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FUNGAL INFECTIONS OF SKIN AND SUBCUTANEOUS TISSUE (A BONIFAZ AND M PEREIRA, SECTION EDITORS)

Chromoblastomycosis in Solid Organ Transplant Recipients

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Abstract

Purpose of review There is growing recognition of melanized fungi as uncommon but important causes of infection among solid organ transplant recipients. Chromoblastomycosis and phaeohyphomycosis exist at opposing ends of the spectrum of disease caused by these fungi. We aim to systematically review the reports of chromoblastomycosis among transplant recipients to assess for trends in epidemiology and clinical outcomes.

Recent Findings We identified 19 reported cases of histologically confirmed chromoblastomycosis among solid organ transplant recipients published between 1985 and 2018. Despite these patients' impaired immunity, chromoblastomycosis remained localized to the skin and subcutaneous tissue in the majority of patients. Clinical outcomes were generally good with medical, surgical, or combined management.

Summary Although chromoblastomycosis has a low incidence in this population, it is important to consider as a cause of chronic, non-healing skin infections. Further research is needed to better elucidate the impact of transplantation on the natural course of this condition.

Keywords Chromoblastomycosis · Melanized fungi · Dematiaceous fungi · Transplantation

Introduction

Chromoblastomycosis (CBM) falls under the umbrella of "implantation mycosis" or "subcutaneous mycoses." Its precise definition in the literature is made difficult by differentiation from phaeohyphomycosis (PHM), a term for other melanized, or dematiaceous, fungal infections. Dematiaceous is a denomination largely referring to fungi with melanin in their cell walls conferring dark pigmentation. CBM was developed as a term in the early 1920s to characterize a new cutaneous fungal infection discovered in Brazil; however, since then, it has been broadly used to describe several species of fungi causing cutaneous infection. PHM was subsequently developed to describe non-CBM dematiaceous fungal infections, entities that are clinically and pathologically distinct [1–3].

Microbiology

The specific species that cause CBM are in the order *Chaetothyriales*, and within this order fall multiple pathogenic species in multiple phylogenetic clusters: *Fonsecaea*, *Cladophialophora*, *Exophiala*, and *Rhinocladiella* [4••]. In terms of specific mycology, diagnosis is made by visualization of muriform cells (also known as "medlar bodies," "meristematic bodies," "copper pennies," or "sclerotic cells") in clinical specimens. These can be seen grossly as superficial pigmented dots. Skin scrapings containing these elements can then be prepared with 10% potassium hydroxide solution and examined under direct microscopy. This will demonstrate single or multiple muriform cells that are round, dark, thick walled, and multiseptate; those near the surface may be filamentous; notably, PHM will not produce these muriform cells [4••, 5, 6].

On fungal culture, most etiologic agents will slowly grow as dark-pigmented colonies. *Exophiala* may have initial yeast components that are uncharacteristic as a phase for most agents of CBM. Incubation time is up to 6 weeks.

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On histopathology, the muriform cells are again demonstrated and often intracellular within giant cells. These can be identified on hematoxylin-eosin stain and further elucidated with Gomori and Fontana stains if unable to visualize sufficient fungal elements. Otherwise, evidence of hyperkeratosis and hyperplasia of the epidermis, and granulomatous changes alternating with atrophy are histopathologic characteristics. The granulomatous infiltrate is found in the dermis with multiple grades of fibrosis. The immunologic responses that produce these granulomatous changes may be altered in a net state of immunosuppression [4••, 5, 6, 7••].

Epidemiology

The above fungi are naturally found in various environmental settings, frequently in plant material, as well as in many agricultural objects and tools through which traumatic exposure and subsequent implantation may occur. A partial list of sources includes plant debris, thorns, wood, bamboo, various agricultural tools, bricks, shoes, and insect stings [4••, 8–13]. Given these sources, CBM is closely linked to agricultural exposures; it is largely considered an occupational disease and affects workers who are exposed to the above described contaminated biologic materials. Furthermore, those who are not wearing protective gear (i.e., shoes and gloves) are at highest risk of exposure [4••, 14].

Geographically, CBM is most prevalent as an endemic fungus in tropical and subtropical regions, most notably in Latin America, the Caribbean, South America, India, China, and Africa [6, 7•, 15–23, 4••5]. Cases have been reported in the USA and Europe, but CBM is not considered endemic in these regions [4••]. There are variations in predominant species based on climate. *Fonsecaea pedrosoi*, for example, appears to be found more frequently in tropical climates while *Cladophialophora carrionii* is seen more often in semi-arid regions [4••, 5, 6, 7•].

Prevalence of disease is higher in males worldwide, primarily of adult age, with varying ratios across the tropics. Interestingly, this elevated incidence in males may relate to differences in sex hormones between the genders rather than differences in environmental exposures [4••]. Still, CBM affects farmers most frequently, likely as a hazard of occupational contact with melanized fungi [15–23].

Pathophysiology and Clinical Manifestations

CBM is characterized by inoculation and implantation of fungi from skin trauma, usually from an environmental source, as described above. Infection progressively develops through the cutaneous and subcutaneous tissues and elicits a granulomatous response. The fungus tends to infect the lower limbs and feet, as well as the palms, arms, and buttocks, areas of the body most likely to be exposed to the inoculum [4••, 7•]. The primary lesion is a papule or growth, which increases in size gradually or spreads locally with satellite lesions.

There are five clinical manifestations of the disease classically [4••, 6]. The nodular type is characterized by an initial lesion of soft, raised pink nodules. These may eventually grow into the large, protruding tumoral type with “cauliflower-like” nodules. Aside from the impressive size these may reach, they also may develop keratosis and scab. The verrucous type is more wart-like with primarily hyperkeratosis. Plaque type is characterized by multiple planar lesions in varying sizes, erythematous and scaly. Cicatricial type lesions cover large body surface areas and have peripheral atrophy and central healing. Lesions can then be further characterized by severity—mild, moderate, or severe—as determined by the number and size of lesions over the body. Most patients suffer from concomitant pruritis and pain [4••, 6, 24].

The primary complications of CBM infections are secondary bacterial infection and ulceration. On some occasions, lymphatic dissemination can occur, and rarely, squamous cell carcinoma in the setting of chronic CBM. Invasive infection otherwise is rare. Another important distinction between CBM and PHM is that the former is found frequently in immunocompetent individuals, while PHM is most commonly found in the immunocompromised. There are exceptions to this principle, as outlined by the review of CBM in solid organ transplant recipients discussed below. Even in the context of immunosuppression, CBM is unlikely to be disseminated and usually is isolated to skin and subcutaneous tissues, though there have been cases of bone, lung, and brain lesions [4••, 6, 25, 26]. Given their relatively uncommon occurrence, it is unclear whether these metastatic sites of infection in CBM are more common in recipients of solid organ transplants.

During the infectious process and initial implantation, the muriform cells that were previously described on histology develop from the initial conidial forms. These are invasive forms of the fungus that allow for survival in the host, and are responsible for the immunologic evasion and granulomatous response that is characteristic of the chronic disease [4••, 27]. CBM infections are characterized by impaired clearance of the fungus by the human host. This is due to various virulence and pathogenic factors that the fungal species are able to utilize. Among the virulence factors utilized by the fungus are thermotolerance, allowing for survival at host body temperatures, as well as various cell wall components including melanin, chitin synthases, and hydrolytic enzymes [4••, 28–31]. Additionally, melanin interferes with proteolytic enzymes and can protect the fungus against nitric oxide and phagocytosis [4••, 28]. Other relevant factors include adherence factors that allow the infectious fungus to adhere to host epithelial tissue.

Host Defenses and Alterations in Immunity

As noted above, CBM is seen most commonly in individuals with intact immune defenses. This is in contrast to PHM, an opportunistic infection in which the same or similar melanized fungi produce subcutaneous cyst-like structures characterized by central necrosis, fibrin deposition, and neutrophilic infiltrates surrounded by epithelioid histiocytes and fibrosis [32]. Fungal hyphae or pseudohyphae predominate in PHM, and the muriform cells of CBM are absent. Despite the pathophysiological differences between CBM and PHM, they exist on a continuum and the boundaries between the two conditions may be imprecisely defined [4••]. Each can be found in both immunologically competent and immunologically compromised individuals. There is growing recognition that dematiaceous fungal infections in immunosuppressed patients may be manifested as CMB, PHM, or a borderline syndrome sharing features of both.

Transplant recipients ordinarily receive combination immunosuppression regimens including calcineurin inhibitors (i.e., tacrolimus, cyclosporine), antimetabolites (i.e., mycophenolate, azathioprine), and corticosteroids. These agents are given in addition to the induction immunosuppression (i.e., thymoglobulin, alemtuzumab) administered at the time of transplantation or during specific episodes of allograft rejection. Taken together, these therapies impair not only adaptive cellular immunity but also humoral and innate immune function [33]. Apart from their effects on T cell activation and proliferation, calcineurin inhibitors may impair neutrophil-mediated defense against fungal infection [34]. Corticosteroids, which have wide-ranging effects on immune function, have been demonstrated to suppress C-type lectin function in mice [35•]. Interestingly, infection with the agents of CBM itself may alter host immunity independently of immunosuppressive drugs. In a mouse model of persistent *F. pedrosoi* infection, there was found to be a deficiency in the innate host toll-like receptor (TLR) recognition of the fungus; administration of TLR ligands improved fungal clearance [36–38]. *Fonsecaea monophora* has been shown to escape C-type lectin receptors on human dendritic cells [38]. This net state of immune impairment, including neutrophil dysfunction, TLR inhibition, and C-type lectin suppression, may facilitate the development of CBM in solid organ transplant recipients and other patients receiving immune-modulating therapies [33].

Transplant-Related Chromoblastomycosis

We conducted a review of all reported CBM infections occurring in solid organ transplant recipients in the English language literature. A search was performed using PubMed (National Library of Medicine, Bethesda, MD, USA) cross-referencing the word "transplant" with the following terms: "chromoblastomycosis," "chromomycosis," "dematiaceous fungi," "*Fonsecaea*," "*Cladophialophora*," "*Exophiala*," and "*Rhinocladiella*." Abstracts and manuscripts were subsequently reviewed to determine whether reported cases likely reflected CBM as opposed to PHM or other fungal infections. Pathology reports describing "muriform cells/bodies," "medlar bodies," "copper pennies," "sclerotic bodies/cells," or "meristematic bodies/cells" were considered to be diagnostic of CBM. Those stating that pathology demonstrated "chromoblastomycosis" or "chromomycosis" were also accepted as such. Cases demonstrating only fungal hyphae without muriform cells (or equivalent terms) were not included. Reference lists from articles describing cases of CBM in transplant recipients were reviewed for additional reports of the infection.

All case reports and case series included in this analysis were reviewed for the following information: age and gender of the affected patient, country of origin, transplanted organ(s), immunosuppression regimen, time from transplantation to CBM presentation, anatomical site(s) of infection, extent of infection (localized, multifocal, or disseminated), pathological findings (muriform cells, hyphae), treatment modalities (medical, surgical), and outcome (under treatment, cured, death, unknown). If the specific country of origin of a patient was not stated, the country of the primary author's affiliation was listed as the geographic location. If the time from transplant to infection was listed only in terms of numbers of years, 1 year was considered to be 12 months. Given the relatively small number of cases included in this review, all analyses were purely descriptive in nature (mean, range, etc.). Statistical analyses were not performed.

The literature review outlined above yielded 19 reported cases of CBM among recipients of solid organ transplants [35•, 39–50]. These are summarized in Table 1. While published series by Agarwal et al. [7•] and Santos et al. [51••] also discussed cases of CBM among transplant recipients, these were not included in Table 1 given their lack of patient-specific details. Case reports/series included in our review were published between the years 1985 and 2018. The mean age of patients included was 50 years (range 9 to 71 years). Four of the 19 infections (21%) occurred in females. All areas of the world were represented in the reported cases as described. These were distributed as follows: Asia (India, n = 3), Africa (Tunisia, n = 1), North America (continental USA, n = 3), South America (Brazil, n = 6), the Caribbean (Haiti, n = 1; Puerto Rico, n = 1), Europe (Spain, n = 3), and Oceania (Australia, n = 1). Of these, 13 patients (68%) resided in either tropical or subtropical zones. The large majority of reported cases of CBM occurred in patients who had received a kidney transplant (16 of 19, 84%). One patient each had received a heart or liver transplant; another was a combined kidney/pancreas transplant recipient. Only one patient (5%) had

Table 1 Reported cases of chromoblastomycosis in solid organ transplant recipients

Age and gender (reference)	Country	SOT	Immunosuppression	Time from SOT (months)	Organism isolated	Pathology	Site	Type of lesion	Treatment	Outcome
50 M [39]	India	Kidney	Prednisone, cyclophosphamide	41	*Rhytidhysteron rufulum*	Muriform cells	Leg	Multiple	Itraconazole	Death
58 M [40]	Tunisia	Kidney, pancreas	Prednisone, tacrolimus, azathioprine	84	*Cladophialophora carrionii*	Muriform cells, hyphae	Arm	Multiple	Posaconazole, surgery	Cured
53 M [41]	Spain	Kidney	Prednisone, cyclosporine	36	*Aureobasidium pullulans*	Muriform cells, hyphae	Leg	Localized	Surgery	Cured
50 M [42]	USA	Heart	Prednisone, cyclosporine, azathioprine		*Exophiala jeanselmei*	Chromoblastomycosis	Leg	Localized		
29 M [43]	Puerto Rico (USA)	Kidney		17		Chromoblastomycosis	Arm	Localized	Surgery	Cured
59 F [44••]	Brazil	Kidney	Prednisone, tacrolimus, mycophenolate	14		Muriform cells, hyphae	Foot	Localized	Itraconazole, surgery	Cured
75 M [44••]	Brazil	Kidney	Prednisone, tacrolimus	12	*Exophiala xenobiotica*	Muriform cells, hyphae	Arms, hands, legs	Disseminated	Itraconazole	Unknown
43 M [44••]	Brazil	Kidney	Prednisone, tacrolimus, azathioprine	36	*Fonsecaea monophora*	Muriform cells, hyphae	Hand	Localized	Surgery	Cured
57 M [44••]	Brazil	Kidney	Prednisone, tacrolimus, azathioprine	1	*Fonsecaea*	Muriform cells, hyphae	Arm	Multiple	Terbinafine	Cured
60 M [44••]	Brazil	Kidney	Prednisone, tacrolimus, mycophenolate	36	*Fonsecaea pedrosoi*	Muriform cells, hyphae	Arm	Localized	Itraconazole, surgery	Cured
54 M [44••]	Brazil	Kidney	Prednisone, tacrolimus, everolimus	24	*Exophiala bergeri*	Muriform cells, hyphae	Leg	Multiple	Itraconazole	Under treatment
56 M [45]	Spain	Kidney	Prednisone, tacrolimus, mycophenolate		*Exophiala jeanselmei*	Chromoblastomycosis	Hand	Localized	Itraconazole, surgery	Cured
55 M [46]	Spain	Liver	Methylprednisolone, azathioprine, cyclosporine ➔tacrolimus	15	*Aureobasidium pullulans*	Muriform cells, hyphae	Lip	Localized	Itraconazole, surgery	Death
71 M [47]	Australia	Kidney			*Fonsecaea monophora*	Muriform cells	Leg	Multiple	Terbinafine, itraconazole	Cured
50 F [48]	India	Kidney	Prednisolone, cyclosporine ➔ tacrolimus, mycophenolate (rituximab for episode of rejection)	12		Muriform cells	Foot	Localized	Itraconazole, surgery	Cured
49 M [35]	Haiti	Kidney	Prednisone, tacrolimus, mycophenolate	60	*Fonsecaea pedrosoi*	Muriform cells	Scalp, legs, brain[1]	Disseminated	Posaconazole, drainage	Cured
45 M [49]	India	Kidney × 2	Prednisone, cyclosporine	18 (1st), 3 (2nd)	*Cladophialophora bantiana*	Muriform cells	Finger	Localized	Terbinafine, ablation	Unknown
33 F [50]	USA	Kidney	Prednisone, azathioprine	24	*Fonsecaea pedrosoi*	Muriform cells	Leg	Multiple	Ketoconazole	Under treatment
9 F [50]	USA	Kidney	Glucocorticoids and anti-lymphocyte serum for rejection	24		Muriform cells	Leg	Localized	Surgery	Cured

Data are shown summarizing 19 cases of chromoblastomycosis occurring in solid organ transplant recipients. Additional cases described by Agarwal et al. [8] and Santos et al. [41] are not included. Age is listed in years

Empty fields reflect data not specifically stated by the individual authors

M male, *F* female, *SOT* solid organ transplant

[1] Fungal involvement of the brain was not confirmed by microbiology or histology; concurrent *Listeria* infection may have been the etiology of brain findings

undergone retransplantation. A wide variety of transplant immunosuppression regimens were utilized (Table 1), with the majority of patients receiving some combination of a calcineurin inhibitor (cyclosporine, tacrolimus), an antimetabolite (azathioprine, mycophenolate), and a corticosteroid. The mean time from transplantation to development of CBM was 29 months (range 1 to 84 months), with all but one occurring greater than 1 year after transplantation.

Reported lesions were most common over the lower extremities (n = 11) and upper extremities (n = 8). Two patients had head lesions noted over the lips and scalp. Eleven patients (58%) had localized disease, six patients (32%) had multifocal disease, and two patients (11%) had disseminated disease. All patients had either muriform cells visualized (or equivalent terms, n = 16, 84%) or pathology findings consistent with "chromoblastomycosis" or "chromomycosis" (n = 3, 16%). Interestingly, nine patients (47%) also had hyphae visualized on pathology.

Among the 18 patients with treatment/outcome data, six patients (33%) were treated with medical therapy alone, four patients (22%) were treated with surgical therapy alone, and eight patients (44%) were treated with a combination of medical and surgical therapy. The most common medications employed were itraconazole (n = 9), terbinafine (n = 3), and posaconazole (n = 2). Excision was the most common surgical technique employed, although radiofrequency ablation and drainage were also utilized [48]. At the times of publication of the original case reports/series, 12 patients (67%) had been cured, two (11%) had remained on treatment, two (11%) had died, and two (11%) had an unknown outcome.

Conclusions

This report adds to the growing recognition of melanized fungi as uncommon but important causes of skin and subcutaneous infections among solid organ transplant recipients. To the best of our knowledge, this presentation of 19 cases of CBM is the largest review of this specific condition in this patient population. The broad spectrum of melanized fungal infections in transplant recipients (including both CBM and PHM together) has been thoughtfully evaluated on a larger scale by other investigators [51, 52].

Given the low incidence of CBM in this population, our relatively small number of cases does not allow for statistical analysis. Despite this limitation, several interesting observations can be drawn from our data. Epidemiologically, our review highlights that CBM can be seen in transplant recipients from geographically diverse regions, including those that are not tropical or subtropical. While approximately one third of the cases in our review are from regions that are not endemic for melanized fungi, it is unclear whether this represents the true epidemiology of CBM, a reporting bias, a diagnostic bias, or the imbalance of transplant services in different regions of the world. Similarly, it is not possible to assess whether the incidence of CBM is increasing in this population based upon our review. Although nearly half of the cases included in this analysis were reported over the past 5 years, there is insufficient data to analyze these epidemiological trends statistically. Working with a larger cohort of patients, Santos et al. failed to demonstrate an increasing incidence of melanized fungal infections in solid organ transplant recipients in their 2017 study [51]. As above, there may be both diagnostic and reporting biases that limit our ability to recognize a trend in this population. Specifically, the prolonged time from transplantation to CBM (averaging 29 months in this review) may impair accurate case identification compared to other transplant-associated fungal infections with more acute presentations (aspergillosis, candidiasis). Despite the current ambiguity in the literature, it seems like a logical hypothesis that transplant-associated CBM cases will increase in frequency as solid organ transplantation becomes more prevalent around the globe.

Whether transplantation itself alters the clinical course of CBM remains similarly unclear. In our review, the large majority of patients demonstrated clinical infection that was confined to the skin and subcutaneous tissues; dissemination was present but comparatively rare. Likewise, clinical outcomes were generally good with cure established in the majority of patients with either antifungal therapy, surgery, or a combination of both. As transplant recipients are at increased risk for PHM, it is essential to appropriately diagnose and stage suspected melanized fungal infections in this population. A combination of physical exam, fungal culture, and histological examination is likely to be most accurate. Novel microbiological diagnostic techniques (i.e., sequencing) may also be helpful. Interestingly, while histology is necessary to confirm the muriform cells of CBM, several cases included in this review also demonstrated fungal hyphae on pathology. This finding, which would traditionally be more associated with PHM, highlights the spectral nature of melanized fungal infections and the imprecise delineations between the clinical conditions they produce.

Further research is necessary to better define the epidemiology, clinical features, and optimal treatment of CBM in solid organ transplant recipients. Until more is known, it is essential that clinicians actively consider this diagnosis in patients at risk as treatment usually results in clinical cure.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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