

# Chromoblastomycosis in Mainland China: A Systematic Review on Clinical Characteristics

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Received: 16 March 2012 / Accepted: 20 September 2012 / Published online: 20 October 2012  
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**Abstract** Chromoblastomycosis is one of the most frequent chronic infections caused by melanized fungi. In order to evaluate the clinical characteristics of chromoblastomycosis in Mainland China, we performed an evidence-based review of published literature. PubMed and Chinese-language database of CNKI, VIP and Wanfang data during January 1990–August 2011 were searched. Epidemiology, clinical features, laboratory findings, therapy and prognosis were analyzed. *Cladophialophora carrionii* was the most common causative agent in the north of the Mainland China, and *Fonsecaea monophora* and *F. pedrosoi* were the most common agents in the southern part of the Mainland China. Infection commonly initiated after the etiologic agents gain entrance through puncture wounds and more common involved extremities of the males. Skin lesions were found in different sites, like the extremities, buttocks, trunk and face, and presented diversity morphology. There were about seven different clinical types found in Mainland China: plaque type, tumoral type, cicatricial type, verrucous type, pseudo-vacuole type, eczematous type and mixed type of lesions. The success of treatment for chromoblastomycosis was related to the causative agent, the clinical form and severity of the lesions.

Most of the patients could be treated successfully with the physical treatment, chemotherapy and/or combination therapy. The itraconazole, terbinafine or a combination of both were commonly medication for these mycosis patients. Physical methods were usually indicated to support chemotherapy with some severe forms and long-lasting cases. Photodynamic therapy has been extended from the oncological field to that of antimicrobial chemotherapy in these years. We applied it on some recalcitrant cases of chromoblastomycosis and found its good clinical response, and hopeful it could be a promising therapy in near future.

**Keywords** Chromoblastomycosis · Clinical characteristics · Mainland China · Treatment

## Introduction

As a chronic, cutaneous and subcutaneous infection, more than 589 cases of chromoblastomycosis (CBM) have been reported in China since the 1950s. It is usually found in tropical and subtropical regions with high prevalence in Shandong Province of Mainland China. So far, it has not been known to cause outbreaks in Mainland China. Infection common initiated after the etiologic agents gain entrance through puncture wounds and more common involved extremities of the males, possible due to occupational reasons. Several melanized fungi are involved with the disease etiology

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in Mainland China, and *Cladophialophora carrionii* and *F. pedrosoi* are the most prevalent agents. CBM usually is observed in immunocompetent hosts, and clinical features are diversity. In order to evaluate the clinical characteristics of CBM in Mainland China, we performed an evidence-based review of published literature. PubMed and Chinese-language database of CNKI, VIP and Wanfang data during January 1990–August 2011 were searched. Epidemiology, clinical features, laboratory findings, therapy and prognosis were analyzed.

## Materials and Methods

We searched the literature of chromoblastomycosis from the PubMed (<http://www.ncbi.nlm.nih.gov/sites/entrez>) and Chinese-language database of CNKI (<http://dlib3.cnki.net/kns50/>), VIP (<http://www.cqvip.com/>) and Wanfang data (<http://www.wanfangdata.com.cn/>) published during January 1990–August 2011 (Hong-kong, Macao and Taiwan were excluded). The search terms were chromoblastomycosis and/or *Fonsecaea* and/or chromomycosis and/or dematiaceous fungi. Articles were evaluated whether they concerned on the details of epidemiology, clinical manifestation, treatment and prognosis. Cases of CBM found in our hospital during these years were also included for reviewed. Data on age, sex, career, immunologic status, clinical features, laboratory findings, treatment, prognosis, reported year and distribution were collected.

## Results

From the primary search of 53 articles, only 43 articles, including 62 CBM patients, were included in this review [1, 2] [(3–7), appendix references (17–52)]. Besides, 25 cases of CBM were found in our hospital during these years, so there were accumulative 87 patients were included for reviewed. The disease was prevalent among males (male/female, 5.21:1) and farmers (56/87) with the mean age at 50.72 years (range 10–79 years). In 57 patients (57/87), the infection was associated with trauma and most cases were usually observed in immunocompetent hosts. Laboratory diagnosis of CBM cases was showed in Table 1. Mostly, the diagnosis was made by

**Table 1** Laboratory diagnosis of CBM cases in Mainland China

Examinations	Positive	Negative	None given
Direct examination	62	5	20
Culture	80	2	5
Histopathology	65	3	19

observing muriform cells through direct examination and histopathology.

## Epidemiological Features

CBM has been reported from 9 provinces of Mainland China with higher prevalence in Guangdong Province (42 cases), Shandong Province (24 cases) and Hebei Province (8 cases) (Fig. 1). Several melanized fungi were involved with the disease etiology. The etiologic agents were identified in cultures in 79 cases. *C. carrionii* was still predominant in northern Mainland China (31/79), and *F. monophora* and *F. pedrosoi* were prevalent in south of Mainland China (23/79, respectively). *F. compact* and *Phialophora verucosa* were present in only one case, respectively. Seventeen of 23 isolates were identified as *F. pedrosoi* only by morphology. All of the *F. monophora* isolates were identified not only by morphology, but also by analyzing ribosomal DNA (rDNA) internal transcribed spacer (ITS) sequence. In recent years, more *F. monophora* has been observed by analyzing rDNA ITS sequence in southern Mainland China. Most infections caused skin lesions, and one case of central nervous system invasion was reported in 1996. In that case, the author documented muriform cells were found in the brain, so the case has been exclude phaeohyphomycosis.

## Clinical Manifestations

The initial lesion preferentially occurred in the unilateral lower limbs (34/75) or unilateral upper limbs (22/75), and different sites, like the buttocks (2/75), trunk (3/75) and face (9/75), were less frequently reported. In addition, lesions of 5 cases were observed in bilateral limbs, 1 case was brain infection, and 11 cases were not given detailed.

The clinical manifestations of CBM showed diversity, mostly includes five different types, viz. nodular

**Fig. 1** CBM has been reported from 9 provinces of Mainland China (during 1990–2011)



type, plaque type, tumoral type, cicatricial type and mixed lesions. In the advanced cases, two more untypical types of lesions, which were eczematous type and pseudo-vacuole types were observed in south of Mainland China (Fig. 2).

#### Treatment and Prognosis

Treatment may be divided into three groups, including physical treatment, chemotherapy and combination therapy. Among 87 cases we reviewed, 66 cases have given the detail of treatment and prognosis (Table 2). Apparently, chemotherapy was the most common choice for the treatment for CBM (41/66). On the other hand, drugs could be combined with physical methods, like thermotherapy (16/66), surgery (4/66) or other therapy, like photodynamic therapy (PDT) (3/66) and laser (1/66). Physical methods were less used alone.

Generally, CBM was very difficult to treat and prone to recurrence, and treatment success depended on several factors. According to the published data, causative agent may be one of the critical factors. *C. carrionii* was the most sensitive in vivo to antifungal drugs, and the cure rate of the infection was higher than *F. monophora* infection or *F. pedrosoi*

infection (both are 8/14, respectively). Therapeutic success could also be related to the time of evolution, extension and sites of lesions and co-morbidities, and to the choice of the antifungal drug and so on. In different lesions locations, face was particularly high in cure rates (7/8), followed by unilateral upper limbs (11/17), unilateral lower limbs (13/24), bilateral limbs (1/2) and trunk (1/1). Mean of infectious history was 7.15 years in cured patients, while infectious history of total patients was 10.94 years.

#### Discussion

In the world wide, chromoblastomycosis was usually found in tropical and subtropical regions, especially in Africa and Latin America [8]. In present literature review, we found that CBM has an endemic in Guangdong Province and Shandong Province of Mainland China. In the past 20 years, less than 100 patients were found or reported in our country. The possible reasons include: firstly, CBM is an endemic disease instead of an emerging disease (it has an endemic in south of Mainland China). Secondly, CBM shows unsatisfactory responses to therapy in most



**Fig. 2** Clinical Manifestations of CBM in Mainland China **a** Plaque type lesion, **b** Tumoral type lesion, **c** Eczymatous type lesion (exhibit a variety of characteristics, including blistering, oozing, flaking or crusting), **d** Cicatricial type lesion, **e** Pseudo-

vacuole type lesion (exhibit characteristics of infiltrated papules and plaques with pseudo-vesicles) **f** Mixed type lesion **g** Verrucous type lesion

cases, so it was less frequently reported because of incomplete clinical information.

In agreement with previous literature, CBM cases are prevalent among males and farmers. The low percentage of CBM cases in females might not be related only to the professional activity. There were some studies showing the specific hormonal binding of mammalian estrogen to proteins in *Paracoccidioides brasiliensis* and an action of estrogen to specifically block the transition from the saprophytic form to the invasive form of the *P. brasiliensis* in vitro [9]. It is

possible that sexual hormones have a similar role on agents of CBM.

The first case was published by Rudolph, who described an exotic disease this disease in the hinterland of the State of Minas Gerais, Brazil [10, 11]. Until now, the most common agents are *Fonsecaea pedrosoi* and *Cladophialophora carrionii*. Genus *Fonsecaea* included 2 species in the past, which were *F. pedrosoi* and *F. compacta*. But nowadays, on the basis of rDNA ITS sequence data, the traditional distinction between *F. pedrosoi* and *F. compacta* was not valid and the

**Table 2** Treatment and prognosis of CBM in Mainland China

Treatment		Cured	Moderate improvement	Loss	Total
Antifungal medication	ITZ	10	6	1	17
	TBF	8	5	0	13
	ITZ + TBF	4	5	0	9
	FLU	1	0	0	1
	KET	0	1	0	1
Antifungal medication + Physical methods	ITZ + Direct application of heat	14	2	0	16
	ITZ + Laser photocoagulation	0	1	0	1
Liquid nitrogen cryotherapy	1	0	0	1	
Surgery + ITZ	2	1	0	3	
Surgery + TBF	1	0	0	1	
Antifungal medication +PDT	3	0	0	3	
Total	43	22	1	66	

ITZ itraconazole, TBF, terbinafine, FLU fluconazole, KET ketoconazole, PDT photodynamic therapy

latter seemed to be no more than a morphological variant from *F. pedrosoi*. And in 2004, De Hoog et al. isolated *F. monophora* from *Fonsecaea* spp. and identified it as a new species [12]. Since that, more *F. monophora* were found and identified by rDNA ITS sequencing. According to our present review, the most common etiologic agents were *C. carrionii*, *F. pedrosoi* and *F. monophora*. We re-evaluated the identification of 24 isolates recovered from patients with chromoblastomycosis in our hospital that were originally identified as *F. pedrosoi* by using rDNA ITS sequence diversity. Twenty strains were found to be *F. monophora*, while four strains corresponded to *F. pedrosoi* [13]. In present literature reviewed, most of *F. pedrosoi* isolates were only identified by morphology. However, the morphologic features of conidial formation in genus *Fonsecaea* lacked distinctive morphological characters, so we hypothesis that many isolates might be misidentified in clinical practice. Moreover, a meristematic mutant of *F. monophora* was found by our former research [5]. Our isolate had different morphology with mostly *F. monophora*, but 100 % genetic homology with reported isolate of *F. monophora*. Molecular identification seems to be a highly specialized and necessary method for identifying the caustic agents of chromoblastomycosis.

Several classifications were proposed to describe the CBM clinical manifestations, the classification introduced by Carión in 1950 were the most commonly used. Among them, nodular, tumoral and

verrucous types were more frequently seen than the cicatricial and plaque types. But in most cases, with the mycosis develop, more than one type of lesions could be observed in the same patient. So, Queiroz-Telles et al. [8] graded lesions not only by type of lesion but also by severity, and the more severe lesions respond more slowly to treatment. According to review published data, we graded the CBM lesions in Mainland China in seven types, which were plaque type, tumoral type, cicatricial type, verrucous type, pseudo-vacuole type, eczematous type and mixed lesions. To our best knowledge, there was no report describe the CBM lesions as pseudo-vacuole type and eczematous type. Both these cases had characteristics of short duration in years and good response to the therapy. Moreover, most mixed lesions covered extensive cutaneous regions with long-standing history and responded bad to the therapy. However, controlled clinical trials are still lack to define the relationship between clinical types and duration of therapy.

Though treatment success of CBM was driven by many impact factors, causative agent was the most critical factor. The cure rate of the *C. carrionii* infection was higher than *F. pedrosoi* infection or *F. monophora* infection. To develop new approaches to the chemotherapy of infections caused by *F. monophora*, we evaluated the in vitro effects of a combination of terbinafine with itraconazole on 18 clinical isolates by using a checkerboard microdilution method. FICI

analysis demonstrated that 12 (67 %) were synergistic, 4 (22 %) were additive, and 2 (11 %) were indifferent, with no antagonism being observed [6]. In advanced, 6 among 8 cases of CBM caused by *F. monophora* were cured (data not shown). Three cases were reported had good response to combination therapy with oral terbinafine and itraconazole. Two cases underwent oral terbinafine or itraconazole alone. One case was cured by combination therapy with oral antifungal medication and PDT. The last 2 cases, which presented sensitive effect to antifungal agents, showed a moderate clinical response to chemotherapy [6]. So far, there was not clear correlation between the results from fungal susceptibility testing and the clinical response. Combined with our former study in vivo and in vitro, we found that CBM caused by *F. monophora* seems more easily to be cured.

Optimal treatment for CBM still in dispute and there were series of therapeutic options for this mycosis. Several treatment regimens have been evaluated in the past, the activity of itraconazole and terbinafine against *F. monophora* has been determined by our former effort [6, 7]. However, treatment failure of CBM was common. The common reasons for the failure may account for long treatment duration, serious side effects like liver injury, drug–drug interactions, and antifungal resistance. Resistance has been demonstrated in sequential isolates of *F. pedrosoi* from patients undergoing long-term therapy with itraconazole [14]. Therefore, alternative antifungal strategies were being actively sought. PDT involves the selective photosensitizer of a target tissue by means of a topically or systemically administered agent that can be subsequently activated by light to produce an oxygen-dependent cytotoxic reaction [15]. PDT for treatment has been investigated in our 3 CBM cases (data not shown). Our results showed that after 3–4 treatment of PDT, total 3 patients got significantly improved, and direct microscopic examination was negative in 2 patients. The overall tolerability of PDT was good, and the adverse effects of PDT for treating CBM were only pain feeling. Lyon et al. [16] also evaluated the clinical applications of PDT for the treatment for chromoblastomycosis and denoting the efficacy of PDT against chromoblastomycosis. Though our study was not enough to provide enough insight into the combination therapy of PDT and antifungal medications and further studies are needed, this therapeutic approach may have a potential role in

the treatment for CBM in near future. In one of the cases reported, a CBM patient caused by *F. pedrosoi* was treated only by three treatment of liquid nitrogen cryotherapy. This case characteristic by short duration of infectious history and the lesion present as a solitary plaque measuring about 1.5 cm × 1 cm. To conclude, our retrospective analyses support previous published data about the therapy of CBM. PDT alone or in combination may be helpful for patients with refractory disease.

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