A prospective case series evaluating efficacy and safety of combination of itraconazole and potassium iodide in rhinofacial conidiobolomycosis

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Abstract

Background Rhinofacial conidiobolomycosis (RFC) is an uncommon subcutaneous fungal infection producing painless swelling with grotesque deformity of the face. Although there are case reports and small case series; there are very few prospective studies evaluating treatment outcome and long-term follow-up.

Objective To evaluate the safety and efficacy of combination of itraconazole (200 mg twice daily) and saturated solution of potassium iodide (SSKI) in patients with RFC.

Methods Ten patients of RFC were studied over a period of 5 years. Diagnosis was confirmed by clinical, histopathological, and microbiological evaluation. Conidiobolus was cultured in four cases and in the rest of the cases, the histopathology was suggestive of RFC. They were treated with itraconazole (200 mg twice daily) and SSKI and followed up for a minimum of 1 year after stopping treatment.

Results The mean age was 38.7 years and the mean duration of symptoms was 22.4 months. Males were predominantly involved (9 : 1). Seven patients responded to the combination treatment, five had complete resolution and two had good improvement (50–75%); however, in two patients the response was minimal (<25% regression of the swelling) and one patient did not show any improvement after 6 months of treatment.

Conclusion Combination of itraconazole and SSKI is an effective treatment modality for RFC with relatively faster onset of action, low relapse rates, and minimal adverse effects. It can be considered as first-line treatment in patients with RFC.

Introduction

Rhinofacial conidiobolomycosis (RFC) or subcutaneous zygomycosis or rhinoentophthoromycosis is a chronic granulomatous fungal infection involving the mucosa and subcutaneous tissues of the nose and face. It is caused by Conidiobolus, a saprophytic fungus that is ubiquitous in distribution and is transmitted by traumatic inoculation of the nasal mucosa with dust or soil containing spores.¹,²

The infection begins as a swelling of the inferior turbinates, with symptoms of nasal obstruction, nasal discharge, and pain due to extension to the paranasal sinuses.³⁻⁴ Clinically the extent of involvement can be divided into three phases. In phase I, involvement is limited to the nasal cavity, paranasal sinuses, and pharynx. In phase II, infection extends to the surrounding subcutaneous tissues, causing facial swelling with involvement of the lips. In phase III, muscles, bones, and viscera are affected.⁴

Despite the ubiquitous distribution of the fungus, RFC is relatively uncommon with approximately 199 cases reported worldwide.⁵⁻⁵ There are very few/small case series and no prospective studies evaluating the treatment
outcome and follow-up of these cases.\textsuperscript{5–10} Therefore, we endeavored to undertake a prospective study of these cases and their management at our centers.

\textbf{Methods}

This was a prospective study of 10 cases of RFC seen at our centers during a span of five years (2008–2012). The diagnosis in all the cases was confirmed after histopathology and culture from nasal mucosa and skin. All the patients were started on itraconazole 200 mg twice a day and saturated solution of potassium iodide (SSKI) 1 g/ml (i.e., 1 drop = 67 mg) starting with five drops thrice a day, which was gradually titrated to a maximum of 30 drops thrice a day depending on patient tolerance. All the patients were given the treatment for a minimum of three months; if the patient had >25\% improvement, the treatment was continued until two months after clinical improvement and in case of no response, alternative drugs were offered to the patients. The treatment response and adverse effects were monitored every month during therapy and the patients were followed up for a minimum of one year after stopping the treatment.

\textbf{Results}

The clinico-epidemiological details and therapeutic outcome are given in Table 1. All the patients were from rural and semi-urban areas in and around the Punjab. The age of the patients ranged from 24 to 65 years (mean age 58.7 years); the mean duration of illness was 22.4 months (6–48 months). All the patients were engaged in agricultural or outdoor occupations, and the initial symptoms were nasal (discharge and pain); however, patients could not recall history of trauma before onset of symptoms/signs. The patients presented to us with an asymptomatic gradually progressive, firm to hard sharply demarcated, subcutaneous indurated swelling on the dorsum of the nose and adjoining cheek area (Figs. 1 and 2), and four patients presented with facial elephantiasis (Fig. 3). In patients with minimal swelling of the nose, anterior rhinoscopy showed lateral nasal wall diffuse swelling and inferior turbinate hypertrophy. There was no significant lymphadenopathy, and the systemic examination was normal in all the patients. Complete blood counts showed eosinophilia in seven patients (differential eosinophil count; 10–25\%); the rest of the parameters and biochemistry were normal. Serology for human immunodeficiency virus was negative. Almost all the cases had consulted various specialists, and five had undergone surgery after they were diagnosed as polyps and fungal sinusitis. All had received various antibiotics earlier but with no improvement; however, none were using local or systemic steroids/immunosuppressants.

Non-contrast computed tomography showed soft tissue swelling of the nasal dorsum and nasal cavity tissues in all the patients, and all the sinuses were opacified with soft tissue mass in four patients with facial elephantiasis. Extra sinus extension to adjacent soft tissue was also seen, but there was no bone erosion.

The histopathology was consistent with RFC in all the patients with features of chronic granulomatous dermatitis in the deep dermis. The inflammatory infiltrate was composed of histiocytes and eosinophils. Twisted and collapsed hyphae with irregular branching and Splendore–Hoeplli phenomenon were seen in six cases (Fig. 4). KOH preparation of nasal biopsy tissue revealed broad, aseptate, thin-walled ribbon-like hyphae with wide-angle branching in three cases, and culture on Sabouraud’s agar was positive (Conidiobolus) in four cases.

Seven patients responded to treatment; five had complete resolution with almost complete disappearance of facial/nasal swelling (Fig. 5), and two had good improvement (50–75\%) (Fig. 6); however, in two patients the response was minimal (<25\% regression of the swelling), and one patient did not show any response after three months of combination. All the seven patients with significant improvement started responding after two months, and therapy was continued until 6–9 months. None of these patients relapsed in the 1–2 years of follow-up.

At the end of six months, the patients with minimal response had negative fungal culture and periodic acid Schiff stain, but histopathology showed changes suggestive of chronic mixed inflammation with fibrosis. Amphoterin B was started in two of them who improved significantly after one month of therapy, but they were unable to continue due to financial constraints, and both relapsed after stopping it. They were continued on SSKI and fluconazole 200 mg/d for six months, which stabilized the swelling, and then patients were lost to follow-up. One patient did not respond to the combination treatment, could not afford amphoterin B or Voriconazole, and stopped coming for follow-up. We observed that patients with facial elephantiasis had a less satisfactory response as compared to those without it (Table 2). All patients with facial elephantiasis had residual deformity after treatment and were advised reconstructive surgery.

Adverse effects associated with itraconazole and SSKI were seen in five patients. These were nausea, vomiting, diarrhea, abdominal pain, and transiently increased hepatic enzyme levels. Two patients developed acneiform eruption. The gastrointestinal complaints improved after a decreasing dose of SSKI and transaminitis (elevated hepatic enzymes) improved after decreasing the dose of itraconazole from 400 to 200 mg/d.
Table 1  Demographic and management details of the patients

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Duration of disease</th>
<th>History of nasal surgery</th>
<th>Culture</th>
<th>Treatment</th>
<th>Duration of treatment (months)</th>
<th>Response at end of treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28/M</td>
<td>8 months</td>
<td>No</td>
<td>Conidiobolus</td>
<td>Itraconazole and SSKI</td>
<td>6</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>2</td>
<td>56/M</td>
<td>2 years</td>
<td>No</td>
<td>Conidiobolus</td>
<td>Itraconazole and SSKI</td>
<td>9</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>3</td>
<td>41/F</td>
<td>1 year</td>
<td>No</td>
<td>No growth</td>
<td>Itraconazole and SSKI</td>
<td>6</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>4</td>
<td>30/M</td>
<td>2 years</td>
<td>No</td>
<td>Conidiobolus</td>
<td>Itraconazole and SSKI</td>
<td>6</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>5</td>
<td>32/M</td>
<td>1 year</td>
<td>No</td>
<td>Conidiobolus</td>
<td>Itraconazole and SSKI</td>
<td>6</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>6</td>
<td>54/M</td>
<td>3 years</td>
<td>Yes/removal of hypertrophied inferior turbinate</td>
<td>Conidiobolus</td>
<td>Itraconazole and SSKI</td>
<td>9</td>
<td>50–75% improvement</td>
</tr>
<tr>
<td>7</td>
<td>24/M</td>
<td>1.5 years</td>
<td>Yes/ polypectomy</td>
<td>No growth</td>
<td>Itraconazole and SSKI</td>
<td>12</td>
<td>50–75% reduction in swelling</td>
</tr>
<tr>
<td>8</td>
<td>27/M</td>
<td>2 years</td>
<td>Yes</td>
<td>No growth</td>
<td>Itraconazole and SSKI</td>
<td>6</td>
<td>25% improvement</td>
</tr>
<tr>
<td>9</td>
<td>30/M</td>
<td>1.5 years</td>
<td>Yes (FESS)</td>
<td>No growth</td>
<td>Itraconazole and SSKI</td>
<td>6</td>
<td>25% improvement in swelling</td>
</tr>
<tr>
<td>10</td>
<td>65/M</td>
<td>4 years</td>
<td>Yes/FESS</td>
<td>No growth</td>
<td>Itraconazole and SSKI</td>
<td>6</td>
<td>No improvement in swelling</td>
</tr>
</tbody>
</table>

FESS, functional endoscopic sinus surgery; SSKI, saturated solution of potassium iodide.
Rhinofacial conidiobolomycosis is a progressive subcutaneous granulomatous infection caused by *C. coronatus*, *C. incongruus*, and *C. lampraugesa*. It is generally divided into four subtypes (Table 3). Clinical features start with unilateral nasal stuffiness followed by swelling of the nose, nasolabial folds, cheeks, lips, and neck. Subsequently, symptoms of dysphagia and nasal obstruction supervene, and rarely the palate, paranasal sinuses, and pharynx may be involved. The most serious impact of the disease is the gross disfigurement and pressure effects of the swelling on adjacent tissues. Although there are reports of a progressive destructive course of the disease with necrosis of the overlying skin, involvement of the underlying bone, and sinus formation leading to mutilation, no case of a mutilating, progressive course was seen in our study.

The initial and most common symptom is unilateral nasal obstruction, mass, or discharge. Patients usually present to otorhinolaryngology (ENT) specialists, and nasal examination may show indolent swelling of the nose, nasolabial folds, cheeks, lips, and neck. Subsequently, symptoms of dysphagia and nasal obstruction supervene, and rarely the palate, paranasal sinuses, and pharynx may be involved. The most serious impact of the disease is the gross disfigurement and pressure effects of the swelling on adjacent tissues. Although there are reports of a progressive destructive course of the disease with necrosis of the overlying skin, involvement of the underlying bone, and sinus formation leading to mutilation, no case of a mutilating, progressive course was seen in our study.

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Disease. This was seen in five of our cases too, who were misdiagnosed as cellulitis, nasal polyps, abscess, and fungal sinusitis, and had undergone surgery.

Clinically, it should be differentiated from rhinoscleroma, rhinosporidiosis, lymphedema, benign and malignant tumors, and lymphoma of the nasal cavity; therefore, mycological and histological examinations are essential for confirmation of diagnosis. The diagnosis of Conidiobolus infection is generally based on histologic examination because cultures for the causative organism are negative in more than 85% of cases.4,5 In our study as well, we could isolate the fungus only in 40% of the cases.

The treatment of RFC has not been well-defined because the disease is infrequently reported. Although a number of antifungals have been used and reported as effective; the choice of the best antifungal agent, its dosage and duration are unclear.4 Daily high-dose antifungal therapy and months of continuous treatment are required for successful management, and this may sometimes be difficult due to poor compliance resulting from adverse effects and drug cost.3,4,8,11 Many antifungal drugs, such as SSKI, amphotericin B, imidazole derivatives (fluconazole, ketoconazole, terbinafine, and itraconazole), or a combination of these drugs,2,4,7–13 have been used for the treatment of RFC with variable results. The available literature shows considerable variations in antifungal susceptibility in diverse isolates of C. coronatus. Two studies reported antifungal susceptibilities of six isolates of C. coronatus against amphotericin B, ketoconazole, micafungin, fluconazole, and flucytosine, and all the isolates were resistant to the antifungals tested.14,15 In another study, three isolates of C. coronatus showed very low MIC and MFC values against amphotericin B.16

**Table 2** Difference in the clinical features and treatment outcome of patients with facial elephantiasis vs stereotypical rhinofacial conidiobolomycosis

<table>
<thead>
<tr>
<th></th>
<th>Facial elephantiasis</th>
<th>Stereotypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>Mean 33 months; median 24 months (24–48 months)</td>
<td>Mean 22.4 months; median 12 months (range 6–48 months)</td>
</tr>
<tr>
<td>Previous nasal surgery</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Response</td>
<td>Excellent – 0, Good – 1, Minimal – 2, No improvement – 1</td>
<td>Excellent – 0, Good – 1</td>
</tr>
<tr>
<td>Drugs</td>
<td>SSKI, itraconazole, amphotericin B</td>
<td>SSKI and itraconazole</td>
</tr>
</tbody>
</table>

SSKI, saturated solution of potassium iodide.

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Table 3 Four subtypes of rhinofacial conidiobolomycosis

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotypical</td>
<td>Nasal symptoms of obstruction, nasal mass, coraza or epistaxis, and/or central facial swelling</td>
</tr>
<tr>
<td>Facial elephantiasis</td>
<td>Gross facial disfigurement and loss of function superimposed on stereotypical type</td>
</tr>
<tr>
<td>Atypical</td>
<td>Facial involvement other than nasal mucosa/skin or infection of another cutaneous site (i.e., foot)</td>
</tr>
<tr>
<td>Systemic</td>
<td>Non-cutaneous/non-sinus fungal infection</td>
</tr>
</tbody>
</table>

patients responded favorably to SSKI and oral itraconazole; however, the response was not uniform and universal. Two patients had minimal improvement, and one was non-responsive to the combination treatment.

SSKI is a useful option for patients in developing countries because it is cheap, safe, gets localized to site of inflammation, and has fibrinolytic activity as well as indirect antifungal effects. However, we have observed that the treatment response with SSKI is delayed (4–6 months), and this slow response along with adverse effects causes a high attrition rate; so we decided to combine SSKI with itraconazole to expedite the clinical response rate. Itraconazole, besides its excellent antifungal activity, also has anti-tumorigenic effects, inhibits angiogenesis, increases interferon γ and affects the hedgehog pathway, which may play a role controlling the inflammation and swelling in RFC. The mean duration of therapy in our patients was 8.7 months. Although relapses have been reported after successful treatment of swelling, we did not observe any relapse in seven patients with good to excellent response in the 1–3 years follow-up.

Two patients with minimal response (<25%) had good response to amphotericin B. However, RFC is a localized non-life-threatening infection, and amphotericin B is not commonly used because of the toxicity, inconvenience of administration, and due to cost.

Surgical resection is seldom helpful in the initial stages of the disease as it may hasten the spread of infection and causes mutilation and fibrosis, which further leads to poor response to treatment and relapses. Five of our patients had undergone nasal/sinus or facial (incision and drainage) surgery before the diagnosis, and three of these patients had poor response/relapsed after stopping treatment. However, facial reconstructive surgery is useful in patients with residual deformity after treatment.

Successful management of infections relies on early diagnosis; we found that the patients who were diagnosed within one year of the disease and had not undergone any surgical procedures before the initiation of treatment responded better than the patients with >2 years of disease duration and previous nasal/sinus surgeries. In the present study, the combination of itraconazole and SSKI was effective in 70% of patients. There are no controlled trials comparing various antifungals with each other or combination with monotherapy. Although synergistic antifungal activity between these drugs has not been proven, we presume that combination therapy is a better option and further studies are warranted to determine the true efficacy of these combinations. There is no consensus about the duration of treatment, but it must be continued for at least six months or until >75% reduction in swelling.

Our study has shortcomings, such as small sample size and no controls/comparison with monotherapy, which need to be addressed in future studies. We observed that a combination of itraconazole and SSKI is an effective treatment modality with a relatively faster onset of action, low relapse rates, and minimal adverse effects. It can be considered as first-line treatment in patients with RFC. Treatment should be started early to avoid complications such as facial elephantiasis and obstruction and to decrease the cost of treatment as well as the morbidity.

References


