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## REVIEW ARTICLE

### CHROMOBLASTOMYCOSIS – REVIEW ARTICLE

\*Anuradha S. Kalabhavi

Department of Microbiology, SDMCMSH, Sattur, Dharwad 580009, India

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#### ABSTRACT

Chromoblastomycosis is a subcutaneous fungal infection. It is caused by the traumatic inoculation of the skin with pigmented saprophytic moulds. There has been frequent reporting of cases of chromoblastomycosis in recent times. This could be attributed to advances in mycology laboratory diagnostic methods. This has resulted in identification of a large number of species belonging to various genera. There has also been a rise in the immunodeficiency status in the community with more patients being diagnosed with conditions like diabetes mellitus which predisposes them to such rare infections. Also the modern medical therapies are increasing the load of immunodeficient patients which is making a large number of patients susceptible to such rare infections. Although infection is rarely fatal, it is characteristically chronic with a varied clinical presentation. To be diagnosed it requires strong suspicion from the clinician and vigilant observation of the microbiologist. There are several treatment modalities, which are often combined and include long courses of antifungals, surgical excision and destructive physical therapies. The availability of a large number of antifungal agents to treat these infections is rewarding to diagnose these infections. Therefore the clinical, microbiological and therapeutic aspects of Chromoblastomycosis are being reviewed here. We are also discussing the case report of a rare presentation of chromoblastomycosis as phagedenic ulcer.

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#### INTRODUCTION

Chromoblastomycosis, also called chromomycosis is a subcutaneous chronic mycosis caused by dematiaceous (black) fungi.<sup>1</sup> It is a slowly progressing localised fungal infection involving exposed parts of the body with no tendency for dissemination. It is characterised by crusted and raised lesions. The fungi present as sclerotic bodies in the lesions, which is a pathognomic feature of this disease. It is distributed worldwide. However it is most commonly seen in tropical and subtropical regions. It is often confused with other clinical conditions which present with polymorphic skin lesions. Chromoblastomycosis is often seen in people who are immunosuppressed or those suffering from malignant diseases. However it is also seen in healthy individuals. Chromoblastomycosis is difficult to treat. Small lesions can be surgically removed with wide and deep excision. Cryotherapy, topical heat therapy, systemic medications, and their combination have been reported to be effective.

#### Aetiology

The disease is caused by several darkly pigmented exogenous fungi of the form family Dematiaceae of the Hyphomycetes under phylum Deuteromycetes. The taxonomical position of causative agents of chromoblastomycosis is in the family Herpotrichiellaceae of the order Dothideales of class Bitunicate Pyrenomycetes i.e. Loculoascomycetes. Among the causative fungi *Fonsecaea pedrosoi* is the most prevalent, and *Phialophora verrucosa*, *Cladosporium carrionii*, *Fonsecaea compacta*, and *Rhinochrysiella aquaspersa* also occur in descending order of frequency. *Cladophialophora arxii*, *Exophiala spinifera*, *Exophiala dermatitidis*, *Exophiala jeanselmei*

and *Wangiella dermatitidis* are also less frequently associated with chromoblastomycosis.

#### Evolution of the term chromoblastomycosis

Chromoblastomycosis was identified in the early 1910s. Increasing number of fungal infections being diagnosed and increase in the number of predisposing conditions led to confusion. The concept of phaeohyphomycosis was introduced by McGinnis in 1983.<sup>2</sup> The differentiation among these diseases became more obvious. The features of Chromoblastomycosis make it a distinct clinical entity. The infection has to be differentiated from mycoses, caused by other dematiaceous fungi, such as mycetoma or phaeohyphomycosis. The term chromoblastomycosis is used for cases in which sclerotic bodies are present in tissue. Sclerotic bodies, also known as Medlar bodies, are globe-shaped, cigar-colored, thick-walled structures that are 4-12 µm in diameter. It was first described by Medlar in 1915.<sup>3</sup> It induces a purulent and granulomatous inflammatory reaction in tissue. Sclerotic bodies multiply by septate formation. The best name to define the disease was recommended as chromoblastomycosis by the International Society for Human and Animal Mycology (ISHAM).<sup>4</sup> The term chromoblastomycosis (chromo – coloured, blasto – budding, mycosis – fungal) was coined by Terra *et al* in 1922 to define a polymorphic fungal disease located on lower limbs, consisting of nodular or verrucous plaques which could probably ulcerate and develop into hyperkeratosis and acanthosis of the affected epithelial tissues.<sup>5</sup>

#### History

In 1911, Alexandrino Pedroso<sup>6</sup> described chromoblastomycosis when he observed presence of sclerotic/ muriform bodies in a patient in San Paulo, Brazil. The organism, isolated from nodular and ulcerated lesions of foot and leg was identified as phaeoid fungus, *Fonsecaea pedrosoi*. However his work was not published until 1920. Meanwhile, Max Rudolph, a German physician, living in Brazil, first described Chromoblastomycosis, in 1914. However, it was only in 1987, that his work was reported by Castro and Castro.<sup>7</sup> Max Rudolph

\*Corresponding author: Anuradha S. Kalabhavi  
Department of Microbiology, SDMCMSH, Sattur, Dharwad 580009,  
India

had published a preliminary communication where the first 6 cases of the disease were described. Rudolph had also isolated a dark-colored fungus from 4 of 6 patients. Rudolph thought this fungus was a type of blastomycete. 1 year later, Lane<sup>8</sup> and Medlar<sup>3</sup> described the pathognomic sclerotic cells and the histological aspects of the disease. They used the term verrucous dermatitis which is still followed as one of the synonyms of the disease. Sclerotic bodies were named as Medlar bodies, in honour of Medlar. The fungi widely accepted to cause chromoblastomycosis include *F pedrosoi*, *P verrucosa*, *C carrionii*, and *F compacta*.<sup>9</sup> Rare cases of chromoblastomycosis caused by *Rhinochadiella aquaspersa* and *Exophiala* species have also been reported, allowing the inclusion of these species among those that cause the disease.<sup>10, 11, 12, 13, 14</sup> A huge array of hitherto unidentified black fungal species are waiting to be listed as causative agents. Because of renewed interest in this condition more intensive and well directed efforts are being made world over to identify the isolates to species and subspecies level giving a new paradigm to the aetiology of chromoblastomycosis.

### Pathophysiology

Histopathologically the characteristic features of the disease include: pseudoepitheliomatous hyperplasia, fibrosis, microabscess formation in the epidermis along with the presence of pigmented sclerotic bodies. The histopathological appearance of these fungi is distinct. It consists of dark brown, subglobose, multicellular structures, 5 to 12 micrometer in diameter that divide by splitting along the septal planes by transverse septa. These structures are called as sclerotic bodies, medlar bodies, copper-pennies bodies or muriform cells. They are pathognomic of chromoblastomycosis. Sclerotic bodies are planate dividing yeast cells with formation of internal septa and are light yellow brown in colour giving a chestnut appearance. Mature cells have intersecting cross walls. They form an adaptive mechanism that facilitates survival of the organism in host tissues despite attack of defensive mechanisms. Hyphal strands are seen when the organism metastasises to other parts. Septate cells may be seen singly, in pairs or clusters. Melanin is produced in the cell walls of muriform bodies which results in a dark brown colouration that can be easily seen in histopathological section stained with haematoxylin and eosin. Melanin pigmentation of phaeoid fungi is also demonstrated by Fontana-Masson stain.

Most of the patients' exhibit organised mixed mycotic granulomas (OMMG), a granulomatous reaction modified by the presence of polymorphonuclear neutrophils. Black dots may be visible on the surface of lesions and represent sites where blood and fungal cells that is sclerotic bodies are expelled from the skin through transepidermal elimination which may be sampled for skin scrapings or culture. The infection usually follows a traumatic cutaneous injury that is often not remembered or realized by the patient. The infectious agents enter into the human body by contact with wood splinters or thorns. The fungi have been isolated from materials like plants, palm trees, grass, and soil in some countries.<sup>13</sup> A warty nodule is produced at the site of entry. The lesion is limited to the skin and the subcutaneous tissue at the site of implantation. Over many years the nodule grows centripetally. When it heals ivory colored scars are seen in the central parts of the lesion. Sometimes the disease spreads to the neighbouring healthy skin. It can involve whole limbs forming plaques. When nodular lesions predominate, the disease assumes a typical cauliflower aspect. Both lymphatic and cutaneous dissemination have been described. A new species of *Fonsecaea*, *Fonsecaea nubica*, morphologically similar to *F pedrosoi* and *F monophora*, has been described in association with chromoblastomycosis.<sup>15</sup> *Rhinochadiella aquaspersa* may also be a causative agent.<sup>16</sup>

### Epidemiology

It is distributed worldwide. However the incidence is greater in tropical and subtropical regions located between 30° N and 30° S.<sup>17</sup> A minute number of cases are also found in temperate climates, such as

in Japan, Canada, Finland, Romania and the Czech Republic.<sup>18, 19, 20, 21, 22</sup> However it is more frequent in warmer climates where people go barefooted and wear minimal clothes. It is more common in males compared to females, agricultural workers and in rural regions. It commonly occurs in North America, Central America, and South America. However chromoblastomycosis does occur worldwide, including Europe, England, India, South Africa, and Australia. The African country of Madagascar, reports the highest incidence. A large number of cases have also been reported in Japan. These fungi are widely distributed as saprophytes in soil and decaying vegetation in all types of climates. The mode of infection is by inoculation of phaeoid fungi into the cutaneous tissues through trauma. The infection is not transmitted from animals or between humans. It commonly affects farmers compared to other occupations.<sup>23</sup> It rarely leads to mortality. The severity of the disease governs the morbidity rate. Initially in the nodular phase, the disease is asymptomatic. When the nodules coalesce, it results in complications leading to formation of large plaques and sometimes it involves the whole limb. The common complications seen are ulceration, lymphedema, and secondary infection. Racial predilection has not been reported. A clear male predominance, is seen although a small number of reports describe similar male-to-female ratios. About 70% of cases are seen in men. The reason for male predominance is not clear. Men are assumed to be more commonly involved in agricultural work. They are more prone to injuries by self-inoculation. Women are more dedicated to house jobs. There may be an inhibitory effect of female hormones on the growth of fungi. This partially explains the relatively low number of cases in females. The disease is most commonly seen in the age group of 30-50 years. The incubation period lasts for several years. Therefore the number of children with chromoblastomycosis is very scarce. The disease is rarely found in children exposed to the same environmental conditions as adults. The entity is caused by several phaeoid molds identical in their tissue form (sclerotic bodies). In the humid tropical areas, *Fonsecaea pedrosoi* is the most common etiological agent whereas in dry and desert areas *Cladophialophora carrionii* predominates.<sup>24</sup> In the United States, *P. Verrucosa* is the most commonly isolated agent of chromoblastomycosis.

### Immunity

The host responses to fungal antigens occur at both cellular and humoral levels. Antibodies have been reported among the patients with different procedures like double diffusion in agar gel. The skin test antigens have been prepared in research settings and limited testing has been found reacting among patients diagnosed as chromoblastomycosis. Antibodies to the phaeoid fungi have been raised in rabbits to examine antigenic relationships among various species and to identify phaeoid isolates by exoantigen testing.

### Clinical presentation

Patients are usually asymptomatic. Patients visit hospital only in cases of secondary infection or elephantiasis. A previous unnoticed or unremembered trauma to the skin is often the site of infection. After several years a small, raised, erythematous, asymptomatic papule develops. It assumes a scaly and infiltrated aspect over several years. It generally leads to either of the 2 most common clinical variants: nodular or plaque. The surface is verrucous, in both types. Lesions spread laterally to contiguous healthy tissue. The verrucous lesions are frequently ulcerated and may be raised about 1 to 3 cm above the skin surface with rough irregular surfaces, giving a cauliflower like appearance and hence it is also called as verrucosa dermatitis. Satellite lesions may also develop because of autoinoculation. Over a long period of time it results in elephantiasis and involvement of the entire lower limb. It is differentiated from other infectious dermatoses namely, cutaneous leishmaniasis, sporotrichosis, cutaneous tuberculosis, and cutaneous mycobacteriosis by the verrucous aspect of the lesion. The disease usually remains localized to the area of the initial infection or neighbouring skin. Lymphatic and haematogenous dissemination may occur, producing metastatic lesions away from the

primary site. The nodular type of lesion normally develops into verrucous, pedunculated, cauliflower like florets. The plaque type spreads peripherally, with an active, raised border, leaving a central healed area with atrophic and yellowish scar tissue. Numerous black dots may be observed on the surface of both clinical variants. Commonly hemopurulent material covering small ulcerations is observed. A common variant, cutaneous localized chromoblastomycosis has been described. It is a well-circumscribed, slow-growing, annular, papulosquamous or papulosquamous- verrucous patch or plaque with no regression despite the use of topical antifungals.<sup>25</sup> These plaques may be atrophic.<sup>26</sup> Secondary bacterial infection may cause the lesion to acquire a characteristic ill odour. Secondary infection may lead to lymph stasis and consequently elephantiasis. Lesions in different stages of development can be found in old cases. Extracutaneous spread occurs because of haematogenous and lymphatic dissemination. Contiguous spread to the underlying bone may result in an osteolytic lesion.<sup>27</sup> The lower extremities are most commonly affected especially the feet. The hands, the arms, and the buttocks are also frequently involved, and sporadic reports mention lesions on the ears, the face, and the breasts. Auricular chromoblastomycosis due to *Fonsecaea pedrosoi*, the most common agent found in Brazil, has been described.<sup>28</sup> Morphological variants occur. Rarely, chromoblastomycosis may resemble sporotrichosis with verrucous nodules and a lymphatic distribution on the forearm expanding into verrucous plaques.<sup>16</sup> Chromoblastomycosis may also be evident as a large cauliflowerlike mass.<sup>29</sup>

#### Differential diagnosis

Chromoblastomycosis has to be differentiated from: Blastomycosis, lobomycosis, protothecosis, sporotrichosis, keratoacanthoma, tuberculosis verrucosa cutis, Hansen's disease, leishmaniasis, mycetoma, candidiasis, yaws, tertiary syphilis, paracoccidioidomycosis and phaeohyphomycosis. In case of chromoblastomycosis identification of the causative agent is made by cultural morphology and microscopic appearance of the sporulation pattern. It cannot be made by appearance of the sclerotic bodies alone.

#### Case report

A 35 yr old female farmer, presented with a history of skin lesion for last 15 years to the dermatology department in our institution. The lesion started as a small nodule on the right cheek which gradually increased in size. Patient later noticed ulceration with visualisation of underlying bone. A provisional diagnosis of basal cell carcinoma or subcutaneous fungal infection was made. Tissue specimen from edge of the lesion was sent to our laboratory for KOH mount and fungal culture. A bit was also sent for histopathology. Histopathological examination as well as PAS stain of section showed numerous branched, septate, dematiaceous hyphae and sclerotic bodies. Diagnosis of chromoblastomycosis was made. Growth appeared after 3 weeks of incubation at room temperature on SDA. The colonies were olive gray to black, with jet black reverse pigmentation. LPCB mount showed dark brown septate hyphae with branching and cladosporium type conidiation suggestive of *Fonsecaea pedrosoi*. Patient was put on oral fluconazole and she responded very well with complete healing of the ulcer. To our knowledge, chromoblastomycosis presenting as phagedenic ulcer on face is rare. Therefore we concluded that mycological investigation for all chronic ulcers should be recommended.

#### Laboratory diagnosis

The most useful test is the direct examination of 10% potassium hydroxide cleared lesion scrapings. Sclerotic bodies, also known as Medlar bodies are seen. They are thick-walled and cigar-colored. These cells are pathognomonic of chromoblastomycosis. But they do not give any specific information about the agent. Dematiaceous hyphae can also be observed. When the specimens collected include the black dots present in the lesions, it is easier to identify the

causative agent. Miranda *et al* in 2005 suggested the use of vinyl adhesive tape for collecting and identifying some types of deep-seated mycoses.<sup>30</sup> Here the infectious agents can be observed in the horny layer of the epidermis in transepidermal elimination events. The biopsy specimen is stained with haematoxylin and eosin, Giemsa stain and Fontana- Masson stain. Slow-growing, dark, velvety colony with a black obverse is seen on culture of the infectious agents. It is isolated on Sabouraud dextrose agar with actidione and other antibiotics. For identification of individual species various characteristics, including conidia production have to be observed. *Exophiala* species, however, seen as so called black yeasts are easily differentiated from other species by their yeast like black glistening growth in the primary culture. This yeast like appearance progressively changes to mycelial form with age and subcultures. The organism grown in liquid media also allows differentiation between *Exophiala* species and other fungi. The former produces yeast like growth while the others grow as small mycelial pellets. The final identification of phaeoid fungus is best studied on slide culture.

#### The conidiogenesis in important phaeoid fungal genera are as follows:

- |                   |   |
|-------------------|---|
| 1. Cladosporium   | Blastoconidia in chains                       |
| 2. Phialophora    | Phialides with collarettes                    |
| 3. Exophiala      | Annelides                                     |
| 4. Wangiella      | Phialides without collarettes                 |
| 5. Rhinocladiella | Annelides and Phialides                       |
| 6. Fonsecaea      | Symptodulae, also phialides and blastoconidia |

Serological tests are used exclusively for research matters, and they are not routinely used or available. A recently isolated, highly specific and sensitive immunoblotting method depicted a 54-kd antigen from *F pedrosoi* that may prove to be helpful in the study of the disease.<sup>31</sup> The black velvety colony has the same macroscopic appearance as the colonies of other chromoblastomycosis-causing agents (eg, *Cladosporium carrionii*, *Fonsecaea compacta*, *Phialophora verrucosa*, *Rhinocladiella aquaspersa*, and *Exophiala* species). Use of an ELISA might be useful to establish remission criteria in chromoblastomycosis caused by *C carrionii*.<sup>32</sup> Duplex polymerase chain reaction is a rapid and specific assay for identification of *Fonsecaea isolates*, mainly for the strains that are difficult to identify using morphological methods.<sup>33</sup> A rapid and sensitive assay for identification of pathogenic species of *Fonsecaea* without sequencing can be obtained using rolling circle amplification (RCA). This simple, sensitive, and low-cost method may prove practical.<sup>34</sup> Lymphoscintigraphy has been used to evaluate lymphedema, but it is not routinely used.<sup>35</sup> The experimental infection has been successfully produced in rats and mice by intraperitoneal inoculation. The cutaneous lesions of chromoblastomycosis in mice on histopathology show granulomas, muriform cells and necrotic foci. The murine model can be used for studying other aspects of infection, such as humoral and cellular immunological mechanisms during the evolution of disease, host resistance and efficacy of antifungal drugs used in this clinical entity.

#### Pathological findings

The cigar-colored fungi are easily seen in haematoxylin and eosin-stained sections in the cutaneous lesions. No special stains are needed. The typical finding is the pseudoepitheliomatous hyperplasia of the epidermis with a diffuse, lymphomononuclear inflammatory infiltrate in the dermis. There is typically a mixed tissue response to the fungus. The same section may also show true and pure abscesses or micro abscesses, granulomas, granulomatous reactions, and abscesses surrounded by a granulomatous reaction with giant cells.<sup>36</sup> Brown-colored, thick-walled fungal cells may be seen inside the giant cells. These muriform fungal cells may be single, 2-celled, or multiple-celled. This is a result of multiplication by septation rather than budding. Haematoxylin and eosin-stained section shows typical sclerotic bodies inside an abscess. Sclerotic bodies present as

round, thick-walled, cigar-colored structures. Transepidermal elimination of the fungal cells is the histologic counterpart of the black dots clinically evident in chromoblastomycosis lesions. In 2007 an unusual dermal response has been described by Jawitz *et al.*<sup>37</sup> It consists of dermal effacement by a spindle cell proliferation arranged in sweeping fascicles.

### Treatment

One of the most characteristic features of chromoblastomycosis is its refractoriness to treatment. Treatment options include oral itraconazole (as monotherapy or with oral flucytosine [5-FC]), locally applied heat therapy, cryosurgery, laser therapy, surgery and combination therapy.<sup>38</sup> Surgical excision of an early, solitary lesion is preferred. Successful treatment of severe chromoblastomycosis with itraconazole and 5-flucytosine association has been reported.<sup>39</sup> Flucytosine acts by inhibiting nucleic acid synthesis and is given orally as 50-150mg/kg per day, in four divided doses. Secondary drug resistance to flucytosine has been reported. Itraconazole can be used for long durations like 3 to 6 months. A combination of flucytosine with amphotericin B, itraconazole and liquid nitrogen has been used effectively. Terbinafine as a daily dose of 500 mg can also be used. At present 2 antifungal agents, itraconazole and terbinafine have significantly improved the treatment and prognosis of the disease. Therapeutic success is related to the causative agent, as well as the clinical form and severity of the chromoblastomycosis. Multiple treatment modalities are often combined, such as long courses of antifungals, surgical excision, and destructive physical therapies, because chromoblastomycosis is one of the most difficult deep mycotic infections to eradicate. The most common complications of chromoblastomycosis are ulceration, secondary bacterial infection, lymphedema that leads to elephantiasis, and myiasis. Leech bites may predispose to bacterial infection. Rare cases of malignant transformation (squamous cell carcinoma) of chromoblastomycosis have been documented in the literature. The prognosis for chromoblastomycosis tends to be good, especially for small and localized lesions. When the affected area is large, as in severe cases, cure is difficult, although control is easily achieved. Cicatricial and unaesthetic scars are the rule after the disease is eliminated.

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