frontotemporal craniotomy. None of these patients had any significant untoward events with amphotericin B treatment. However, after surgery one patient had diminution in vision and the other had a stroke. Twenty one patients survived, four left against medical advice, and 10 died. Duration of follow up ranged from 10 months to 11 years with a mean (SD) of 39.6 (34.1) months.

A complete necropsy was performed in two patients. In one softening and necrosis of the frontal lobes (fig 2A) with haemorrhagic infarction of the left posterior occipital cortex secondary to herniation was noted. There was no cavernous sinus thrombosis. Microscopically, multiple mucormycotic brain abscesses and vasculitis with infarction were seen. The other patient had extensive vasculitis with infarction in the right temporal lobe.

The predictors for survival included lag time between the first symptom referable to mucormycosis and treatment with amphotericin B (lag time between 3–9 days v 10–45 days, survival 85% v 55%, p<0.05), facial and lid gangrene (33% v 71%, p<0.05) hemiplegia (50% v 72%, p<0.05), and the cerebral invasion by mucorale (50% v 72%, p<0.05). Those with loss of vision, ophthalmoplegia, palatal necrosis, and altered sensorium at presentation also had a poor survival (p<0.05). However, diabetic ketoacidosis did not affect the survival outcome (p>0.05). Those who received surgical treatment in addition to amphotericin B had a better survival than who received amphotericin B alone.

**DISCUSSION**

ROCM typically originates in the nasal or oral mucosa, spreads to the paranasal sinuses, and enters the orbit via the ethmoid and maxillary sinuses or via the nasolacrimal duct. Intracerebral extension may occur from the orbit via orbital apex, orbital vessels, or via cribriform plate. Diabetes predisposes to this infection, as is seen in the majority of instances of ROCM (60%–81%) in different series. Ketoadiabetes in diabetes offers an added advantage to this
fungal invasion, as is seen in half of our patients. The acidic milieu reduces the binding of iron to transferrin, thereby more free iron and lack of a dialysable inhibitory factor in patients with diabetes offer favourable conditions for fungal multiplication.

Yohai et al reviewed 145 case reports of ROCM, 60% of them had diabetes, and analysed their ophthalmic and non-ophthalmic signs and symptoms occurring at any time during the course of disease. Similarly Ferry and Abedi reported 16 cases of ROCM; 13 (81%) of them had diabetes. We have compared our observations with these two available series where the majority of the patients had diabetes.

Periorbital swelling and pain were observed in 66% and 43% of patients by us, compared with 43% and 11% respectively by Yohai et al. Ptosis in absence of ophthalmoplegia was reported in 3% of patients, whereas all our patients with ptosis had concomitant ophthalmoplegia. Ophthalmoplegia (89% v 67%) and proptosis (83% v 64%) were more frequently observed by us compared with others. These were attributed to direct infiltration of retro-orbital tissue in 25, cavernous sinus thrombosis in two, and two had both. Visual loss was observed in 80% of our patients, compared with 65% reported by Yohai et al and 25% by Ferry et al. It was attributed to central retinal artery occlusion in seven, endophthalmitis in two, cavernous sinus thrombosis in four, while in others orbital vascular involvement could have been the possible cause. Cavernous sinus thrombosis due to mucormycosis is typically associated with vision loss as was seen in all our patients. Endophthalmitis has been rarely reported (1%) with ROCM but in our series two (6%) patients had it. Overall it seems that orbital manifestations were more common in our patients than reported in the literature. This could be due to delay in admission, thereby permitting spread of infection to the orbital tissue. Orbital manifestations are due to ischaemic necrosis of the intraorbital cranial nerves, orbital cellulitis, or rarely ocular invasion by mucorales.

With regard to nasofacial and oral manifestations, our patients had more extensive involvement than reported by Yohai et al particularly with regard to facial swelling (46% v 30%), facial paraesthesia (34% v 20%), nasal ulceration or necrosis (74% v 48%), palatal necrosis (29% v 32%), and infranuclear facial palsy (46% v 22%). Similarly, Ferry et al reported black eschar of skin, nasal mucosa, or palate in only 19% of their patients.

The occurrence of central nervous system involvement in the form of brain abscesses involving the frontal and temporal lobes was observed in 20% of patients whereas Yohai et al reported this in 8% of their patients. However, altered sensorium (29%), hemiparesis (17%), and meningeal signs (11%) were comparable with others. It must be realised that if sensorium does not improve with normalisation of pH, anion gap and electrolytes in a patient with diabetic ketoacidosis, mucormycosis should be considered. Worsening of sensorium in a patient with established mucormycosis suggests cerebral invasion or a major vascular occlusion by mucorales. Of our two patients with sino-orbital mucormycosis who developed altered sensorium...
during the recovery phase of ketoacidosis, one had internal carotid artery occlusion and the other had hydrocephalus due to post-infarct perilesional oedema.

Computed tomography or magnetic resonance imaging are useful modalities to assess the extent of the disease. In our study paranasal sinuses were involved in all patients, with ethmoid and maxillary being the most frequent, while Ferry et al. and Yohai et al. reported sinus involvement in 69% and 79% respectively. Orbital involvement observed as an orbital mass and/or thickening of the recti and optic nerve were seen in the majority (80%) of our patients. Intracranial extension with cerebral lobe involvement were observed in 20% compared with 8% by Yohai et al. Cavernous sinus thrombosis usually results from spread of infection from the orbit and appears as a filling defect within the enhancing sinus or as a lateral convexity, was evident in 11% which was comparable with others. Internal carotid artery thrombosis is a rare complication, which manifests as a massive cerebral infarction on imaging, and flow defect on colour Doppler imaging was seen in one of our patients.

The diagnosis of mucormycosis can be made by direct microscopy or histopathological examination, or by culture on Sabrout’s agar. The detection of asperate hyphae with right angled branching is pathognomonic. Cultures are often negative and positive results alone are not sufficient to make the diagnosis as mucorales can be grown from specimens taken from an uninfected mucosal and skin surfaces. All patients had tissue diagnosis either on smear and/or biopsy from affected tissues and culture was positive in some (23%) of them.

Amphotericin B is partially effective therefore surgical debridement becomes essential. Antral wash, lateral rhinotomy, pansinusectomy, orbital exenteration, and sometimes intracranial surgery are performed depending upon the extent of the disease. Extensive orbital involvement by mucorales required orbital exenteration in 11 (42%) patients and nine (82%) of them survived. This is in concurrence with other observers who feel orbital exenteration may be life saving in an actively inflamed orbit with a blind, immobile eye. Factors associated with poor survival in ROCM include (i) delay in diagnosis and treatment, (ii) hemiparesis, (iii) bilateral sinus involvement, and (iv) facial necrosis. Yohai et al. reported survival of 63% of patients with a lag time from seven to 12 days and 44% in those with a lag time of 13 to 30 days. In our analysis, 85% patients survived who had lag time from three to nine days, but only 5% survived with a lag time of 10 to 45 days. Similarly, those with hemiplegia, facial/eye lid gangrene, and cerebral invasion by mucorales had a poor survival in our series as also reported by Yohai et al.

Patients who received surgical treatment in addition to amphotericin B had a better outcome than those who received amphotericin B alone. This is in agreement with observations made by others. However, survival outcome was not affected by the presence of ketoacidosis in our study, possibly because of extensive disease and late presentation. However, our survival rate was comparable to that reported in western countries (68% v 70%–73%) in different series.

In conclusion, our patients with ROCM exhibited more extensive ophthalmic and cerebral involvement compared with their western counterparts, probably because of late presentation. Delay in treatment and associated complications were major predictors of survival outcome.

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**REFERENCES**


Pre-aortic paraganglioma

A 49 year old man with chronic headaches, longstanding anxiety, and fatigue presented with poorly controlled hypertension. Type 2 diabetes had been diagnosed recently. There was no history of palpitations, flushing, or chest pain; blood pressure was 170/100 mm Hg. Physical examination was otherwise normal.

His history prompted the measurement of urine catecholamines. Urine metadrenaline was raised at 85.6 μmol/24 hours (normal 0–5.5) and urine noradrenaline was markedly raised at 15388 μmol/24 hours (normal 90–600); urine dopamine and adrenaline were normal. I131MIBG scintigraphy showed increased isotope uptake in the epigastric area (arrow, fig 1). Abdominal computed tomography showed a lobulated mass in the region of the left coeliac axis (arrow, fig 2). A large vascular pre-aortic phaeochromocytoma was subsequently removed. Blood pressure and glucose tolerance normalised after surgery.

Phaeochromocytomas are rare tumours accounting for fewer than 1% of cases of hypertension. Extra-adrenal tumours termed paragangliomas occur in 10% of patients and arise from neural crest derivatives. They predominantly secrete noradrenaline. Phaeochromocytomas occur equally in both sexes and usually present in the third and fourth decades of life. Ninety percent of tumours are sporadic, while 10% occur as part of an inherited syndrome like multiple endocrine neoplasia type 2, Von Hippel-Lindau syndrome, or neurofibromatosis.

In the absence of classical paroxysms, the symptoms of catecholamine excess may be protean and non-specific. A high index of suspicion remains the cornerstone of diagnosis.

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