Squamous Cell Carcinoma Derived From Chronic Chromoblastomycosis in Brazil

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Background. Chromoblastomycosis (CBM) is a chronic fungal infection caused mainly by the melanized fungi Fonsecaea species. The chronic lesions may be predisposed to develop into cancer, the most serious complication of the disease.

Methods. In this report, 7 cases of squamous cell carcinoma (SCC) resulting from chronic CBM in patients from Maranhão in the Brazilian Amazon are described.

Results. The 7 patients presented with SCC that resulted from chronic CBM, caused by Fonsecaea species >10 years’ duration. The malignant lesions occurred independent of the antifungal therapy and all patients underwent curative amputation, except for 1 patient who developed metastases in the inguinal and intra-abdominal lymph nodes and thigh muscles. A majority of previous reports have focused on the malignant transformation of CBM described in only 1 patient each. This is a first report describing a group of patients from a single Brazilian state.

Conclusions. Here, we provide new epidemiologic data on malignant CBM lesions, an endemic disease that is seemingly neglected worldwide. We reinforce the idea that typically chronic lesions may be predisposed to turn malignant.

Keywords. chromoblastomycosis; squamous cell; carcinoma; melanized fungi; Fonsecaea spp.

Melanized or dematiaceous fungi are typically ubiquitous, often found in soil and decaying plants [1–3]. They cause severe infections, even in patients without metabolic or immune disorders. Black fungi from the order Chaetothyriales and family Herpotrichiellaceae mainly cause chromoblastomycosis (CBM), the most common form of subcutaneous mycosis in addition to sporotrichosis and mycetoma. CBM is characterized by chronic cutaneous and/or subcutaneous lesions at the site of fungal entry secondary to trauma. It is seen in rural areas of tropical and subtropical countries, especially Madagascar, South Africa, and Latin America (Venezuela, Brazil, and Mexico), and interestingly, is more common in males, possibly due to their greater extent of physical activity [4, 5]. The lesions frequently arise from injuries, particularly in the lower limbs, which are generally more exposed to the fungus in soil and decaying plants. The condition initially presents as a solitary papular nodule, worsening to a wart or vegetating (friable and easily bleeding) plaque resembling a cauliflower, occasionally with a tumor-like appearance. However, other patterns may also be observed (eg, scars and ulcers). There appears to be remarkable polymorphism in the presentation of lesions, where the most aggressive and disabling manifestation is possible malignant transformation. However, this extreme is considered rare by some authors [5–7], likely due to the lower number of reports to date. The most frequent complication is bacterial secondary infection, but the most severe complication remains malignant transformation [8, 9]. Here, we demonstrate that malignancy may be more common in CBM than shown by current data, comprising individual case reports. Thus, we aim to draw the reader’s attention to a secondary condition that could be life-threatening.
Here, we describe 7 cases of malignant transformation of CBM in Maranhão state, part of the Brazilian Amazon. We also provide detailed literature about previously reported cases.

**CASE REPORTS**

A total of 7 men, aged 55–81 years, from Maranhão State, Brazil (ethics protocol 220.342) were diagnosed with chronic CBM between 1997 and 2013. The diagnosis was confirmed by isolation of Fonsecaea species on Sabouraud dextrose agar. Figure 1 shows representative photographs of lesions from all patients, including verrucous plaques (n = 3), tumoral lesions (n = 2), cicatricial lesions (n = 1), and infiltrative plaques (n = 1). The diagnosis of cancer was made by histopathology (Figure 2) in all patients, confirmed as well-differentiated (42.86% of cases) and poorly differentiated squamous cell carcinoma (SCC) (57.14%). Of the 7 patients, 6 developed SCC during or after treatment with itraconazole. Interestingly, 1 patient was not treated with antifungal agents and the disease worsened to cancer after an episode of osteomyelitis. Patient details are presented in Table 1. Subsequently, 5 patients had the affected limb amputated, 1 patient was cured after excision of the malignant lesion, and 1 patient had intra-abdominal metastasis, progressing to death 10 months after amputation of the affected lower limb.

**DISCUSSION**

The first report of malignant transformation of CBM lesions was described by Caplan in 1968 [10] in a patient from Nicaragua, presenting with vegetating and verrucous plaque lesions on both legs, the left thigh, and right hand, which evolved over approximately 11 years. Additional cases of tumors derived from CBM were subsequently described, summarized in Table 2 [5, 10–18]. Most previous reports have focused on malignant transformation of CBM, being described in only 1 patient each. This is the first report describing a group of patients from a single state in Brazil. Regarding evolution of the disease in cases previously described, 70% were cured after surgical excision. In our study, 83.3% were cured after resection of the lesion, but 3 patients had recurrence of CBM lesions. These patients remain under treatment with itraconazole. We believe that CBM is often neglected, considered as an infectious disease mainly affecting poor patients involved in labor related to farming, for example, cultivation of the babaçu coconut (Orbignya phalerata) [19].

Metastasis of cutaneous epithelial neoplasms is relatively uncommon, but in widespread lesions, metastasis may occur to the lungs and deep brain [12]. Interestingly, a primary lesion on the lateral region of the foot metastasized to the thigh and lymph nodes in the inguinal and intra-abdominal regions in 1 of our patients. Complications were observed 3 months after amputation of the affected limb due to the tumor, and the patient is currently receiving chemotherapy and radiotherapy. Other neoplasms of a nonepithelial lineage have also been observed in chronic lesions of CBM, for example, acral lentiginous melanoma without nodal or distant metastases [14]. Other cases of neoplastic transformation without detailed description.
of characteristics of the injuries and time elapsed, etiological agent, treatment, and clinical outcome have been reported [7, 9, 20].

Despite evidence of malignant transformation of previous scars or chronic wounds, such developments are considered relatively uncommon [9]. Several causes of chronic wounds may predispose the patient to Marjolin ulcers with subsequent neoplastic degeneration. Characteristically, SCC arises in burn scars, traumatic wounds, varicose ulcers, unhealed lesions of lupus vulgaris, tropical ulcers, and osteomyelitis with cutaneous dissemination [21–23]. Paracoccidioidomycosis, leishmaniasis, and lobomycosis are also examples of diseases in which skin involvement proves important, with chronicity marked by diagnostic delay, due to low morbidity and mortality rates. A delay in healthcare seeking of a few months or years results in a greater likelihood of complications of a noninfectious nature, as observed in neoplastic transformation [21–26].

It is difficult to determine whether the chronic inflammation associated with CBM acts as a carcinogen or co-carcinogen. The presence of polymorphonuclear cells and activated macrophages promotes the release of enzymes and free radicals that have been reported to experimentally induce malignant transformation of cells in culture [15, 20]. However, the pathophysiological basis for this process has not been well elucidated. Chronic inflammation and metabolic products of phagocytosis are often accompanied by excessive production of reactive oxygen and nitrogen species, which potentially damage DNA, lipoproteins, and cell membranes. Inflammatory cells, particularly neutrophils, also release arachidonic acid metabolites including prostaglandins and leukotrienes, which may promote cell damage. The expression of COX-2 is induced by inflammatory cells and may have some impact on carcinogenesis [27].

From another point of view, it is worth mentioning that voriconazole, a second-generation triazole, may be related to the development of skin cancer, particularly SCC, following photosensitivity reactions in patients, when it is used for prophylaxis of invasive fungal infections [28], especially after lung transplant [29]. The mechanism of voriconazole-induced skin cancer probably involves production of its primary metabolite, voriconazole N-oxide [30]. However, this hypothesis was not considered with regard to the chronic use of itraconazole. Some authors demonstrated that itraconazole reduces malignant lesions in mice by inhibiting the Hedgehog signaling pathway, which is an important pathway for pathogenesis of basal cell carcinoma. Overall, the protective effect or the occurrence of skin cancer with chronic use of itraconazole remains unclear [31].

Considering our clinical findings, we believe that the age of the lesions, injury severity, and vegetating lesions may be involved in the increased risk of malignant transformation. Indeed, the suspicion of malignant transformation should arise.
### Table 1. Description of Patients Who Developed Malignancy in Lesions of Chromoblastomycosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Clinical Lesion</th>
<th>CBM/Lesion Location</th>
<th>Neoplastic/Lesion Location</th>
<th>Disease Duration, y</th>
<th>Neoplasia Type</th>
<th>Infectious Agent</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>Verrucous plaque, ulcerated</td>
<td>Left leg</td>
<td>Left leg</td>
<td>15</td>
<td>Well-differentiated SCC</td>
<td><em>Fonsecaea</em> spp</td>
<td>Healing after surgical resection</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>Verrucous plaque, ulcerated</td>
<td>Left leg</td>
<td>Left leg</td>
<td>20</td>
<td>Well-differentiated SCC</td>
<td><em>Fonsecaea</em> spp</td>
<td>Healing after surgical resection</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>Tumoral lesion</td>
<td>Right leg</td>
<td>Right leg</td>
<td>26</td>
<td>Poorly differentiated SCC</td>
<td><em>Fonsecaea</em> spp</td>
<td>Death after metastasis to the lower abdomen</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>Tumoral lesion</td>
<td>Right arm</td>
<td>Second finger of right hand</td>
<td>20</td>
<td>Poorly differentiated SCC</td>
<td><em>Fonsecaea</em> spp</td>
<td>Following the CBM</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Verrucous plaque</td>
<td>Left leg</td>
<td>Left leg</td>
<td>11</td>
<td>Poorly differentiated SCC</td>
<td><em>Fonsecaea</em> spp</td>
<td>Healing after surgical resection</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>Cicatricial lesion</td>
<td>Right arm</td>
<td>Right arm</td>
<td>10</td>
<td>Well-differentiated SCC</td>
<td><em>Fonsecaea</em> spp</td>
<td>Following the CBM</td>
</tr>
<tr>
<td>7</td>
<td>88</td>
<td>Verrucous plaque, ulcerated</td>
<td>Right leg</td>
<td>Right leg</td>
<td>30</td>
<td>Poorly differentiated SCC</td>
<td><em>Fonsecaea</em> spp</td>
<td>Healing after surgical resection</td>
</tr>
</tbody>
</table>

Abbreviations: CBM, chromoblastomycosis; SCC, squamous cell carcinoma.

### Table 2. Summary of Reported Cases of Chromoblastomycosis With Malignant Transformation

<table>
<thead>
<tr>
<th>Authors (Ref)</th>
<th>Sex</th>
<th>Age, y</th>
<th>Disease Duration, y</th>
<th>Geography</th>
<th>Site Affected</th>
<th>Agent</th>
<th>Neoplasia Type</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caplan [10]</td>
<td>M</td>
<td>60</td>
<td>11</td>
<td>Nicaragua</td>
<td>Left leg and thigh</td>
<td><em>Fonsecaea pedrosoi</em></td>
<td>Epidermoid anaplastic carcinoma</td>
<td>Healing after surgical resection</td>
</tr>
<tr>
<td>Foster &amp; Harris [11]</td>
<td>M</td>
<td>Middle-aged</td>
<td>&gt;10</td>
<td>Solomon Islands</td>
<td>Shoulder</td>
<td>Not reported</td>
<td>Well-differentiated SCC</td>
<td>Healing after surgical resection</td>
</tr>
<tr>
<td>Foster &amp; Harris [11]</td>
<td>M</td>
<td>66</td>
<td>20</td>
<td>Australia</td>
<td>Left knee</td>
<td>Not reported</td>
<td>Well-differentiated SCC</td>
<td>Death after widespread metastases</td>
</tr>
<tr>
<td>Takase et al [12]</td>
<td>M</td>
<td>62</td>
<td>8</td>
<td>Japan</td>
<td>Lung</td>
<td><em>F. pedrosoi</em></td>
<td>SCC</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gon &amp; Minelli [14]</td>
<td>M</td>
<td>70</td>
<td>30</td>
<td>Brazil</td>
<td>Left lateral malleolus</td>
<td><em>F. pedrosoi</em></td>
<td>Acral lentiginous melanoma (Clark IV)</td>
<td>Healing</td>
</tr>
<tr>
<td>Esterre et al [15]</td>
<td>F</td>
<td>61</td>
<td>6</td>
<td>Madagascar</td>
<td>Left ankle</td>
<td><em>Cladophialophora carrionii</em></td>
<td>Moderately differentiated SCC</td>
<td>Healing</td>
</tr>
<tr>
<td>Torres et al [16]</td>
<td>M</td>
<td>72</td>
<td>31</td>
<td>Mexico</td>
<td>Buttocks, perineum, groin</td>
<td><em>F. pedrosoi</em></td>
<td>Moderately differentiated epidermoid carcinoma</td>
<td>Death</td>
</tr>
<tr>
<td>Jamil et al [17]</td>
<td>M</td>
<td>69</td>
<td>21</td>
<td>Malaysia</td>
<td>Right hand</td>
<td><em>F. pedrosoi</em></td>
<td>SCC</td>
<td>Healing after surgical resection</td>
</tr>
<tr>
<td>Rojas et al [18]</td>
<td>F</td>
<td>63</td>
<td>18</td>
<td>Venezuela</td>
<td>Lower left limb and back</td>
<td><em>C. carrionii</em></td>
<td>SCC</td>
<td>Death</td>
</tr>
</tbody>
</table>

Abbreviations: Ref, reference; SCC, squamous cell carcinoma.
when new lesions, mainly ulcers (not related to secondary infection), appear during the healing phase of the disease, reinforcing the need for biopsy.

In this context, the management of difficult-to-treat infectious lesions raises concerns, as complete cure is rarely achieved in severe cases. In this scenario, CBM is noteworthy, as injuries involving large areas, warty or tumor-like lesions, and chronicity leads to the maintenance of an inflammatory process for a long period of time, spanning decades, which may eventually result in malignant transformation, followed by loss of limbs or even death in cases of disseminated disease.

We conclude that histological examination of follow-up biopsy should be performed mainly when new ulcers appear during the healing process of CBM.

Notes

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References