

Case Report

Diagnostic dilemma in a case of chronic invasive fungal sinusitis solved using a novel diagnostic test

Malavika Suresh*, Maneesh Shivaputra Ganamukhi, Sobhana Chandran, Saranya Sasikumar

Department of ENT, Mazumdar Shaw Medical Centre, Narayana Hrudayalaya, Bangalore, Karnataka, India

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*Correspondence:

Dr. Malavika Suresh,

E-mail: malavika.sreelakam@gmail.com

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ABSTRACT

Fungal infections of the paranasal sinuses are a spectrum of diseases rather than one distinct entity. The prevalence of fungal sinus disease has been increasing in recent decades, especially in immunocompetent individuals. The indiscriminate use of antibiotics and immunosuppressive drugs has partially been attributed to this. The diagnosis of invasive fungal disease still imposes a challenge to medical professionals occasionally. Here we present an interesting case of a middle-aged immunocompetent male who presented to us with non-specific symptoms of chronic invasive fungal sinusitis. The routine investigations for diagnosing fungal sinusitis turned out to be futile and the result of serum galactomannan test helped to identify and treat his condition.

Keywords: Fungal sinusitis, Immuno competent, Chronic invasive Aspergillosis, Orbital apex, Serum galactomannan

INTRODUCTION

Fungal sinusitis is a major contributor of chronic rhinosinusitis worldwide. The prevalence has been steadily increasing especially in tropical countries. Several controversies surround the categorization of fungal rhinosinusitis. In 1965, Hora broadly divided fungal sinusitis into invasive and non-invasive forms depending on its potential to invade epithelium. Depending on the duration of the disease, invasive fungal sinusitis is further divided into acute (<4 weeks), sub-acute (4-12 weeks) and chronic (>12 weeks) invasive fungal sinusitis.¹

Acute invasive fungal rhinosinusitis (FRS) can result in dramatic tissue invasion through mucosa, bone, neurovascular structures and surrounding organs. This disease entity is usually found in immunocompromised individuals and is associated with poor outcomes.

Unlike its acute counterpart, chronic invasive fungal sinusitis (CIFS) typically presents in otherwise healthy individuals.² Symptoms are often nonspecific and can

include nasal obstruction, facial pain, rhinorrhoea, headaches and epistaxis. Left untreated, it can result in proptosis, altered mental status, seizures and intracranial complications. The common causative organisms in CIFS are saprophytic fungi such as the zygomycetes (mucor, rhizopus, rhizomucor) and multiple species of *Aspergillus*.² In our country, *Aspergillus* species is found to be the major contributor of this disease process. The lack of obvious predisposing factors can present a diagnostic dilemma which will delay the much needed medical or surgical intervention, which was the scenario with our patient.

CASE REPORT

A 38-year-old immunocompetent male, who is a chronic smoker, presented to the ear, nose and throat (ENT) outpatient department (OPD) with complaints of progressive left sided nasal obstruction, nasal discharge and left eye ptosis since the past 10 months. He developed left sided facial pain initially which progressed to a left sided hemi cranial pain 8 months ago. He also developed blurring of vision with restriction of eye movements in all

directions, anosmia and complained of significant weight loss. Since the past 5 months he has not noticed a progression of the above-mentioned symptom spectrum. Initially he was evaluated at a hospital at his native where magnetic resonance imaging (MRI) of the brain, orbit and para nasal sinuses (PNS) was done. It revealed a hyperintense lesion near the orbital apex and the cavernous sinus with mild mucosal thickening of the left paranasal sinuses. He was subsequently diagnosed with Tolosa Hunt syndrome based on symptom profile and radiological finding and put on oral steroids for 3 months. Patient was subsequently referred to a higher centre due to non-improvement of symptoms for further evaluation. A repeat MRI showed progression of disease with evidence of a soft tissue enhancing lesion in left cavernous sinus extending into the superior orbital fissure with hyper intensity and atrophy of left orbital and masticatory muscles, mucosal enhancement of the left ethmoid and maxillary sinuses and asymmetric involvement of left alveolar region. Tissue from left nasal cavity was sent for KOH which revealed the presence of septate fungal hyphae. The patient underwent Endoscopic Sinus Surgery for disease clearance but the intraoperative tissue samples sent showed only chronic inflammatory changes with no evidence of fungal elements or invasion. A contrast enhanced computed tomography (CECT) of the paranasal sinuses (Figure 1) was done at our centre which also revealed findings similar to the MRI done earlier. Since the radiological suspicion of Invasive sinus disease was very high, the patient underwent repeat nasal endoscopy and biopsy at our centre. The biopsy again revealed evidence of only non-specific chronic inflammation with no evidence of granulomas or neoplasm. With a high clinical suspicion of CIFS, we decided to send his serum sample for Galactomannan assay. The test result was significant with a value of 0.76. This result ascertained the diagnosis of CIFS in him and we subsequently started him on long term oral voriconazole treatment (200 mg BD). The patient is currently showing slow progressive improvement in symptoms after 3 months of treatment and is being kept on close follow up.

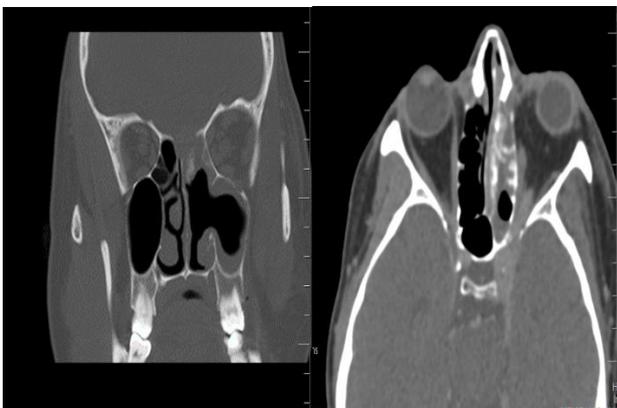


Figure 1: (a) Coronal section of CECT showing extension of disease into the orbit, and (b) axial section of CECT showing orbital apex involvement by the disease.

DISCUSSION

Fungal spores are abundant in the atmosphere and hence readily encounter anatomical structures relevant to ENT surgeons. Inhaled fungi form part of the normal sinonasal flora and are destroyed by the normal functioning immunological cascades. With the prolonged use of antibiotics, poor ventilation, dark and moist environments as well as immunocompromised status, these immunological pathways are disrupted and fungi develop pathological potential making fungal infections more likely.³ Previous case reports have associated CIFS with the use of topical nasal steroids and chronic sinonasal disease, however, there is a lack of clear consensus regarding putative predisposing factors.²

Diagnosis of CIFS, as outlined by de Shazo et al requires - radiologic evidence of chronic rhinosinusitis, and histopathological evidence of fungal hyphae within the sinonasal mucosa, submucosa, blood vessels or bone.² Prominent tissue necrosis may also be present, although the associated inflammatory infiltrate is variable.⁴ CIFS should be considered in any patient with chronic sinusitis in whom CT para nasal sinuses (PNS) shows focal or diffuse areas of radiodensity or when decreased T1 and T2 weighted signal intensities are present on MRI of PNS.⁴ However, findings on CT and MRI are often non-specific making the timely diagnosis of CIFS difficult. Extensive research is in progress to develop newer tests which will aid in the diagnosis of CIFS. These include measurement of biomarkers such as beta D glucan and galactomannan; and tests like radioallergosorbent test (RAST) for fungus and polymerase chain reaction (PCR).^{5,6}

Galactomannan is a cell wall component of *Aspergillus* species and *Penicillium* species which is excreted by the fungus during its growth phase. The galactomannan index (GMI) test is used extensively in Europe and was food and drug administration (FDA) approved for diagnosis of *Aspergillosis* in 2003. It is an enzyme-linked immunosorbent assay (ELISA)-based test that uses the rat monoclonal antibody EB-A2. The antibody recognizes a galactomannan epitope that contains galactofuranose, a polysaccharide present in various moulds.⁷

The significant value in serum specimen is >0.5 for all ages while values >1 is considered significant for bronchoalveolar lavage (BAL) specimens. The level of galactomannan antigenaemia is found to be proportional to the fungal tissue load and has a prognostic value.⁸ Initial baseline testing followed by serial monitoring in the first two weeks of initiation of treatment acts as a good prognostic indicator. In addition, 6-week galactomannan titres is a useful tool to assess treatment outcome.⁹ In 2016, Patterson et al cited that serum and BAL galactomannan levels are an accurate indicator of invasive aspergillosis in both adult and paediatric populations.⁵ In 2015, Neofytos et al conducted a study

on 47 patients with invasive *Aspergillosis* and found that the decreasing geometric mean increase (GMI) titres in BAL samples during the first 2 weeks of IA treatment can predict favourable clinical responses at 6 and 12 weeks after initiation of therapy. A meta-analysis of 17 studies by de Heer et al in 2015 also demonstrated the role of BAL galactomannan levels in the diagnosis and prognosis of IA.⁸

A study conducted in 2018 in India observed a high sensitivity and specificity (both 90%) of serum GM for the diagnosis of IA and a lower sensitivity (56.4%) for diagnosis of invasive fungal infections in general.¹⁰ This could be because of the contribution of non *Aspergillosis* species such as *Candida* and *Mucorales* species in causing invasive fungal infections and the inability of GMI to detect these species.⁹ Other studies have reported 71–89.7% sensitivity and 89–98.1% specificity for IA diagnosis by serum galactomannan levels among immunocompromised patient.^{11,12}

Galactomannan is present in various species and hence cross reactivity is an issue.⁷ In a study conducted by Nucci et al in 2014 it was found that all 18 patients diagnosed with invasive fusariosis were found to show significant serum galactomannan levels. But the GMI levels were more frequently positive and the average GMI values were as high as 6.382 unlike in IA which was just above 0.5. In such cases other parameters such as the presence of metastatic skin lesions and positive blood cultures, which are far more common in invasive fusariosis, should also be taken into consideration.⁷

After an extensive review of literature, it can be concluded that there is a severe dearth of Indian literature about the diagnosis and management of CIFS even though the prevalence is not so rare in the subcontinent. A high index of clinical suspicion is the basis of diagnosis of CIFS in several cases since most often the cultures are negative for fungal growth and CT findings are often non-specific.¹³ In such situations, an adjuvant test like serum galactomannan assay will definitively aid in the early diagnosis of CIFS and help in reducing the disease burden of the patient.

CONCLUSION

Galactomannan optical index assay provides a ray of hope in providing accurate and rapid screening of IA. In the current scenario, there are only a few centres in India that perform this test, hence making its use limited. A good sensitivity and specificity makes it a valuable screening tool. In our case, the measurement of serum galactomannan level helped steer the diagnosis in favour of CIFS and start appropriate treatment. There is scope for a larger study to be undertaken to understand the performance of this test in the Indian setting and to help provide a greater insight into its role in diagnosing IA and assessment of treatment outcome.

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