

Chromoblastomycosis Leading to Squamous Cell Carcinoma: An Overlooked Outcome of a Neglected Tropical Disease

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PRACTICE POINTS

- Chromoblastomycosis is recognized by the World Health Organization as a neglected tropical disease and principally affects agricultural workers in tropical and subtropical regions.
- Long-standing or refractory chromoblastomycosis can lead to substantial morbidity, including lymphedema, secondary bacterial infections, extensive scarring, functional impairment, and squamous cell carcinoma (SCC).
- The development of SCC is thought to be related to chronic inflammation and prolonged disease duration (>10 years). Advanced cases may require extensive surgical excision or amputation.
- Early recognition with support of direct microscopy or histopathology, timely antifungal treatment (often with itraconazole), and a low threshold for repeat biopsy of new ulceration or rapidly changing lesions may prevent malignant transformation and disability.

Chromoblastomycosis is a neglected tropical skin disease acquired through traumatic inoculation of dematiaceous fungi. It is characterized clinically by a chronic granulomatous infection of the skin and subcutaneous tissue. Delays in diagnosis and limited access to antifungal therapy contribute to prolonged disease, recurrent inflammation, and debilitating sequelae. A rare but devastating complication

is squamous cell carcinoma (SCC) associated with long-standing lesions, which may necessitate extensive surgery or amputation and can be fatal. In this review, we summarize reported epidemiology and clinical risk factors for SCC complicating chromoblastomycosis. We also discuss plausible inflammatory mechanisms of malignant transformation and propose pragmatic clinical and public health interventions, including decentralized microscopy-based diagnosis, timely antifungal access, and biopsy-triggered surveillance of chronically inflamed lesions, to reduce preventable morbidity.

Chromoblastomycosis is a neglected tropical implantation mycosis caused by dematiaceous fungi that leads to substantial morbidity. This condition is diagnosed microscopically by visualizing the characteristic thick-walled, single, or multicellular clusters of pigmented fungal cells (also known as medlar bodies, muriform cells, or sclerotic bodies).¹ The main causative fungi varies by geographic region, but most commonly is caused by *Cladophialophora carrionii*, *Fonsecaea* species, *Phialophora verrucosa* species complex, and *Rhinochrysiella aquaspersa*.²⁻⁴ Standardized treatment guidelines have not been established, but itraconazole typically is considered first-line regardless of causative fungi.⁵ Terbinafine, other azoles, and topical immunomodulators, either as monotherapy or in combination, may be appropriate alternative or adjunctive options for refractory disease, although supporting data are limited.⁶⁻⁹

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Complications from chromoblastomycosis are common, particularly in long-standing, severe, or refractory disease. An analysis using billing codes in the United States found 14% (35/255) of hospitalized patients with chromoblastomycosis had lymphedema.¹⁰ In Mexico, 63% (32/51) of patients with chromoblastomycosis developed secondary bacterial infections.¹¹ Skin fibrosis and ankylosis also can occur and cause mobility issues and decreased quality of life. An infrequent but potentially life-threatening complication¹² is the development of squamous cell carcinoma (SCC) associated with chronic lesions, representing a preventable end-stage complication of delayed diagnosis and treatment (Figure).

In this review, we summarize reported epidemiology and clinical risk factors for SCC complicating chromoblastomycosis. We also discuss plausible inflammatory mechanisms of malignant transformation and propose pragmatic clinical and public health interventions, including decentralized microscopy-based diagnosis, timely antifungal access, and biopsy-triggered surveillance of chronically inflamed lesions, to reduce preventable morbidity.

Epidemiology and Risk Factors

The epidemiology of SCC developing from chromoblastomycosis is not well understood due to gaps in national and global surveillance. Some studies have found that 2% to 13% of patients with chromoblastomycosis developed SCC.^{4,11,13-15} Based on case reports and case series, a symptom duration of more than 10 years appears to be the most substantial risk factor for the development of SCC rather than host immune status.¹⁶⁻¹⁸ Severity, specifically the size of the injury, and vegetating lesions also have been suggested as risk factors for the development of SCC.¹⁶ Additionally, the appearance of new lesions (mainly ulcers not related to secondary infection) that appear during the healing phase should raise the suspicion of SCC and warrant a biopsy for evaluation.¹⁶

Pathophysiology

The exact mechanism of malignant transformation has not been elucidated, but histopathologic features suggest substantial epidermal proliferation. In some cases, this leads to pseudoepitheliomatous hyperplasia, a non-malignant hyperproliferative state that is an important differential HPV to leishmaniasis and lupus vulgaris.¹⁹ The chronic inflammation from long-standing chromoblastomycosis likely contributes to the further malignant transformation to SCC.

Polymorphonuclear cells and activated macrophages seen in chronic inflammation can promote the release of enzymes and free radicals that has led to malignant transformation *in vitro* but has not been investigated specifically in chromoblastomycosis.¹⁶ Additionally, chronic inflammation and metabolic products of phagocytosis often are accompanied by excessive production of reactive oxygen and nitrogen species, which can damage DNA, lipoproteins, and cell membranes. Other



FIGURE. A and B, Squamous cell carcinoma resulting from long-standing chromoblastomycosis on the forearm and lower extremity. C, Squamous cell carcinoma in a 44-year-old man from Indonesia following a 17-year history of chromoblastomycosis.

potential contributors include the expression of cyclooxygenase 2 and release of arachidonic acid metabolites (eg, prostaglandins, leukotrienes), which can damage the cell and promote carcinogenesis. It is not clear whether similar mechanisms account for the development of SCCs in other chronic skin inflammations or infections such as cutaneous tuberculosis or Marjolin ulcers.²⁰

Clinical and Public Health Interventions

Squamous cell carcinoma arising in the setting of chromoblastomycosis warrants prompt oncologic evaluation and definitive surgical management, which may require extensive surgical excision and, in advanced disease, amputation.^{14,17,18} Advanced malignant tumors can be difficult to manage and can result in death.^{21,22} Additionally, clinicians

should maintain a low threshold for biopsy in long-standing chromoblastomycosis, particularly when lesions demonstrate new ulceration, rapid growth, bleeding, pain, malodor, or failure to improve with appropriate antifungal therapy.¹⁶ Recurrent or new lesions after amputation may indicate persistent or recurrent infection and may require continued antifungal management alongside cancer care.¹⁶

Squamous cell carcinoma arising from chromoblastomycosis results after substantial diagnostic delays, allowing chronic inflammation to transform infection into malignancy. Separating benign inflammation-associated epidermal proliferation from transformation to SCC requires histopathologic skill. An assay based on increased expression of chromosome 15 open reading frame 48 (C15orf48), an immune regulatory protein, has been developed to aid in this distinction; however, it is not widely available.²³

Raising awareness of chromoblastomycosis among clinicians and communities, particularly in rural areas where the disease is more common, is critical to improve health care-seeking behaviors and expedite access to care pathways.² Furthermore, access and training on microscopy to diagnose chromoblastomycosis in decentralized areas can facilitate earlier diagnosis in primary health care settings rather than waiting for diagnosis in tertiary care settings, at which point disease usually is advanced. Global implementation of existing programs that use microscopy (eg, malaria in rural areas) can be partnered with frontline health worker cross-training on chromoblastomycosis diagnosis to improve appropriate identification of disease.²⁴ Finally, improving access to affordable antifungals, particularly itraconazole, is necessary along with further research into novel therapeutic strategies. Approaches that utilize local manufacturing and pooled procurement could help expand treatment availability in parallel with diagnostic improvement initiatives.²⁵

Final Thoughts

Squamous cell carcinoma resulting from chromoblastomycosis is a devastating complication, often leading to limb amputation. The true prevalence is unknown, but it occurs more commonly in long-standing disease without appropriate therapy. The appearance of new lesions or ulcers after initial improvement should increase suspicion and lead to biopsy and careful pathologic evaluation. Prevention of SCC requires increased clinical awareness, early diagnosis, and timely initiation of antifungal treatment. Enhanced surveillance among individuals with chromoblastomycosis would help to better understand its prevalence, associated risk factors, and impact on quality of life.

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