Journal of Advances in Microbiology Research

E-ISSN: 2709-944X
P-ISSN: 2709-9431
JRM 2020; 1(2): 61-66

www.microbiojournal.com
Received: 11-02-2020
Accepted: 16-03-2020

**Ezemba Chinyere C**
Department of Microbiology, Chukwuemeka Odumegwu Ojukwu University, Anambra, Nigeria

**Anyaogu Ebuka V**
Department of Microbiology, Chukwuemeka Odumegwu Ojukwu University, Anambra, Nigeria

**Etikudike Victor O**
Department of Microbiology, Chukwuemeka Odumegwu Ojukwu University, Anambra, Nigeria

**Osuala Oluchi J**
Department of Pharmaceutical Microbiology and Biotechnology Madonna University Elele Rivers, Nigeria

**Ezemba**
Chychy Gilgal Laboratories and Consultancy Services. Ichida, Anambra, Nigeria

**Arinze S**
Department of Microbiology, Chukwuemeka Odumegwu Ojukwu University, Anambra, Nigeria

**Madukwe Chiamaka J**
Department of Microbiology, Chukwuemeka Odumegwu Ojukwu University, Anambra, Nigeria

**Correspondence**
**Ezemba Chinyere C**
Department of Microbiology, Chukwuemeka Odumegwu Ojukwu University, Anambra, Nigeria

# Pathogenesis and *Immunology of Chromoblastomycosis*: A review

**Ezemba Chinyere C, Anyaogu Ebuka V, Etikudike Victor O, Osuala Oluchi J, Ezemba, Arinze S and Madukwe Chiamaka J**

**Abstract**
Chromoblastomycosis (CBM), commonly known as chromo mycosis. It is regarded as the most popular mycoses which is caused by melodized or brown-pigmented fungi, and a popular implantation fungal infections. It's a chronic skin and subcutaneous tissue infection caused by a fungus. A traumatic injury and the inoculation of microorganisms from a specific group of Dematiaceous fungi are the most common causes of infection (usually *Fonsecaea pedrosoi, Phialophora verrucosa, Cladophialophora carrionii).* Lesions of chromoblastomycosis can be veracious, nodular, tumoral, plaque-like, or atrophic. It can be said to be common in tropical and subtropical areas, although there have been a few cases reported in temperate areas as well. The condition primarily affects current or past farm laborers, primarily men, and frequently has crippling consequences. CBM can lead to inability to labor due to fibrotic sequelae and a slew of clinical problems, and if not caught early enough, the condition can be resistant to antifungal treatment. Direct examination, culture, and histopathology are used as diagnostic procedures. Despite a number of therapeutic options, including extensive courses of antifungals, surgical excision, and damaging physical therapy, the disease remains one of the most difficult to eradicate deep mycotic infections. This review seeks to elaborately discuss the pathogenesis and immunological response to Chromoblastomycosis.

**Keywords:** Chromoblastomycosis, Direct examination, Lesions, Mycotic infections, Fungi

## Introduction
Implantation mycoses, also known as "subcutaneous mycoses," can be defined as one of heterogeneous fungal infections caused by a variety of different types of transcutaneous trauma [1]. Global infections like implantation phaeohyphomycosis (PHM) and ento-mophthoromycosis, as well as endemic mycoses like sporotrichosis, eumycetoma, lacaziosis (lobomycosis), and chromoblastomycosis (CBM), are among the implantation mycoses [2]. Also known as chromomycosis, CBM is one of the most popular implantation fungal infections, being the most common of the fungal diseases because of the presence of the melanized or brown pigmented fungi. CBM predominantly present in persons living in tropical and subtropical zones around the planet. This disease is distinguished by:

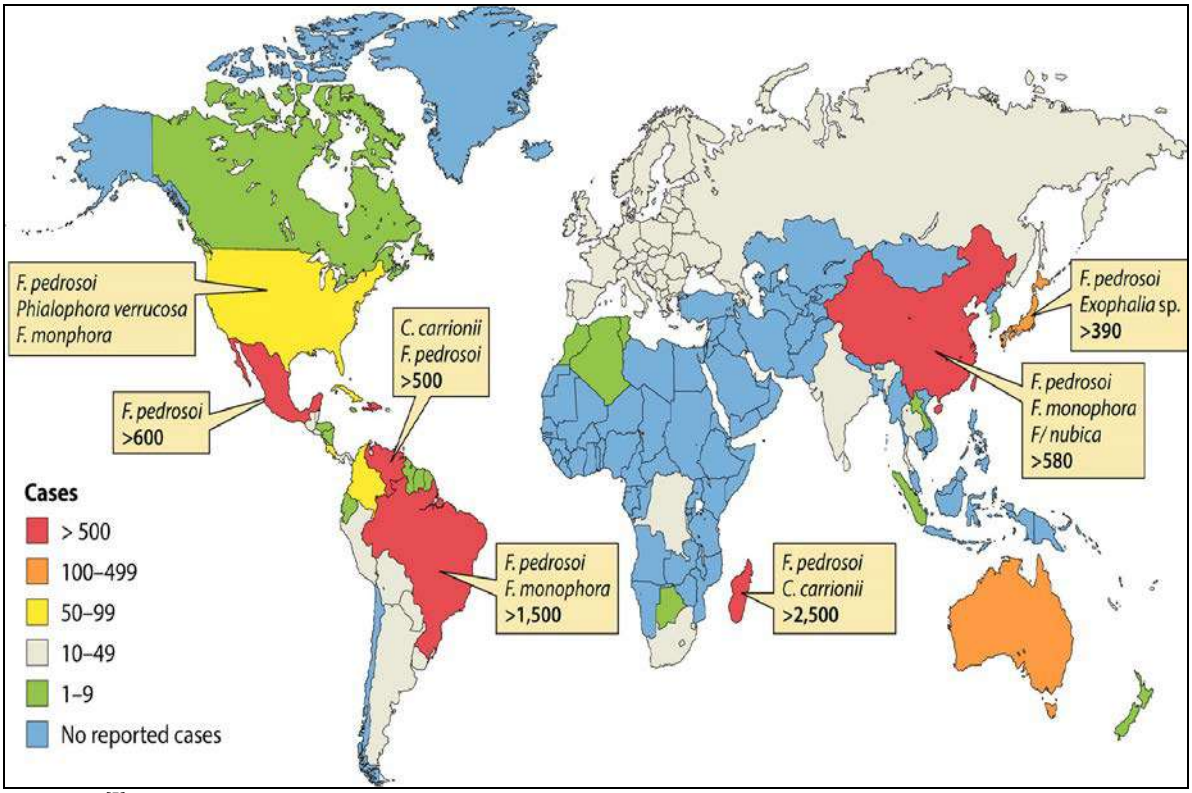
1. Traumatic inoculation by implantation from the environment which can lead to initial an initial cutaneous lesion at the site of inoculation
2. Progressive and chronic implication of cutaneous and subcutaneous tissular structures, and fibrous granulomatous response with embedded microabscesses and often tissue proliferation
3. A non-protective T helper type 2 (Th2) immune response with ineffective humoral involvement
4. Formation of muriform cells (morphological aggregation of two to four fungal cells with transverse and longitudinal septation) [3].

Clinically, CBM lesions are of different forms hence they are being misdiagnosed as other viral and noninfectious disorders. Advanced cases of this disease can result to this disease may lead to inability to perform labor due to fibrotic sequelae and some clinical complications that if not attended to early, can lead to an obstruction in therapy.
Chromoblastomycosis is an orphan illness that is often overlooked. It has a global burden equivalent to or greater than mycetoma, and it is largely an occupational fungal illness like mycetoma. It should be classified as a truly neglected disease, as defined by the WHO, because of its global spread, impact on the poor, and refractoriness [4].

**Geographic Distribution of Chromoblastomycosis**

The genera *Fonsecaea* and *Cladophialophora* are the most frequently associated with CBM. *Rhinocladiella* infections are uncommon, but a few cases have been linked to members of the *Phialophora* and/or *Exophiala* genera. Infections with *F. pedrosoi* and *C. carrionii* are common in tropical and subtropical endemic areas around the world. Several publications have been written about the reservoirs of the most prevalent CBM agents: *Fonsecaea pedrosoi* is found in humid climates, whereas *C. carrionii* is found in semiarid areas [5].

CBM, like the majority of endemic mycoses, is not a reportable disease. As a result, neither the incidence nor the prevalence of this mycosis can be accurately estimated. Instead, statistics from surveys and case studies reveal that the prevalence of CBM varies from 1:6,800 in Madagascar to 1:8,625,000 in the United States (United States). The disease is seen primarily between the latitudes of 30°N and 30°S in tropical and subtropical regions of the world. Latin America, the Caribbean, Africa, and Asia account for the bulk of instances. The majority of the patients come from Brazil, Mexico, Venezuela, India, Australia, and southern China [5].




**Source:** [5]

**Fig 2:** Worldwide distribution of Chromoblastomycosis based on the series of reported cases

**Pathogenesis and Host Defense**

According to recent research, the reduced fungal clearance in CBM infections is as a result an increase in the virulence activities or virulence factors of the causative organisms and its pathogenicity [6]. Certain virulence factors such as modification of the cell surface, Modifications of the cell surface, hydrophobicity, remodeling of the fungal cell wall, secretion of proteolytic and hydrolytic enzymes, adhesion molecules, incorporation of aromatic hydrocarbons, assembly of siderophores, and especially the presence of melanin are found in the causative organisms for the disease. Most of the virulence and features of the pathogenicity of Chromoblastomycosis infections are similar to those found in other pathogenic fungus diseases. Melanin, muriform cells, cell adhesion, and hydrophobicity are all important factors in the pathogenicity of CBM [6].

The host immunological mechanisms against CBM are poorly characterized, including activities of the immune cells and hormones. Some research has demonstrated the importance of the cellular response in the host-fungus interaction, implying that fungal persistence in situ is the primary driver of CBM evolution [6].

**Immunology of infection**

The invasive form of the fungus (hyphae, spores, or sclerotic bodies) has yet to be identified. The presence of hyphae and spores of *F. pedrosoi* was discovered on the surface of *Mimosa pudica* thorns. Inside the thorns, however, sclerotic entities comparable to those identified in patient tissues were discovered [7]. Preparing a special medium that causes the formation of sclerotic bodies allowed researchers to study various types of mycelium.

In this case of CBM, neutrophils and macrophages are critical cells in the immune response. Patients show a typical granulation reaction regulated by polymorph nuclear neutrophils. Dendritic cells are the initial line of defense. Fungal antigens were found in the cytoplasm of dermal macrophages. Dermal dendrocytes and Langerhans cells showed similar characteristics. The expression of CD 86, HLA-DR, and CD 83 receptors is higher in CBM patients' cells. Dendritic cells produce TNF-, IL-10, and IL-12 in response to spores. Dendritic cells produce large amounts of IL-10 and small amounts of IFN- after being stimulated with *F. pedrosoi* antigen in patients with a severe form of CBM [7].

In the cell-mediated response, CD4+ and CD8+ T lymphocyte populations, B lymphocytes, and macrophages have their roles to play. The infection of thymus-depleted mice gave rise to the development of CBM lesions, while mice lacking NK cells and macrophages and healthy mice, recovered the lesions 4-6 weeks after the initial infection. The resultant lesions possessed a significant amount of sclerotic cells. Antibodies *to F. pedrosoi* antigens and delayed hypersensitivity were found. The immune response in CBM is influenced by lymphocytes, as evidenced by the fact that lymphocyte transplant from healthy mice led in full recovery within two months [7]. Further research revealed that immunizing mice with live *F. pedrosoi* spores causes a massive inflow of CD4+ lymphocytes into the lymph glands. After further stimulation with a specific antigen, activated T cells proliferate in vitro and release IFN-. Furthermore, in mice lacking CD4+ cells, there are more severe alterations, delayed hypersensitivity, and reduced IFN- production in CBM compared to wild strains. The foregoing parameters are unaffected by the absence of CD8+ cells. In humans, a similar situation exists, where people with severe forms of the disease produce significant amounts of IL-10, have low levels of IFN-, and isolated lymphocytes are unable to multiply [7]. Small quantities of IL-10 are discovered in mild cases of the condition, as well as a high level of IFN- and enhanced lymphocyte proliferation [7]. Studies show that CD4+ T lymphocytes that produce IFN- play a critical role in the immune defense against *F. pedrosoi*.

The presence of causative organisms of CBM reduces the expression of MHC-II and CD8 receptors on macrophages, as well as nitric oxide release by these receptors, according to Hayakawa *et al.* (2017) Using a specially produced media, da Silva et al. demonstrated that the disruption of Langerhans cell maturation was caused by spores, not sclerotic cells, as evidenced by a decrease in the expression of CD40 and B7-2 receptors on their surface.

Langerhans cells can phagocytize one, rarely two *F. pedrosoi* spores, whereas dermal macrophages can internalize four to five spores. Although they may be near sclerotic bodies, Langerhans cells do not phagocytize them [7]. The ability of macrophages to phagocytize depends on the fungus that causes CBM infection, as well as the presence of complement proteins. In comparison to *P. verrucosa* and *C. carrionii*, *F. pedrosoi* and *Rhinocladiella aquaspersa* are phagocytized more frequently. *P. verrucosa* and *R. aquaspersa* are particularly susceptible to complement-dependent phagocytosis. The mortality of fungal cells is unrelated to their phagocytosis. Against *F. pedrosoi*, *C. carrionii*, and *P. verrucosa*, there was little or no cytotoxic effect. Langerhans cells, on the other hand, block the formation of hyphae from both sclerotic cells and spores, regardless of phagocytosis [8]. Discovered that melanin in *F. pedrosoi* cells inhibits macrophage nitric oxide production.

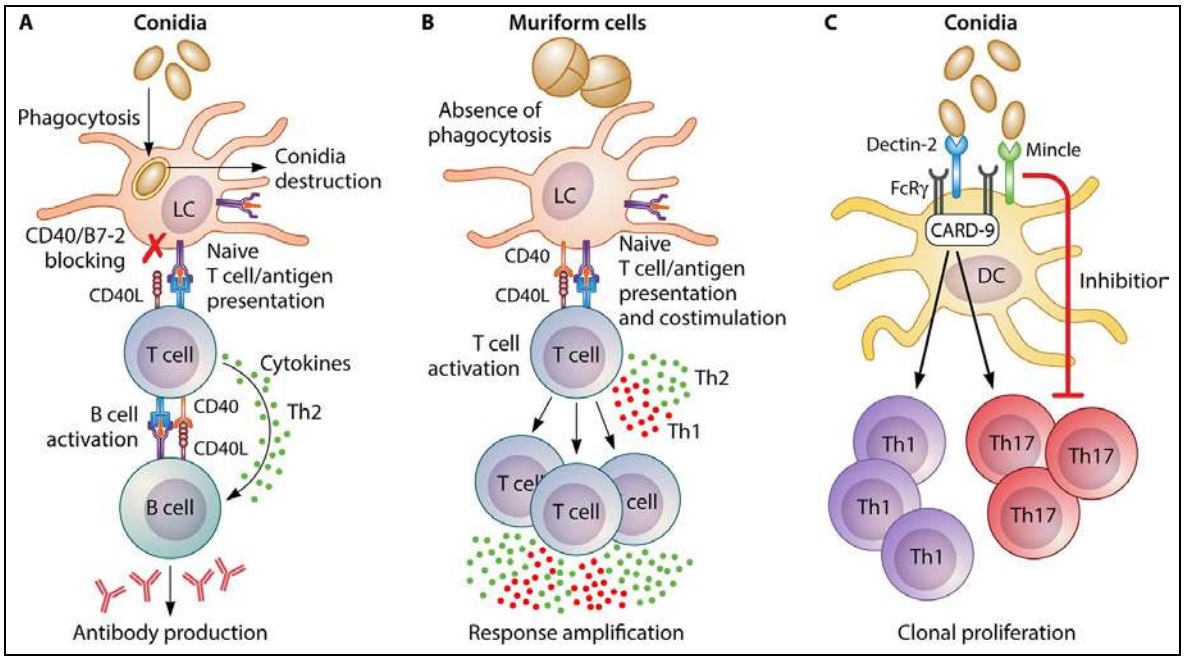



**Fig 2:** CBM immunology

Langerhans cells (LCs) found at the epidermis are usually the first line of defense, and their reactions to conidia and meristematic cells are different.

(A) First, the they recognize the conidia then engulfment and destruction of the conidia sets in. this is followed by costimulatory molecule inhibition. T cells may be exposed to conidial antigens, causing B cells to generate antibodies against CBM pathogens.

(B) In the presence of muriform cells, there may be activation and multiplication of naïve Tcells hence improving the immunological response even if the LCs do not carry out the engulfment.

(C) The C-type lectin dectin-2 or Mincle can be used to recognize conidia by dendritic cells (DCs). However, the dectin-2 route leads to T-cell activation with proliferation of Th1 and Th17 cells, while Mincle signaling blocks the same process, in a clear indication of PRR antagonism of the immunological response following identification of CBM fungus by DCs.

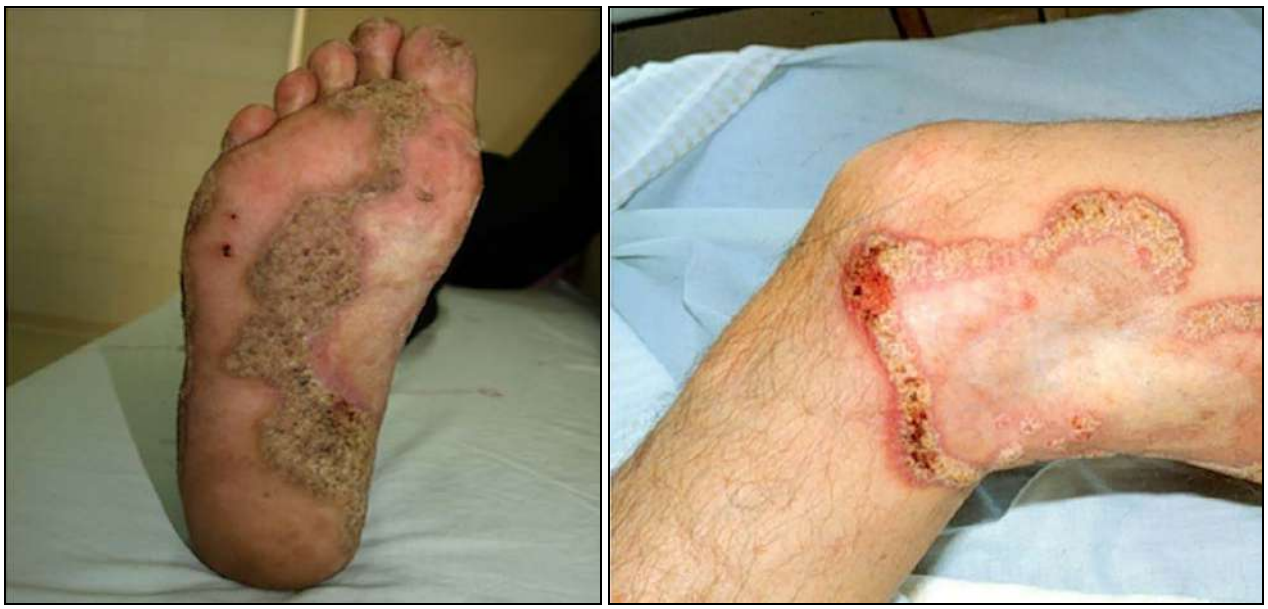
Source: [8]

**Table 1:** Response of the innate immune system to agents of Chromoblastomycosis

| Innate host defense component | Type of specimen or method | Aim | Result(s) |
|---|---|---|---|
| Antigen-presenting cells | Skin specimen of CBM patient | Determination of the role of MPs and DCs in CBM | There is accumulation of the fungal antigens in the cytoplasm of skin MPs and dermal FXIIIa DCs |
| | *In vitro* evaluation of interaction of *F. pedrosoi* with *in vivo*-activated MPs | Determination of the function of MPs in CBM | There was a fungi static effect of MPs in *F. pedrosoi* delaying formation of germ tube and hyphae |
| | Phagocytic index determination, cytokine and NO production by MPs | To determine if the MP fungicidal activity is dependent on fungal species | There was a Higher phagocytic index for *F. pedrosoi*, *C. carrionii*, and *R. aquaspersa*; complement-mediated phagocytosis is more important for *P. verrucosa* and *R. aquaspersa* |
| | *In vitro* assays and *in vivo* model of CBM | Impaired MP function during *F. pedrosoi* infection | Impaired NO production of MPs and down regulation of MHC-II and CD80 expression |
| | Conidia of *F. pedrosoi* and mouse peritoneal MPs | Role of MPs in CBM | Ingestion of conidia by a typical phagocytic process, with formation of phagosomes |
| | Specimens from patients with severe and mild forms of CBM | Role of DCs in severe forms of CBM | DCs induced CD4 T-cell activation *in vitro*, expression of HLA-DR and costimulatory molecules CD86, TNF, IL-10, and IL-12; inappropriate T-cell response in *F. pedrosoi* infection |
| | *F. pedrosoi* conidia or muriform cells with LCs from BALB/c mice | Cell type-dependent phagocytosis of CBM fungi | LC phagocytosis in conidia but not in muriform cells; inhibition of LC maturation by conidia but not by muriform cells |
| Cytokine production | Specimens from patients with severe and mild forms of CBM | Cytokine profile was dependent on fungal species and infection severity | IL-1 production in *F. pedrosoi* and *R. aquaspersa* infections, while IL-6 production in *C. carrionii* infection; severe form of CBM showed increased IL-10 levels, decreased IFN-levels, and inefficient T-cell proliferation; mild form of CBM showed decreased IL-10 levels, increased IFN- levels, and efficient, T-cell proliferation |
| | Specimens from patients with severe and mild forms of CBM | Cytokine profile was dependent on infection severity | Severe form of CBM showed increased IL-10 and decreased HLA-DR and costimulatory molecule expression |
| | Specimens from patients with CBM | Impact of therapy at different time points on cytokine profile and PBMC Proliferation | After 6 month of treatment, increased IFN levels, while after 1 year., decreased proliferation of T cells and IFN- levels and increased IL-10 levels |
| | Specimens from patients with CBM | Impact of itraconazole on cytokine profile | After 3 month of itraconazole, decreased plasma levels of TGF- (clinical improvement); after 6–12 month, rein creased TGF- levels (fibrotic scars or slow clinical improvement) |

[a] MPs, macrophages; DCs, dendritic cells; CBM, Chromoblastomycosis; TLRs, Toll-like receptors; PMNs: polymorph nuclear leukocytes; CLRs, C-type lectin receptors

**Source:** [7]



**A** **B**

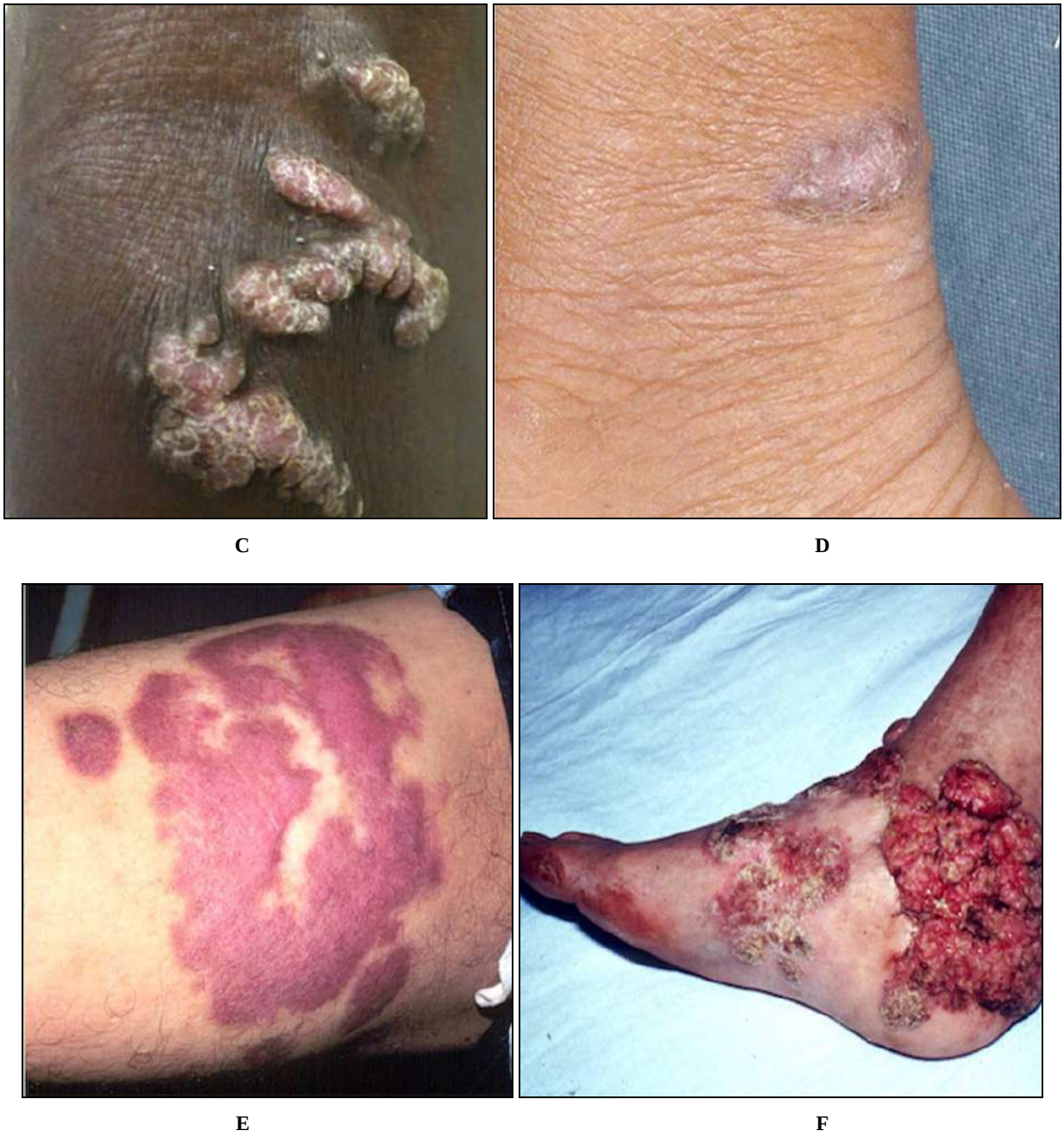



**Fig 4:** Some lesions found in patients with Chromoblastomycosis

(A) Hyperkeratotic verrucous lesion on the sole of the foot. (B) Cicatricial lesion with verruca showing serpiginous and verrucous contours (C) Confluent nodular lesions on the knee. (D) Initial lesion with a 3-month duration in the lower leg. (E) Soft violaceous plaque lesion in the root of the thigh. (F) Tumoral (cauliflower-like) lesion on the posterior part of the foot.
Source: [9]

## Conclusions

CBM is a fungal disease that has been neglected but prevalent in low income developing countries in Asia, Africa, and Latin America's tropical and subtropical geographical regions. This implantation mycosis's burden and medical impact are clearly underestimated. Within the *Chaetothyriales*, pathogenic species are polyphyletic. *Fonsecaea pedrosoi*, *F. monophora*, *Cladophialophora carrionii*, *Rhinocladiella aquaspersa*, *Phialophora* species, and *Exophiala* species are among the organisms that commonly cause CBM. CBM is caused by a variety of factors, including global geographic distribution and natural reservoirs. CBM primarily affects adult males and is classified as an occupational disease in many countries, affecting agricultural laborers, gardeners, lumberjacks, farm product dealers, and other workers who come into contact with polluted soil and plant materials. Nodular, tumoral (cauliflower-like), veracious, scarring, and plaque are the five types of lesions that have been traditionally defined. CBM must be confirmed in the lab through direct mycological examination and/or histopathology. The detection of muriform cells in clinical samples is essential for this disease's diagnosis. The earliest lesions are surgically removed, and more advanced clinical forms are treated with antifungal medication. The most often used antifungal medication in the treatment of CMB is itraconazole, and posaconazole has a possible function in this disease's treatment. Thermotherapy, laser therapy, and photodynamic therapy are examples of alternative physical

therapeutic procedures that may be beneficial. Reduced environmental traumatic transcutaneous inoculation in susceptible individuals should be the goal of infection prevention.

**Conflict of Interest**
Not available

**Financial Support**
Not available

**References**

1. Lupi O, Tyring SK, McGinnis MR. Tropical dermatology: Fungal tropical diseases. Journal of American Academy of Dermatology. 2015;53:931-951.
2. Savioli L, Daumerie D. World Health Organization Department of Control of Neglected Tropical Diseases. Sustaining the drive to overcome the global impact of neglected tropical diseases: Second WHO report on neglected tropical diseases. World Health Organization, Geneva, Switzerland; c2013.
3. Pang KR, Wu JJ, Huang DB, Tyring SK. Subcutaneous fungal infections. Dermatologic Therapy. 2014;17:523-531.
4. Queiroz-Telles F, Santos DW. Challenges in the therapy of chromoblastomycosis. Mycopathological. 2013;175:477-488.
5. Pedroso A, Gomes JM. Sôbre quatro casos de dermatite verrucosaproduzida pela *Phialophora verrucosa*. Anthropology, Sociology and Medicine. 2020;11:53-61.
6. Moore M, Almeida F. Etiologic agents of chromomycosis (Chromoblastomycosis of Terra, Torres, Fonseca and Leão, 1922) of North and South America. Review of Biological Hygiene. 2015;6:94-97.
7. Gugnani HC, Egere JU, Suseelan AV, Okoro AN, Onuigbo WI. Chromo mycosis caused by Philaphora pedrosoi in eastern Nigeria. Journal of Tropical Medical Hygiene. 2018;81:208-210.
8. Naka W, Harada T, Nishikawa T, Fukushiro R. A case of chromoblastomycosis: with special reference to the mycology of the isolated *Exophiala jeanselmei*. *Mykosen*. 2016;29:445-452.
9. Hofmann H, Choi SM, Wilsmann-Theis D, Horre R, Bieber T. Invasive chromoblastomycosis and sinusitis due to *Phialophora verrucosa* in a child from northern Africa. Mycoses. 2015;48:456-461.

**How to Cite This Article**
Chinyere CE, Ebuka VA, Victor OW, Oluchi JO, Ezemba, Arinze S, *et al*. Pathogenesis and Immunology of Chromoblastomycosis: A review. Journal of Advances in Microbiology Research. 2020;1(2):61-66.