CASE REPORT

TREATMENT OF SEVERE CHROMOBLASTOMYCOSIS WITH ITRACONAZOLE AND 5-FLUCYTOSINE ASSOCIATION

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SUMMARY

Chromoblastomycosis is a chronic human melanized fungi infection of the subcutaneous tissue caused by traumatic inoculation of a specific group of dematiaceous fungi through the skin, often found in barefooted agricultural workers, in tropical and subtropical climate countries. We report the case of a male patient presenting a slow-growing pruriginous lesion on the limbs for 20 years, mistreated over that time, which was diagnosed and successfully treated as chromoblastomycosis. Besides the prevalence of this disease, treatment is still a clinical challenge.

KEYWORDS: Chromoblastomycosis; Itraconazole; 5-Flucytosine; Subcutaneous mycoses.

INTRODUCTION

Chromoblastomycosis (CBM) is a chronic human melanized fungi infection of subcutaneous tissue caused by traumatic inoculation of a specific group of dematiaceous fungi (usually Fonsecaea pedrosoi or Cladophialophora carrionii) through the skin. It has been described worldwide, but it is most commonly seen in tropical or subtropical climates. It may be encountered as an occupational-related disease, mainly in male barefooted-agricultural workers.

Differential diagnoses may include infectious diseases, such as blastomycosis, paracoccidioidomycosis, leishmaniasis and verrucose tuberculosis, and non-infectious disorders, as sarcoidosis and psoriasis. We report a patient from the state of Rio Grande do Sul with CBM diagnosed by histology, and who responded successfully to oral itraconazole (ITZ) and 5-flucytosine (5-FC) combined therapy.

CASE REPORT

A 55-year-old male agricultural worker presented with a 20-year-old, slow-growing, pruriginous and erythematous plaque with well-defined borders and covered by “black dots”, extending from the left ankle to the left mid thigh (Fig. 1-A). His medical history was remarkable only for the diagnosis of insulin-dependent diabetes mellitus since he was 40 years old. Several ointments had been used to treat the condition, as well as oral ITZ, fluconazole (FCZ) and terbinafine (TBF), with no major improvement. No fungal growth was obtained after culture of biopsy specimens. Melanized fungi cells were seen in hematoxylin and eosin tissue sections as shown in Fig. 1-B. Clinical and histological findings were compatible with the diagnosis of severe CBM, with presence of clustered muriform cells. The disease severity, according to QUEIROZ-TELLES et al. score was severe. Treatment with oral ITZ 400 mg daily and 5-FC 2 grams q.i.d. was initiated. Within two months, dramatic clinical improvement was observed, and by the end of 12 months complete clinical healing of the lesion was achieved (Fig. 2). Follow-up of the laboratorial exams were performed every three months and included blood cell count, creatinine and liver function panels, and showed no alterations until the last consultation (Table 1).

DISCUSSION

CBM is a therapeutic challenge for which there is no treatment of choice. Several drug options are suggested, based on reports of non-comparative studies and case series, rather than randomized controlled trials. Treatment may depend on the etiological agent, size and extent of the lesions, the patient’s individual tolerance, status of the immune system and economic features, but is often associated with low cure rates and high relapse rates. Besides that, clinical, mycological and histopathological data can be used to guide appropriate antifungal drug choice.

Small lesions in the early stages can be treated with surgical resection.
with curettage and desiccation. Treatments with carbon dioxide laser, cryotherapy and topical heat also have been reported. However, recurrences are common. Moderate and severe forms, with widespread lesions, usually require systemic treatment. While amphotericin B, thiabendazole, 5-FC and ketoconazole are variably effective in this condition, ITZ and TBF demonstrated the best results at high doses for 6-12 months. However, a cure is difficult to achieve, and prolonged remission is an acceptable outcome. Given the high relapse rate of the disease, therapeutic combinations may increase the cure rate. In our patient, systemic antifungal treatment with ITZ associated with 5-FC was used for 12 months with excellent response.

Due to the lack of new antifungal compounds, in the 1970s the combination of antifungal drugs was considered for treatment of subcutaneous mycoses. 5-FC - a pyrimidine derivative, with main action in inhibiting the synthesis of nucleic acids of the fungal cells, active in vitro and in vivo against yeasts (Candida albicans and Cryptococcus neoformans, Aspergillus sp. and dematiaceous fungi) - was the only drug that had no activity directly to the fungal membrane and that could be combined with other antifungal substances.

Based on the additive effect observed in vitro, BOPP introduced in 1976 the combination of intravenous amphotericin B with 5-FC in the treatment of CBM. This combination proved to be advantageous...

Table 1: Laboratorial exams of the chromoblastomycosis patient

<table>
<thead>
<tr>
<th>Exams</th>
<th>Date</th>
<th>08/28/09</th>
<th>10/19/09</th>
<th>12/17/09</th>
<th>04/06/10</th>
<th>06/18/10</th>
<th>10/04/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC*</td>
<td></td>
<td>4,79 mil</td>
<td>4,74 mil</td>
<td>4,84 mil</td>
<td>4,92 mil</td>
<td>4,75 mil</td>
<td>5,22 mil</td>
</tr>
<tr>
<td>Hb**</td>
<td></td>
<td>12,5</td>
<td>13,3</td>
<td>13,6</td>
<td>13,7</td>
<td>13,3</td>
<td>13,9</td>
</tr>
<tr>
<td>Leucocytes</td>
<td></td>
<td>8550</td>
<td>6350</td>
<td>7180</td>
<td>8070</td>
<td>8170</td>
<td>10330</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>1,06</td>
<td>1,12</td>
<td>1,2</td>
<td>1,19</td>
<td>1,11</td>
<td>1,07</td>
</tr>
<tr>
<td>TGP</td>
<td></td>
<td>12</td>
<td>23</td>
<td>18</td>
<td>17</td>
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<td>17</td>
<td>20</td>
<td>19</td>
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<td>18</td>
</tr>
</tbody>
</table>

*RBC = Red blood cells; **Hb = Hemoglobin.
over monotherapy with 5-FC\textsuperscript{12}. However, the related nephrotoxicity of amphotericin B and prolonged period of hospitalization for drug administration have motivated the search for less toxic regimens. The association of two oral compounds, 5-FC and thiabendazole, was tried with enthusiastic results\textsuperscript{13,14}.

The combination of ITZ and 5-FC, although assessed in a small number of patients, was very effective even in severe forms of subcutaneous mycoses\textsuperscript{9,10,19}. Pharmacological data on antifungal drugs demonstrated an additive effect against fungi - where 5-FC acts by causing suppression of the yeast’s DNA synthesis and ITZ acting on the fungi’s cytoplasmatic membrane - by inhibiting the synthesis of ergosterol, an important substance for fungal growth\textsuperscript{16}. Despite an insufficient number of cases to compose a detailed comparison, the combined therapy of ITZ and 5-FC may be an excellent option for severe or unresponsive cases of CBM after monotherapy with ITZ or terbinafine. Due to the difficulty in acquiring 5-FC in Brazil at present, the accomplishment of a comparative study involving a larger number of patients is missing.

Finally, it is important to consider that treatment success depends also on an early diagnosis and the choice of the appropriate antifungal agent.

RESUMO

Tratamento de cromoblastomicose severa com a associação itraconazole e 5-flucitosina

Cromoblastomicose é uma infecção fúngica crônica do tecido subcutâneo causada pela inoculação traumática de um grupo específico de fungos através da pele, encontrados eventualmente em trabalhadores do campo descalços em países de clima tropical e subtropical. Relatamos aqui o caso de um paciente do sexo masculino com uma lesão dermatológica de crescimento lento e pruriginosa nos membros inferiores por 20 anos, diagnosticada e tratada com sucesso para a cromoblastomicose. Apesar da prevalência desta doença em nossa região, o tratamento ainda é um desafio.

CONFLICTS OF INTEREST

Nothing to report.

REFERENCES