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MAIN ARTICLE

Indolent mucormycosis of the paranasal sinus in immunocompetent patients: are antifungal drugs needed?

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Abstract

Objective: To report the clinical characteristics and treatment outcomes of indolent paranasal mucormycosis in immunocompetent individuals.

Materials and methods: A retrospective review of four immunocompetent patients with indolent mucormycosis of the paranasal sinus managed by endoscopic sinus surgery only was performed. One year of regular follow up comprised angled endoscopy and repeated paranasal sinus computed tomography three months after surgery.

Results: Clinical symptoms were non-specific. Pre-operative paranasal sinus computed tomography showed opacification of the unilateral maxillary sinus with focal calcification but without bony destruction or extension to the orbit or cranium. All patients underwent endoscopic sinus surgery without administration of antifungal agents. There was no recurrence on regular clinical and radiological follow up.

Conclusion: For indolent paranasal mucormycosis in immunocompetent patients, endoscopic sinus surgery can be the treatment of choice, and the administration of antifungal drugs may not be necessary.

Key words: Mucormycosis; Paranasal Sinuses; Amphotericin B; Surgical Procedures, Operative; Immunocompetence

Introduction

Fungal sinusitis is subdivided into invasive and non-invasive types based on the presence of microscopic evidence of fungal hyphae within the tissues. The most important principle in treating patients with chronic fungal sinusitis is to distinguish between invasive and non-invasive disease, because the treatment and prognosis are very different. However, invasive and non-invasive fungal sinusitis share many clinical features: they may occur in immunocompetent or immunocompromised individuals, may have an acute or chronic course, and may extend beyond the thin walls of the sinuses into the orbit or brain.[1]

Mucormycosis of the nasal cavity and paranasal sinuses is an uncommon, opportunistic fungal infection that often has an aggressive, life-threatening course. Patients with this condition are generally diabetic or immunosuppressed. The most effective treatment consists of reversing the source of immunocompromise, immediate surgical debridement, and administration of systemic antifungal drugs (e.g. amphotericin B). However, there is uncertainty regarding the most appropriate therapy for indolent sinonasal mucormycosis in apparently immunocompetent individuals.

In this study, we assessed the one-year clinical and radiological results of indolent paranasal mucormycosis in immunocompetent patients treated with endoscopic sinus surgery alone, as well as characterising these patients' clinical features and treatment aspects.

Materials and methods

We undertook a retrospective review of four immunocompetent patients diagnosed with indolent mucormycosis of the unilateral paranasal sinus and managed with endoscopic sinus surgery only between 2007 and 2009. Demographic data were collected along with information on patient symptoms, previous sinus surgery, radiographic findings, primary pathology and comorbidities. Surgical reports and post-operative radiographic studies were reviewed, and outcomes were assessed using subjective and objective measures determined at the most recent follow-up appointment.

The study was approved by the relevant institutional review board.

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Results

Patient characteristics

The patients comprised one man and three women, with a mean age of 65.5 years. Clinical symptoms were non-specific and included postnasal drip, foul odour and nasal stuffiness. All patients had previously been healthy and reported no concurrent disease, medication, significant medical history or facial trauma, with the exception of one patient with well-controlled diabetes mellitus (Table I).

Paranasal sinus computed tomography (CT) was performed in all patients pre-operatively, and showed total or subtotal opacification of the unilateral maxillary sinus with focal calcified densities in all four cases. In no case was there bony wall destruction of the involved sinus or extension into the orbit or cranium (Figure 1). Two patients had an inflammatory polyp in the ipsilateral paranasal sinus.

Outcomes

Because fungal sinusitis was suspected in all patients based on their symptoms and paranasal sinus CT, all underwent endoscopic sinus surgery, with uncinectomy, ethmoidectomy and middle meatal antrostomy. Thick, grey-green, clay-like material was found filling the maxillary sinus and was removed.

Post-operatively, the patients were given a cephalosporin for 3 days and then discharged following the usual protocol for fungal sinusitis surgery.

The diagnosis of mucormycosis was based on a histopathological report identifying broad, non-septate, right-angled branching hyphae. Although the histopathological appearance confirmed the presence of mucormycosis after discharge, no antifungal drug was administered to any patient.

Regular follow up consisted of monthly angled endoscopy and repeated paranasal sinus CT three months after surgery. The average duration of follow up was 15.7 months. There was no recurrence in any patient. The three-month paranasal sinus CT showed no recurrence (Figure 2).

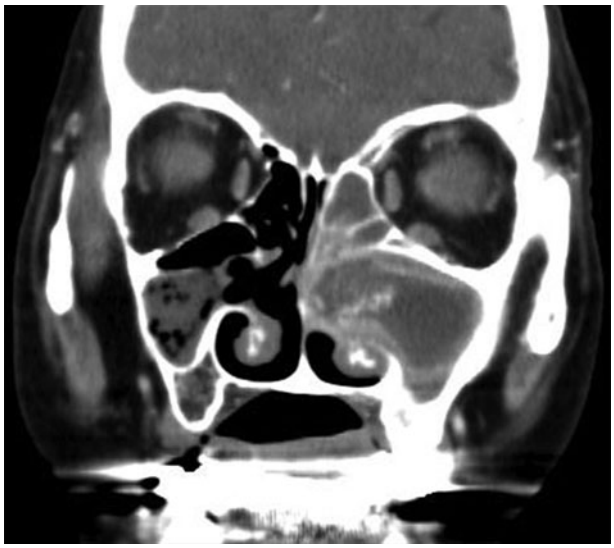

FIG. 1

Pre-operative, coronal, paranasal sinus computed tomography image showing total opacification of the left maxillary sinus with focal calcified densities, without bony destruction or invasion of the orbit or brain.

Discussion

Mucormycosis refers to any fungal infection by members of the order Mucorales, which is in the class Zygomycetes. Most pathogenic species are members of the family Mucoraceae. In immunocompetent hosts, the killing and removal of mucorales species is mediated by both neutrophils and macrophages.[2] Therefore, deficiencies in circulating neutrophils (e.g. due to neutropenia) and impaired phagocyte function (e.g. in diabetes mellitus during steroid therapy) are risk factors for this infection.[3] Most diseased patients are immunologically or metabolically compromised, with diabetic patients constituting the largest group with the rhinocerebral form of the disease.[4] In some immunocompetent patients, the disease is associated with local predisposing factors such as chronic rhinosinusitis or penetrating trauma.[5,6]

Artis *et al.* reported that serum from diabetic ketoacidotic patients has the ability to stimulate fungal proliferation only while the patients are acidotic; the simple addition of glucose, up to 1000 mg/dl in nutrient broth, did not stimulate the growth of *Rhizopus oryzae*.[7] Our fourth patient, who had well-controlled diabetes mellitus, showed no acidosis and had a chronic, non-invasive case of mucormycosis, in the form of a fungal ball in the operation field. Some authors have reported the successful treatment of paranasal mucormycosis in controlled diabetics using only the Caldwell–Luc procedure.[8,9] Thus, hyperglycaemia

TABLE I
PATIENT CLINICAL CHARACTERISTICS*

Pt no	Age (y)/gender	Clinical symptoms	Duration (mth)	Underlying disease	Involved sinus	FU (mth)
1	67/F	Foul odour, postnasal drip, nasal stuffiness	5	None	L MS	17
2	60/M	Postnasal drip, nasal stuffiness	4	None	L MS	24
3	68/F	Foul odour, postnasal drip, nasal stuffiness	4	None	R MS	12
4	67/F	Foul odour, postnasal drip	36	Controlled diabetes	L MS	10

*All patients were treated with endoscopic sinus surgery alone and all survived. Pt no = patient number; y = years; mth = months; FU = follow up; F = female; L = left; MS = maxillary sinus; M = male; R = right

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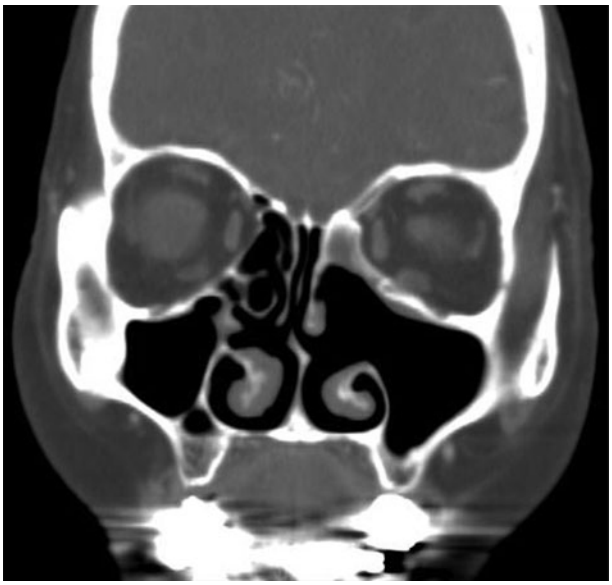

FIG. 2
Post-operative, coronal, paranasal sinus computed tomography image taken three months after endoscopic sinus surgery, showing no recurrence or residual lesion in the left maxillary sinus.

per se might not play a major role in the pathogenesis of invasive mucormycosis.

Invasive mucormycosis in the nose and paranasal sinuses presents initially with the signs and symptoms of acute bacterial rhinosinusitis; these usually progress very rapidly in the invasive form of the disease.[4] Patients with rhino-orbital-cerebral mucormycosis typically show other signs and symptoms within 72 hours of the first symptom. The leading symptom is fever (44 per cent), followed by nasal ulceration or black, necrotic tissue in the nose (38 per cent), periorbital or facial oedema (34 per cent), visual changes (30 per cent), headache (25 per cent), and facial pain (22 per cent). Ultimately, 80 per cent of patients develop a necrotic lesion of either the nasal or oral mucosa.[10] However, the presenting symptoms and physical findings are often subtle in indolent paranasal mucormycosis in immunocompetent patients.[11,12] In our series, the symptoms and signs were similar to those of chronic rhinosinusitis or fungal sinusitis, and the mean duration of the clinical symptoms was four years. It is worth mentioning that in invasive mucormycosis, spread into the orbit or brain takes place within a few days of onset of the disease.

The treatment of invasive mucormycosis requires correction of the cause of immunocompromise, aggressive surgical debridement and systemic antifungal drugs.[13] However, amphotericin B treatment is limited by toxicity, which may be acute (with fever, rigors and anaphylaxis) or chronic (predominantly renal, with rising creatinine levels).

There is uncertainty regarding the most appropriate therapy for apparently immunocompetent patients with indolent sinonasal mucormycosis. Most reports suggest that a cure can be achieved with aggressive surgical debridement in combination with long-term antifungal drug therapy; both treatments are used because of concern over the risk of progression to fulminant disease.

There are only three previously reported cases which appear to have been cured by endoscopic sinus surgery without long-term antifungal drugs post-operatively; however, these outcomes seem to have been achieved without a reasonable basis.[11,14] Because the clinical, radiological and operative findings did not suggest invasive fungal sinusitis in our patients, all were treated with endoscopic sinus surgery alone, with no long-term systemic or local antifungal drugs, despite the post-operative histopathological diagnosis of mucormycosis (obtained after discharge).

- **Mucormycosis of the nasal cavity and paranasal sinuses is often life-threatening in immunocompromised patients**
- **Treatment involves reversing immunocompromise, immediate surgical debridement and systemic antifungal drugs**
- **In this small series of immunocompetent patients, indolent paranasal mucormycosis was cured with endoscopic sinus surgery alone, without long-term antifungal drugs**

The underlying disease and presence of invasion are important determinants of survival; the overall mortality rate is approximately 62 per cent in rhinocerebral mucormycosis and 16 per cent in sinus infections without cerebral involvement; by way of comparison, the survival rate is 75 per cent in patients with no systemic disease, 60 per cent in diabetics and 20 per cent in those with other disorders.[15] However, our literature review did not identify any investigation of the relationship between prognosis, host immunity and disease localisation. In our series, the excellent prognosis indicated that host immunity may be as important as disease extent in determining the treatment and outcome of indolent paranasal mucormycosis.

Conclusion

Paranasal sinus mucormycosis is extremely rare in immunocompetent patients; thus, the present series included only a small number of cases. However, we suggest that even if paranasal sinus mucormycosis is not suspected pre-operatively based on clinical features and paranasal sinus CT, endoscopic sinus surgery may be sufficient treatment for indolent cases in immunocompetent hosts without CT evidence of brain or orbit invasion, and long-term antifungal drugs might not be necessary.

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