Case Report

Chronic Invasive Nongranulomatous Fungal Rhinosinusitis in Immunocompetent Individuals

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Chronic invasive nongranulomatous fungal rhinosinusitis is a well-described but uncommon type of fungal rhinosinusitis (FRS). While the prevalence of chronic FRS is 0.11% in healthy individuals, only 1.3% of them are in nongranulomatous invasive nature.

The majority of the cases in the literature have been reported from developing countries mostly located in the tropical regions, as typically occurring in the background of diabetes mellitus or corticosteroid treatment. The current paper reports four consecutive cases, who were diagnosed within a short period of six months at a single center of a country located outside the tropical climate zone. None of the patients had a comorbid disease that may cause immune suppression or a history of drug use. The only risk factor that may have a role in development of chronic invasive nongranulomatous FRS was that all of our patients were people working in greenhouse farming. Three cases underwent endoscopic sinus surgery, and one case underwent surgery with both endoscopic and external approaches. Systemic antifungal therapy was initiated in all cases in the postoperative period with voriconazole 200 mg orally twice a day. All patients achieved a complete clinical remission. Chronic invasive nongranulomatous FRS should be kept in mind in the presence of long-standing nonspecific sinonasal symptoms in immunocompetent individuals, particularly with a history of working in greenhouse farming.

1. Introduction

Fungal rhinosinusitis (FRS) encompasses a spectrum of sinonasal diseases with distinct clinical courses, histopathologies, and disease outcomes. FRS is classified into two groups as invasive and noninvasive depending on invasion of the mucosal layer by fungi. Noninvasive FRS includes saprophytic fungal infestation, fungal ball, and allergic FRS. Invasive FRS is subdivided into acute invasive, chronic nongranulomatous invasive, and chronic granulomatous types [1].

Chronic nongranulomatous invasive FRS is a well-described but uncommon type of FRS. While the prevalence of chronic FRS is 0.11% in healthy individuals, only 1.3% of them are in nongranulomatous invasive nature [2]. In this paper, four consecutive immunocompetent patients with chronic invasive nongranulomatous FRS, who were diagnosed over a period of 6 months at a single center (June 2015–October 2015), were presented along with the literature.

2. Case Presentation

The current study was conducted in accordance with the Declaration of Helsinki and with approval from the Institutional Ethics Committee. Written informed consent was obtained from the patients.

All patients were farmers from rural areas. A comprehensive head and neck examination was performed in all cases. Complete blood cell counts and serum chemistry panel, including hepatic and renal function tests, were evaluated. Radiological evaluation was carried out by computed tomography (CT) scan. None of the patients had a comorbid disease that may cause immune suppression or a history of drug use. Three cases underwent endoscopic sinus surgery, and one case underwent sinus surgery with both endoscopic and external approaches. A Gomori methenamine-silver stain was used in the histopathological diagnosis. The diagnosis of chronic invasive FRS was made by the demonstration of silver
Rhinosinusitis is a common public health problem that affects approximately 20% of the population [2]. While viruses and bacteria are the infectious agents detected in the majority of...
**Table 1: Characteristics and outcome of the patients.**

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age/gender</strong></td>
<td>58 yrs/male</td>
<td>43 yrs/male</td>
<td>60 yrs/female</td>
</tr>
<tr>
<td><strong>Immune suppression</strong></td>
<td>− − −</td>
<td>− −</td>
<td>− − −</td>
</tr>
<tr>
<td><strong>Symptom onset to diagnosis</strong></td>
<td>6 months</td>
<td>24 months</td>
<td>9 months</td>
</tr>
<tr>
<td><strong>Left orbital pain</strong></td>
<td>Nasal obstruction</td>
<td>Dizziness</td>
<td>Headache</td>
</tr>
<tr>
<td><strong>Symptoms at presentation</strong></td>
<td>Swelling on the face</td>
<td>Headache</td>
<td>Headache</td>
</tr>
<tr>
<td><strong>Nasal cavity</strong></td>
<td>+ +</td>
<td>− −</td>
<td>− − −</td>
</tr>
<tr>
<td><strong>Osteomeatal complex</strong></td>
<td>+ +</td>
<td>− −</td>
<td>− − −</td>
</tr>
<tr>
<td><strong>Maxillary sinus</strong></td>
<td>+ +</td>
<td>− −</td>
<td>− − −</td>
</tr>
<tr>
<td><strong>Ethmoidal sinuses</strong></td>
<td>+ +</td>
<td>+ (right posterior)</td>
<td>+ (right posterior)</td>
</tr>
<tr>
<td><strong>Sphenoid sinus</strong></td>
<td>+ (left side)</td>
<td>+ (left side)</td>
<td>+ (right side)</td>
</tr>
<tr>
<td><strong>Frontal sinus</strong></td>
<td>+ +</td>
<td>− −</td>
<td>− − −</td>
</tr>
<tr>
<td><strong>Bilateral involvement</strong></td>
<td>− − −</td>
<td>− −</td>
<td>− − −</td>
</tr>
<tr>
<td><strong>LP destruction</strong></td>
<td>ESS</td>
<td>ESS combined with external frontal sinus surgery</td>
<td>ESS</td>
</tr>
<tr>
<td><strong>ESS</strong></td>
<td>ESS combined with external frontal sinus surgery</td>
<td>ESS</td>
<td>ESS</td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
<td>A. fumigatus</td>
<td>A. flavus</td>
<td>A. fumigatus</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>Nongranulomatous CIFRS</td>
<td>Nongranulomatous CIFRS</td>
<td>Nongranulomatous CIFRS</td>
</tr>
<tr>
<td><strong>Medical treatment</strong></td>
<td>Voriconazole</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Follow-up time</strong></td>
<td>10 months</td>
<td>8 months</td>
<td>7 months</td>
</tr>
<tr>
<td><strong>Disease recurrence</strong></td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

LP: lamina papyracea, ESS: endoscopic sinus surgery, and CIFRS: chronic invasive fungal rhinosinusitis.
cases, fungi are responsible for certain particular subtypes [6].

Acute invasive FRS is an opportunistic fungal infection almost exclusively affecting immunocompromised individuals. Classical hosts include those receiving multiagent chemotherapy for a hematologic malignancy and those who are neutropenic or those with aplastic anemia [7]. The disease manifests with an acute onset and has a fulminant course. In a case series of 29 patients, Monroe et al. reported a six-month overall survival of only 18% [8].

In contrast to acute invasive disease, chronic forms of invasive FRS including granulomatous and nongranulomatous types are mostly seen in apparently healthy individuals [2]. Although these two forms of chronic invasive FRS are considered separate entities, they share many clinical and pathologic features. *Aspergillus* species are the most common fungi isolated in both forms. Tissue invasion by fungi occurs over a prolonged period (several weeks or months), rather than hours as in acute invasive FRS [7]. Patients often present with nonspecific symptoms and have an indolent clinical course. Therefore, they are usually associated with delayed diagnosis, which may increase the morbidity as well as mortality [7]. Despite the lack of comparative data, no significant differences in disease outcomes have been documented [1]. Both forms are treated in a similar fashion [5].

The distinction between granulomatous and nongranulomatous types of chronic invasive FRS is primarily based on pathological findings [1]. Granulomatous type is characterized by the presence of submucosal noncaseating granuloma consisting of foreign body or Langhans-type giant cells. Fungal hyphae are usually sparse, and there is extensive fibrosis. In contrast, there is a dense accumulation of hyphae in non-granulomatous type but the inflammatory infiltrate is sparse [4].

The majority of chronic invasive FRS cases in the literature have been reported from developing countries mostly located in the tropical regions of South Asia, Middle East, Africa, and South America [9]. The hot and humid climate in these regions creates a suitable environment for fungal growth and proliferation of spores. In addition, the high number of people working in agricultural activities increases the risk of intense exposure to fungal spores and development.
of fungal infection in a healthy individual. However, most of these reported cases include examples of granulomatous type.

Available data regarding chronic nongranulomatous invasive FRS are relatively sparse as compared to acute invasive and chronic granulomatous FRS. In most instances, the disease occurs in the background of diabetes mellitus or prolonged corticosteroid treatment [1]. In a multi-institutional analysis including 18 patients with invasive FRS (of them 8 were chronically nongranulomatous and 10 were acutely invasive), Pagella et al. reported a disease-related mortality rate of 25% for chronic invasive nongranulomatous FRS compared with 40% for acute invasive disease [10]. The majority of patients with chronic invasive disease had diabetes mellitus (87.5%) as comorbidity. On the other hand, in a small case series of 6 patients with chronic nongranulomatous invasive FRS, D’Anza et al. reported that all patients were free of disease at last follow-up, with a range of 1 to 27 months [11]. In this series, also all patients had systemic comorbidities, with diabetes mellitus being the most common.

In contrast to previous reports, none of the patients in our series had any comorbidities or history of corticosteroid use that may alter immune functions. In addition, our country remains outside the tropical climate zone. Apparently, the only risk factors in our patients were that they were rural and were working in greenhouse farming and the fact that four cases are being reported from a single center within a short period of six months is clinically important.

The treatment of invasive FRS, including both acute and chronic subtypes, requires an effective surgical debridement and systemic antifungal therapy [5]. The aim of the surgery is to provide adequate sinus ventilation by the removal of devitalized tissues and to facilitate the penetration of antifungal agents. Amphotericin B, voriconazole, itraconazole, posaconazole, and caspofungin are antifungal agents that are effective against *Aspergillus* species [12]. In the single randomized controlled trial comparing voriconazole with amphotericin B, voriconazole was associated with better response and survival rates and fewer side effects than amphotericin B [13]. The duration of antifungal therapy has not been optimally defined in clinical practice guidelines. On the other hand, immune status of the patient, extent of the disease, and stabilization of all clinical and radiographic manifestations have been proposed to be the main factors in decision making for duration of treatment [12]. An important issue that should be considered in the use of voriconazole is that it may lead to transient visual disturbances (44%) [13].

![Figure 3](image_url)
In one of the cases in our series, a partial visual impairment occurred in the third week of the treatment; however it resolved spontaneously within 72 hours after stopping voriconazole.

In conclusion, chronic invasive nongranulomatous FRS should be kept in mind in the presence of long-standing nonspecific sinonasal symptoms in immunocompetent individuals with a history of working in greenhouse farming.

**Competing Interests**

The authors declare that they have no conflict of interests.

**References**


[10] F. Pagella, F. De Bernardi, D. Dalla Gasperina et al., “Invasive fungal rhinosinusitis in adult patients: our experience in...


