Non-invasive Fungal Rhinosinusitis

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14.1 Case Presentation

A generally fit and well 63-year-old lady presented to her GP complaining about retro-orbital headache and mucopurulent discharge. She was initially treated as having a common cold. Later on, the patient developed double vision and ptosis on the left eye. She was subsequently referred to our department for further investigations and definite treatment. On clinical examination, she complained about persistent nasal congestion and mucopurulent discharge. Headache and opthalmological symptoms deteriorated over the time. Flexible nasendoscopy revealed mucopurulent discharge coming from the sphenoethmoidal recess. Ophthalmology review confirmed left oculomotor nerve palsy while CT scan showed complete opacification of the left sphenoid sinus and thickening of the sinus walls (Fig. 14.1). She was started empirically on intravenous broad spectrum antibiotics with no significant clinical improvement. The patient underwent endoscopic sinus surgery, during which the surgeon identified debris coming out of the widened sphenoid ostium (Fig. 14.2). Histological evaluation of the specimen showed nonseptate fungal colonies accompanied by cellular debri and numerous neutrophils. The patient was under regular follow up for 6 months, and no recurrence was noted. Endoscopic evaluation of the nose was unremarkable and the ocular symptoms eventually improved.

Fig. 14.1 CT sinuses demonstrating complete opacification of the left sphenoid sinus

14.2 Background Knowledge

Fungal Rhinosinusitis (FRS) is commonly classified into two categories based on histopathological evidence of mucosal layer invasion by fungi:

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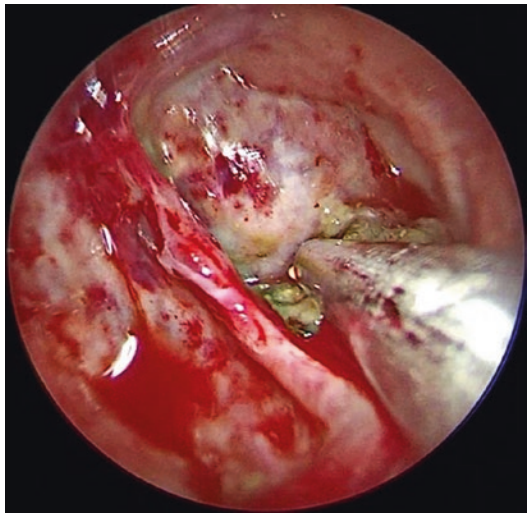

Fig. 14.2 Intraoperative photograph. After wide sphenoidotomy, the fungal ball is debrided and removed

invasive and non-invasive. The invasive diseases include (1) acute invasive (fulminant) FRS, (2) granulomatous invasive FRS, and (3) chronic invasive FRS. The non-invasive forms of FRS include (1) saprophytic fungal infestation, (2) fungal ball, and (3) allergic fungal rhinosinusitis (AFRS).

14.2.1 Saprophytic Fungal Infestation

Saprophytic fungal infestation refers to fungal colonization of the secretions of the sinonasal mucosa. Often seen in patients with a history of previous sinus surgery leaving an inflamed or crusted nasal mucosa with impaired mucociliary clearance, which subsequently gets infected with inhaled fungal spores. It is not invasive and is confined to inflamed and ulcerated/crusted sinonasal mucosa. It is usually diagnosed by endoscopy in an asymptomatic patient; however, it can present with a foul smell in the nasal cavity. This form of FRS is speculated to precede the development of a "fungus" ball. Treatment consists of mechanical removal on endoscopy and nasal douching to avoid recurrence. No formal surgical intervention is advised.

14.2.2 Fungus Ball

A fungal ball is characterized by a non-invasive dense accumulation of fungal hyphae within the mucosa of the paranasal sinuses. According to recent recommendations, fungal ball is considered the most accurate term for this entity as opposed to old non-specific terms, such as "mycetoma" and "aspergilloma".

Fungus ball of the paranasal sinuses is mostly presented in middle-aged to elderly immunocompetent persons with the mean age being in the seventh decade. In most series, it is more prevalent in the female population (2:1). These fungal balls are more frequently identified unilaterally, with the most common site being the maxillary sinus, followed by the sphenoid sinus.

The pathogenesis of the disease is not entirely understood, and no apparent risk factors for the formation of the fungal ball have been described. It has been speculated that certain components of sealers, such as zinc oxide, may play a role. However, the presence of fungus ball in patients without a previous history of dental treatment combined with the fact that fungus ball may be created in the frontal or sphenoid sinus suggests that unknown factors may be involved.

14.2.2.1 Clinical Approach

Diagnosis

The clinical picture of a fungal ball is usually non-specific and nasal discharge, nasal obstruction, headache, and facial pain have all been described. However, it can be recognized as an incidental radiological finding in an asymptomatic patient. It is not uncommon to be encountered as a part of the investigation and treatment for chronic rhinosinusitis (CRS) resistant to traditional medical treatment. The suspicion of a fungus ball is usually raised radiologically by a CT scan. CT scans generally show heterogeneous, hyper-dense sinus opacity, with microcalcifications or metallic appearance, partial or total.

The diagnosis is generally confirmed intraoperatively when 'cheesy' and 'clay-like' inspissated mucous is found within the sinus. The

aggregation of fungal hyphae within one or more sinuses with no evidence of invasion on histopathology, a predominance of eosinophils, granuloma, or allergic mucin, establishes the diagnosis. Culture for fungus is positive in only 30% of the cases, although fungal hyphae are identified on histopathologic examination in more than 90% of the cases.

Fungal balls are not invasive, therefore systemic or topical antifungal medications are not recommended. Treatment consists of endoscopic sinus surgery based on the location of the fungus ball (middle antrostomy, sphenoidotomy, and ethmoidectomy) and management of any contributing factors (i.e., oroantral fistula or retained dental amalgam). Any fungal material should be removed, and the sinus should be irrigated. It is also crucial to biopsy surrounding the mucosa to rule out any microscopic invasion by fungi. The success rate is high with a recurrence rate reported to be as low as 1% after surgical removal.

Topical or systemic antifungal medications should be considered only in case of a fungus ball presenting in an immunocompromised patient. Therefore, close observation of these patients to exclude invasive disease has been recommended instead of prescribing expensive medications with questionable evidence and potential side effects.

14.2.3 Allergic Fungal Rhinosinusitis

This is the most common form of fungal sinus disease and the third form of non-invasive fungal sinusitis. Allergic FRS is usually presented in immunocompetent, atopic patients complaining about symptoms of chronic rhinosinusitis (CRS) resistant to standard conservative medical therapy. Histopathology, AFRS shares similarities with allergic bronchopulmonary aspergillosis. Fungi associated with this disease are diverse, and cultures most commonly grow dematiaceous species, such as Bipolaris, Curvularia, and Alternaria.

The physiopathology of AFRS is controversial and not completely understood. The IgE-Mediated Type I Hypersensitivity and, possibly, IgG-mediated antigen-antibody complex formation (type III hypersensitivity), according to Gell and Coombs classification, are the most commonly cited mechanisms in the development of AFRS. Sinonasal eosinophilia and inflammation initiate a cycle of chronic edema, mucociliary dysfunction, stasis of secretions, combined with viscid allergic mucin, easily obstructs the normal drainage pathway. The fungi that provoke the hypersensitivity live and grow in the mucin stimulating the hypersensitivity reaction continuously.

The typical patient will suffer from chronic rhinosinusitis with nasal polyps refractory to conventional medical and even surgical therapy. Patients may have used several courses of antibiotics and topical nasal medications without resolution of their symptoms. Some clinical characteristics showing an alert sign for the clinician include a young (average age of 22 years), immunocompetent patient with unilateral or asymmetric paranasal sinuses findings, history of atopy, nasal polyposis, and relatively pain-free. In more severe cases, patients will present with proptosis, telecanthus, or gross facial dysmorphia. Patients may discharge a semisolid, thick, viscous consistency of yellow-green, white-brown, gray, brown, or black colour, described by some as a peanut butter appearance and consistency, called allergic/eosinophilic mucin. This mucus is composed of degranulating eosinophils in a background of mucin and fungal hyphae. The histological examination is of primary importance and with show eosinophilia, Charcot-Leyden crystals (a breakdown product of degranulating eosinophils) and non-invasive fungal hyphae. In addition to eosinophils, inflammatory infiltration with lymphocytes and plasma cells is also encountered.

CT images frequently present a dense, unilateral or asymmetric involvement of one or more paranasal sinuses, most commonly of the ethmoidal and maxillary sinuses. The most classical finding of AFRS on CT is the ‘double density’ sign. This is caused by metallic densities of fungal hyphae within the eosinophilic mucin surrounded by hyperplastic mucosa. Bony erosion may allow the disease to invade the neighboring

Table 14.1 Bent and Kuhn criteria

Major	Minor
Type I hypersensitivity	Asthma
Nasal polyposis	Unilateral disease
Characteristic CT findings	Bone erosion
Eosinophilic mucin without invasion	Fungal cultures
Positive fungal stain	Charcot-Leyden crystals
	Serum eosinophilia

CT computed tomography

tissues, affecting vital organs such as the brain, orbit, and large vessels. Peripheral enhancement caused by the inflamed mucosa and a central low signal on both T1 and T2 is the characteristic findings on MRI.

The most widely accepted diagnostic criteria were published by Bent and Kuhn, based on the histologic, radiographic, and immunologic characteristics of the disease (Table 14.1).

14.2.3.1 Treatment

The ideal treatment of patients with AFRS is still elusive and controversial. The management aims to remove as much antigenic and inflammatory load as possible and restore ventilation and drainage of the sinuses something that is achieved by functional endoscopic sinus surgery (FESS). Complete ventilation of the paranasal sinuses and removal of all nasal secretions, fungal mucin, fungal debris, nasal polyps with respect of the underlying mucosa not only decreases the fungal antigens but also allows access for post-operative treatment.

As for the post-operative treatment, it includes either immunomodulation (immunotherapy and/or corticosteroids) or antimicrobial and antifungal medications. Post-operative treatment should start instantly after surgery by nasal saline irrigation if a good long term outcome is to be achieved. Systemic corticosteroids are valuable in the post-operative period and coupled with nasal sprays are the most effective agents in preventing recurrences. Oral antifungals have been used in the post-operative management of AFRS to reduce the fungal load and, as a result, the immune response to it. However, given their disputed benefit and their side effects, they should be used as a last resort in patients not adequately responding to steroid therapy. The evidence for the use of topical antifungals and leukotriene modulators (i.e., Montelukast) is inadequate, and no recommendations have been made for their routine use.

Immunotherapy has also been shown to be very efficient, and when combined with surgery and medical treatment with corticosteroids, it prevents recurrences and reduces the need for corticosteroids in the future. Lastly, monoclonal antibodies constitute a novel therapy in patients suffering from CRS with nasal polyps and concomitant asthma. By targeting IgE, IL-5 cytokine pathways, omalizumab, and mepolizumab have shown encouraging results, and biologic therapy seems to be safe and well-tolerated. However, high-quality trials designed to assess these therapeutic alternatives for this specific subpopulation of patients with AFRS are called before recommendations can be made on their use.

Summary and Author's Comments

1. It is speculated that fungi play a developmental role in CRS, but their exact mechanisms remain unclear.
2. The wide variety of clinical manifestations in fungal sinus disease makes it a challenging entity to be diagnosed and treated effectively.
3. High-quality randomized controlled trials are required to determine the real benefit of immunotherapy, antifungal therapy and monoclonal antibodies in the treatment of AFRS.
4. AFRS is considered a chronic disease that may recur even after radical surgical and aggressive medical therapy and appropriate follow-up.

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