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Role of postoperative systemic Itraconazole in Management of Allergic Fungal- Rhino Sinusitis (AFS)

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Background: Allergic fungal rhinosinusitis is an increasingly recognized cause of refractory chronic sinusitis, the clinical and pathological features of such diagnosis remains a matter of conjecture for which several theories have been offered. Most patients experience remittent disease despite corticosteroid therapy and aggressive sinus surgery.

Objective: To present our experience in managing twenty patients with AFS divided into two groups to compare the outcome after addition of oral itraconazole to our treatment protocol.

Methods: Twenty patients with clinically diagnosed (AFS), treated with functional endoscopic sinus surgery followed by postoperative systemic and topical nasal steroids with or without oral itraconazole for at least 3 months.

Results: Significant improvements in the itraconazole arm (group A) were noted regarding the early signs of relapse.

Conclusion: Systemic itraconazole is an effective adjunctive to systemic and topical steroid therapy.

Keywords: Allergic fungal rhinosinusitis, systemic antifungal, management outcome.

INTRODUCTION

Over the past 2 decades, allergic fungal sinusitis (AFS) has become increasingly prevalent. It is now believed to be an allergic reaction to aerosolized environmental fungi, usually of the dematiaceous species in an immunocompetent host. Most patients with (AFS) have history of allergic rhinosinusitis, approximately 5-10% of patients affected by chronic rhinosinusitis actually carry a diagnosis of allergic fungal sinusitis (AFS). The incidence of AFS appears to be impacted by geographic factors. Review of the world’s literature reveals the majority of sites reporting cases of AFS to be located in temperate regions with relatively high humidity.

Allergic fungal rhinosinusitis is generally recognized as a disease distinct from other fungal forms of sinusitis. Most common among adolescents and young adults (mean age at diagnosis 21.9 y), it is invariably associated with nasal polyposis and the presence of allergic fungal mucin. It is estimated that approximately 5% to 10% of those patients with chronic rhinosinusitis actually carries a diagnosis of AFS.

The exact pathophysiology of AFS remains a matter of conjecture for which several theories have been offered. One popular theory proposed by Manning and colleagues is based on the assumption that AFS exists as the nasal correlate of allergic bronchopulmonary aspergillosis, and suggests that several interrelated factors and events lead to the development and perpetuation of the disease.

Patients typically have gradual nasal airway obstruction and production of semisolid nasal crusts that, on inquiry,
match the gross description of allergic fungal mucin. The development of nasal airway obstruction may have been so gradual that the patient is unaware of its presence. Likewise, if facial dysmorphia is present, its progression is often so slow that its identification escapes the patient and family members. Pain is uncommon among patients with AFS and suggests the concomitant presence of a bacterial rhinosinusitis.\(^{(5)}\)

The accumulation of allergic fungal mucin eventually leads to the increasingly well-recognized radiographic findings characteristic of AFS.\(^{(6)}\) Bone erosion and extension of disease into adjacent anatomic areas was encountered in 20% of the patients and was more likely to occur in the presence of bilateral, advanced disease.\(^{(7)}\)

Fungal cultures of allergic fungal mucin may provide some supportive evidence helpful in the diagnosis and subsequent treatment of AFS, but must be interpreted with caution. It is important to realize that the diagnosis of AFS is not established or eliminated based on the results of these cultures.\(^{(3)}\) Histopathologically, it is impossible to definitively identify the species of various fungi that can be associated with the disease process, and concomitant fungal cultures are required to determine the particular fungus.\(^{(10)}\)

Medical control of the disease has made use of various combinations of antifungal medications, corticosteroids, and immunotherapy with varying degrees of disease control. Successful treatment of AFS requires that the treatment plan account for each factor responsible for the propagation of the disease. This comprehensive approach to management depends on complete removal of all fungal mucin (usually requiring surgery), and long-term prevention of recurrence through either immunomodulation (immunotherapy and/or corticosteroids) or fungistatic antimicrobials.\(^{(8)}\) Systemic antifungal therapy for AFS was initially proposed to control the theoretical potential for progression to invasive forms of fungal sinusitis.

As the potential for AFS recidivism is well recognized and ranges from 10% to nearly 100%. AFS recidivism appears to be influenced by long-term postoperative therapy. It is important to realize, however, that AFS recidivism remains high despite appropriate surgery and also postoperative medical therapy.\(^{(9)}\)

Antifungal therapy was often used in an attempt to provide some degree of control over recurrence of AFS. The early use of amphotericin B yielded to the use of less toxic agents, such as ketoconazole, itraconazole, and fluconazole, but the poor in vivo activity of these agents against dematiaceous fungi was soon discovered. Topical application of antifungal agents may hold some benefit in the control of postoperative recurrence, and studies of this form of treatment are currently underway.\(^{(10)}\)

Antifungal medications may cause potentially serious side effects, which warrant consideration when these preparations are used as a form of treatment for AFS. The well-known complications associated with amphotericin B include acute renal failure, anemia, agranulocytosis, acute liver failure, cardiopulmonary hypertension, and hemorrhagic gastroenteritis. Itraconazole and fluconazole offer a slightly safer form of antifungal therapy, but may still give rise to drug-induced cardiac dysrhythmias, hepatic dysfunction, urticaria, and anaphylaxis.\(^{(11)}\)

Our objective was to evaluate the response of the addition of systemic itraconazole (300 mg/ day for 3 consecutive months) to the traditional treatment regimen of AFS.

**PATIENTS AND METHODS**

This Prospective randomized controlled clinical study done on twenty patients with clinically diagnosed (AFS), they were treated with endoscopic sinus surgery followed by postoperative systemic and topical nasal steroids with or without oral itraconazole 300mg \(\text{day} \times 3 \text{ consecutive months}) to the traditional treatment regimen of AFS.

It was conducted at Ain Shams University Hospitals from May 2008 to December 2011, following Institutional Review Board approval. All patients were diagnosed as AFS based on a modification of the Bent and Kuhn criteria (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Criteria Used for the Diagnosis of Allergic Fungal Rhinosinusitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nasal polyposis.</td>
</tr>
<tr>
<td>2. Characteristic computed tomographic scan features.</td>
</tr>
<tr>
<td>3. Allergic mucin on histologic examination or characteristic appearance on endoscopic examination.</td>
</tr>
<tr>
<td>4. Raised total serum immunoglobulin E.</td>
</tr>
</tbody>
</table>

All patients were fully evaluated according to the following scheme:

- Full otorhinolaryngological history and physical examination, including fibro-optic flexible nasal endoscopy. Preliminary diagnosis of AFS was made based on the clinical finding of nasal polypos both unilateral and bilateral.
Computed tomographic (CT) scan axial and coronal cuts both soft tissue and bone window cuts to confirm the diagnosis with specific radiological findings (Fig.1).
- Laboratory investigations (liver trans-aminases), any patient with history of liver affection or elevation of liver enzymes was excluded from the study.
- Total serum immunoglobulin E (IgE).

The nature of the procedure was explained to the patients and an informed consent, with an emphasis on the possibility of hepatic affection secondary to chemical hepatitis, was obtained from all patients. Then the 20 patients were subdivided randomly into 2 equal groups Group A and Group B, 10 patients each randomly divided.

Functional Endoscopic sinus surgery was the primary treatment done for all patients in both groups by the same surgeons and following the same protocol. After surgery all patients (Both Group A and B) started systemic antibiotic ceftriaxon 1 gram/ day for five consecutive days along with saline nasal douches and paracetamol 500 mg as pain killer when needed.

In addition, immediately after endoscopic surgery, Oral prednisone was started at 60 mg/day, for 10 days immediately postoperative and reduced to a maintenance dose of 20 mg/day for 4 to 6 weeks along with topical nasal steroid (fluticasone propionate.2bucks in each nostril twice daily) in all patients.

Only group A patients (Group A) received oral Itraconazole 100 mg.3 tablets a day, (300 mg/day) for 3 consecutive months and it was stopped if liver enzymes were elevated during the monthly lab screening.

During follow up period ranging from 3-12 months (mean 6.4 months), all patients had regular follow up visits every one month for nasal examination including office endoscopy using 30 degree nasal scope or flexible fiber optic nasal scope with or without topical anesthesia (if needed) to document the findings and to detect any signs of recurrence and a chart was set to document the findings of each patient.

Our protocol was based on following up our patients for a relatively short period to detect the early signs of recurrence without changing the management protocol or increasing the doses of medications.

C.T. scan were done for all patients at 3 and 6 months postoperatively as part of the protocol of follow up and any gross findings were documented. Fig 2 demonstrates the post-operative findings after successful management with both surgery and systemic steroids and antifungal drugs.

In addition, liver transaminases done prior and then monthly afterwards to monitor for the hepatic side effects of itraconazole.
RESULTS

The current study included 20 patients, 7 males (30.8%) and 13 females (69.2%). Their age ranged from 16-56 years (mean =25.3 ± 3.43 years), clinically, all patients presented with nasal obstruction, with or without history of bronchial asthma. Examination of the nose showed nasal polyps along with thick greenish mucus secretions in almost all patients in both groups of the study.

In all patients, CT Scanning showed marked soft tissue sinus mucosal hyperplasia, usually throughout multiple sinuses, the allergic mucin is often seen as “hyperattenuating” on CT “it refers to increased imaging signal characteristic of high density material such as mineral or bone and is visualized as a white image in soft tissue cuts. Table 1 summarizes the demographic characteristics of group A (study group), while Table 2 summarizes the demographic characteristics of group B (control group).

At surgery, apart from nasal polyps, the characteristic features were the presence of thick greenish-brown mucus, which was difficult to remove by simple suction. Histopathology of the material submitted to the laboratory showed edematous nasal polyps and pale basophilic or eosinophilic mucin containing sloughed respiratory epithelial cells, chronic inflammatory cells with prominent eosinophils and fungal hyphae. No evidence of tissue invasion was recognized in any patient.

Six patients (60%) of group A (itraconazol treated group) had endoscopic and radiological improvement and this improvement was maintained during the follow up period, while three (30%) had recurrence of sinus and nasal polyps within 6 months, and one patient had to stop treatment after two months due to elevation of liver transaminases two folds above normal values.

On the other hand, eight patients (80%) of group B had evidence of recurrence of nasal polyps and radiological evidence of AFS during 6 months of follow up and the other 2 patients (20%) showed no clinical or radiological signs of deterioration during the follow up period.
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Table 2. Summarizes the demographic characteristics of group A (study group).

<table>
<thead>
<tr>
<th>Serial</th>
<th>Gender</th>
<th>Laterality</th>
<th>Age</th>
<th>Complications of treatment</th>
<th>Follow up at the end of 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>Bilateral affec-</td>
<td>17y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>Unilateral</td>
<td>35y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>Bilateral,</td>
<td>45y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>Bilateral</td>
<td>28y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>bilateral</td>
<td>33y.</td>
<td>Elevation of liver enzymes</td>
<td>Excluded before completing the follow up period</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>bilateral</td>
<td>40y.</td>
<td>-</td>
<td>Recurring polypi in both sides</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>Unilateral (rt.)</td>
<td>42y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>bilateral</td>
<td>37y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>bilateral</td>
<td>23y.</td>
<td>-</td>
<td>Recurrent nasal polyps in rt. side</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>bilateral</td>
<td>50y.</td>
<td>-</td>
<td>Radiological evidence of recurrence</td>
</tr>
</tbody>
</table>

Table 3. Summarizes the demographic characteristics of group B (control group).

<table>
<thead>
<tr>
<th>Serial</th>
<th>Gender</th>
<th>Laterality</th>
<th>Age</th>
<th>Complications of treatment</th>
<th>Follow up at the end of 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>Bilateral</td>
<td>39y.</td>
<td>-</td>
<td>Recurrent polypi</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>Bilateral</td>
<td>18y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>Bilateral,</td>
<td>54y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>Bilateral</td>
<td>38y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>Bilateral</td>
<td>22y.</td>
<td>-</td>
<td>Radiological recurrence</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>Unilateral (lt.)</td>
<td>47y.</td>
<td>-</td>
<td>Recurring polypi</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>Unilateral (rt.)</td>
<td>31y.</td>
<td>-</td>
<td>No evidence of recurrence</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>Bilateral</td>
<td>32y.</td>
<td>-</td>
<td>Evidence of bilateral recurrence</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>Bilateral</td>
<td>44y.</td>
<td>-</td>
<td>Recurrent nasal polyps</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>Bilateral</td>
<td>33y.</td>
<td>-</td>
<td>Radiological evidence of recurrence</td>
</tr>
</tbody>
</table>
DISCUSSION

AFRS is a chronic disease with a very high recurrence rate if not followed up closely. Recurrence occurs despite thorough surgical removal of all visible allergic mucin and diseased mucosa; the reasons for recurrence are unclear, many theories were set by different authors trying to explain for this high recurrence.

The ideal treatment should be safe, effective and simple with a high rate of success, and without major complications.

In accordance to the previous literature, our demographic data showed that 69% of the patients were females and the mean age of presentation was 25 yrs (±3 months) and this matches also with the results of Marple and Mabry.

All Patients were diagnosed as AFS based on a modification of the Bent and Kuhn criteria; as clinically, all patients presented with nasal obstruction, with examination revealed nasal polyps and thick greenish mucus secretions in almost all patients in both groups of the study, with radiological evidence of unilateral or bilateral opaque, multiple sinuses involvement and the characteristic hyper dense opacities in CT in all cases.

The predisposing factors and the exact pathogenesis of AFRS are uncertain and still unclear. Our patients tended to be healthy individuals with no or few comorbidities.

Traditionally, antifungals have been avoided in the treatment of AFS; the rationale underlying this approach includes the immune competence of the patient population, lack of fungal invasion, and the toxicity of the most effective antifungal drugs.

Despite surgical debridement and corticosteroid therapy, disease recurrence remains common in up to two-thirds of patients, and corticosteroid therapy is not infrequently associated with limiting side effects.

In the few available reports of antifungal therapy, the treatment was limited to a period of 1-3 weeks, which is far shorter than courses used for successful treatment for these organisms in any other site of affection. Hypothetically, antifungal therapy may aid in decreasing the fungal burden by limiting fungal re-growth after surgery, thus reducing the antigenic load and subsequent hypersensitivity response in these allergic processes.

Our results showed remarkable improvement in response to the addition of systemic itraconazole (300 mg/day for 3 months) to the treatment regimen of AFS patients with a postoperative short course of systemic steroid and maintenance with topical steroid spray, as 60% of group A had endoscopic and radiological improvement and this improvement was maintained during the follow up period, while 30% had recurrence of sinus and nasal polyps within 6 months, and only one patient (10%) developed elevation of liver enzymes and returned back to normal after few months of stoppage of itraconazole. On the other hand, 80% of group B had evidence of recurrence of nasal polyps and radiological evidence of AFS during 6 months of follow up.

In accordance to our results, Rains and Mineck reported using up to 400 mg of itraconazole a day and then tapering down to 200 mg a day over 3 months without any major side effects, they reported only a 4% prevalence of elevated liver enzymes.

Also, Denning et al. used itraconazole in a small group of patients (6 patients) and found that they were able to decrease the amount of prednisone required to prevent disease relapse and progression.

Also, similar results were obtained in a larger group of 55 patients by Stevens et al. who performed a randomized double-blind controlled study of itraconazole for 8 months versus standard systemic corticosteroid therapy and were able not only to decrease the steroid requirements but improve several surrogate markers of pulmonary function, including exercise tolerance, FEV1, and chest radiograph improvement.

So according to our results we propose that prolonged antifungal therapy should be instituted in all patients with AFS to achieve good results regarding the rate of recurrence and the need for high doses of systemic steroids in order to control the symptoms.

But we were confronted with some limitation such as; the incidence of many patients with hepatic affection in our community and the fact that oral antifungal drugs always carry the risk of initiating a fatal attack of drug induced hepatitis, which necessitates exclusion of many patients before the start of the treatment, this might need further follow up of our patients for longer periods and documentation of the course of their disease, as longer follow up is definitely needed to assess for the need of booster doses or addition of more medications such as immunotherapy or systemic steroid maintenance.

CONCLUSION

Despite the relatively short follow up period in the current study, Systemic itraconazol is an effective adjunctive to systemic and topical steroid therapy during the early post-operative course of management of Allergic fungal sinusitis.
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REFERENCES


