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Mini-Review of Published Reports on Coccidioidomycosis in China

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Abstract Coccidioidomycosis is a deep mycotic infection endemic to Americas. Although it has also been reported to occur in non-endemic areas, it has rarely been reported in China. We reviewed the literature on case reports of coccidioidomycosis in China from 1958 to 2015. A total of 30 cases were reported from 11 provinces in China, and 23 (76.7 %) cases were men, and 23 (76.7 %) were in 30–60 years old. Twenty-seven (90.0 %) cases were reported from southern China. Twenty-four (80.0 %) cases had no history of exposure in endemic areas. Three cases were immunosuppressed, four cases had chronic disease, and 23 cases (76.7 %) were otherwise healthy. Twenty cases (66.6 %) had related lung infection, six had skin infection, three cases were in lymph node, and one in the cornea, one in the bone and joint, and three had systemic disseminated infection. All of the 30 cases were diagnosis upon finding spherules in histological examination. Interestingly, 12 (40.0 %) patients underwent surgery and removed the focus of infection because they were misdiagnosed or suspected of tumor or cancer previously. Fifteen cases (50.0 %) were treated with amphotericin B, fluconazole, clotrimazole or ketoconazole. Diagnosis of coccidioidomycosis is complex, and misdiagnosis can occur easily in non-epidemic areas such as China.

Keywords Coccidioidomycosis · Case report · Literature review · China

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Introduction

Coccidioidomycosis (CM) is a fungal infection caused by the dimorphic fungi *Coccidioides* species, which has a regional distribution and higher prevalence in the southwestern deserts of the USA, northern Mexico, and in some areas of Central and South America [1, 2]. The incidence of CM has increased in non-endemic areas as well as in HIV patients and transplant recipients [3–5]. Although CM has been reported to occur in China, little information about this disease is available. In this article, we review the current literature on the disease from 1958 when the first case reported to July 2015 in China.

Materials and Methods

The current literature on CM in China was conducted by searching PubMed and MEDLINE database, and

the Chinese databases, such as China National Knowledge Infrastructure, WANFANG and VIP databases. Both English and Chinese were searched as the publication language. The keywords used included CM, and publication time was from 1958 when the first CM case was reported to July 2015. We collected and sorted the features of the CM cases according to the following aspects: age, gender, locality, history of travel to endemic areas, underlying diseases, diagnostic methods, treatment procedure and prognosis. Outcomes were described either as survival with relief of symptoms after a regimen of antifungal treatment, or as death. All searched results were carefully identified by investigators by abstract or original paper to confirm that cases included in this study were primary report rather than repeat reports.

Results

The first imported Chinese case was from Tianjin, China [6], in 1958; the patient suffered from a primary skin coccidioidomycosis. The first local CM case was described from Shandong Province [7] in 1963. Until July 2015, a total of 30 cases were presented from 21 reports (Table 1) [6–26]. Twenty-three cases (76.7 %) were men, and 23 patients (76.7 %) were in 30–60 years old. The oldest is 81-year-old, and the youngest is only 5-month-old.

The 30 cases are from 11 provinces of China (Table 2). Twenty-seven (90.0 %) cases were reported from southern China, and three cases were reported from northern China. Eleven cases among the 30 cases were reported over 50 years (from 1958 to 2007), and 21 cases reported in next 8 years (from 2008 to 2015).

As shown in Table 1, there are only six cases (20.0 %) with a history of exposure in endemic areas, and the rest (80.0 %) had no history of traveling to or living in endemic areas, or underwent occupational exposure. Three cases were immunosuppressed, including one HIV-infected, one treated with radiation for cancer and one case using immunosuppressants. Four cases suffered from chronic disease: coronary heart disease, chronic bronchitis, chronic cholecystitis and gout. The remaining 23 cases (76.7 %) were otherwise healthy.

Twenty cases (66.6 %) had related lung infection, six had skin infection, three cases were in the lymph nodes, one in the cornea, one in bone and joint, and three systemic disseminated infection in the brain, meningitis, liver, thoracic vertebra and kidney. Twenty-seven cases were infected through the respiratory tract, one lung infection was due to inhalation of seawater, one skin infection was due to occasionally swept out containers shipped from the USA, and one corneal lesion was infected after ocular injury.

All of the 30 cases (100 %) were diagnosis upon finding spherules by histological examination (HE stained) or periodic acid–Schiff (PAS) or periodic acid silver methenamine (PASM) stained in biopsy specimen; two diagnoses were confirmed by mycologic culture; one by antibody test, and one by histological examination in autopsy. Notably, 40.0 % (12/30) of patients underwent surgery because they were misdiagnosed or suspected of tumor or cancer previously. Fifteen cases (50.0 %) had received antifungal treatment at diagnosis; 14 cases of them were cured, while one died. In the remaining four patients, one was lost to follow-up, and three passed away without any therapy.

Discussion

The incidence of CM is increasing in endemic areas and in non-endemic areas [3–5]. Although it has been reported to occur in China, little information about these cases is available. The reason for this may be that the body of literature on the topic has been published in languages other than English, mainly in Chinese and has not been accessible to many investigators. Here, we review the literature on cases of CM from 1958 to 2015. The results show that 30 cases of CM were reported in 11 provinces of China from 1958 to 2015. Eleven cases were diagnosed during the first 50 years (from 1958 to 2007), and 19 cases were reported in next 8 years (from 2008 to 2015), implying the incidence of CM has increased in China.

Risk factors for infection include residence in or travel to a CM endemic region, or occupations with high risk of exposure [5]. Notably, there are only 20.0 % with a history of exposure in endemic areas, and the rest had no history of traveling to or living in endemic areas, or undergoing occupational exposure. Whether there are other possible sources of infection or whether the infection of Coccidioides originated from local in China remains unknown. The risk factor

Table 1 Published reports of Chinese CM cases diagnosed by histological and microscopy

References	Patient characteristics						
	Sex/age	Underlying disease	Travel history	Site of infection	Specimens/method of identification	Treatment	Outcome
Gan et al. [6]	M/35	Gout	Arizona, California, USA	Skin	Resection tissue/culture	Surgery	Remission
Mu and Chen [7]	M/43	NM	None	Systemic, skin	Exudate/culture	None	Died
Wu and Xu [8]	M/31 F/32	Healthy	None	Lung	Sputum/culture	CTZ	Cured
Fu et al. [9]	F/26	Healthy	None	Lung	Biopsy/PAS	KTZ	Remission
Li et al. [10]	F/45	Ocular injury	None	Cornea	Biopsy/PAS, GMS	Surgery AMB	Cured
Zhu et al. [11]	M/52	AIDS and TB	None	Skin	Skin biopsy	NM	NM
Koehler et al. [12]	M/32	Healthy	California	Lymph node disseminated	Biopsy/NM	ABLC	Remission
Liu and Gu [13]	M/37	drug user IS	None	Meninges, lung	Autopsy/HP	None	Died
Ceng et al. [14]	F/44	Healthy	None	Lung	Pulmonary biopsy/HE	Surgery	NM
Geng et al. [15]	F/49	Healthy	NM	Bone (humerus)	Biopsy/PAS	Surgery	NM
Ouyang et al. [16]	M/5 months	Healthy	NM	Disseminated	Autopsy/HP	None	Died
Gao et al. [17]	M/38	Healthy	NM	Skin, lymph nodes	HP	Surgery	Remission
Xu et al. [18]	M/75	Healthy	Arizona	Lung	Pulmonary biopsy/PAS, GMS	Surgery	Remission
Kwok et al. [19]	M/50	Health	California, Arizona	Lymph node	Lymph node biopsy	FLZ	Remission
	M/42	Carcinoma radiotherapy	California	Disseminated lung	Pus/culture	FLZ AMB	Died
Lian et al. [20]	M5, F3/mean 42.8	All healthy	All none	All lung	Pulmonary biopsy/PAS, GMS	FLZ KTZ	Remission in 7, lost to follow-up in 1
Liang and Hu [21]	M/33	Healthy	None	Meninges, lymph nodes	Lymph node biopsy, CSF/culture	FLZ	Remission
Yu et al. [22]	M/81	Chronic bronchitis	None	Lung	Pulmonary biopsy/PAS	Surgery FLZ	Remission
Zong et al. [23]	M/74	SS IS	None	Lung	Pulmonary biopsy/PAS	Surgery FLZ	Remission
Lan et al. [24]	M/14	Seawater aspiration	None	Lung	BALF/GMS and PAS	AMB	Remission
Tang and Tsang [25]	M/43	Healthy	Occupational exposure	Skin	HP, antibody	FLZ	Remission
Wang et al. [26]	M/71	CHD	Arizona	Lung	Biopsy/HE, PAS	surgery	Remission

Occupational exposure contact with materials imported from USA

M male, *F* female, *NM* not mentioned, *AMB* amphotericin B, *FLZ* fluconazole, *CTZ* clotrimazole, *KTZ* ketoconazole, *ABLC* amphotericin B lipid complex, *PAS* periodic acid–Schiff, *PASM* periodic acid silver methenamine, *HP* histopathology, *CSF* cerebrospinal fluid, *IS* immunosuppression, *TB* tuberculosis, *SS* sicca syndrome, *CHD* coronary heart disease

Table 2 Geographic distribution of cases

Province	No. of case	Province	No. of case
Fujian	8	Hubei	2
Hong Kong	4	Shandong[a]	2
Zhejiang	4	Hunan	1
Jiangsu	3	Shanghai	1
Guangzhou	2	Tianjin[a]	1
Jiangxi	2	Total cases	30
Total provinces	11		

[a] The provinces located in northern China

for *Coccidioides* spp. infection also involves immunocompromised or other underlying disease [3–5]. In this review, only three cases were immunosuppressed and four cases had chronic disease; the remaining 23 (76.7 %) were otherwise healthy, suggesting that immunocompetent persons may also be affected by *Coccidioides*.

The lung is the primary site of involvement by Coccidioides, as infection follows inhalation of airborne arthroconidia. In this review, 66.7 % of cases had lung infection, which is same as previous reports [1, 2]. The route of infection is mainly through the respiratory tract, but infections contracted from non-respiratory routes (e.g., in utero exposure, animal bites) have been reported [27, 28]; however, these are rare. In the present literature review, one lung infection was due to choking on seawater [24], one skin infection was due to occasionally swept out containers shipped from the USA [25], and one corneal lesion was infected after ocular injury (paper published in Chinese) [10], which insinuates that the infection route of *Coccidioides* may be through the wound on skin or mucous membrane.

Diagnosis of CM is complex, and misdiagnosis can occur easily in non-epidemic areas [29]. We found that 40.07 % of patients underwent surgery because they were misdiagnosed or suspected of tumor or cancer previously. The reasons for misdiagnosis in non-epidemic areas are that pulmonary CM mimics primary lung cancer [30, 31], the lack of physician's awareness and vigilance of the disease, and the biphasic fungi's diverse forms [32]. Therefore, physicians, cytologists and pathologists should be aware of the disease and the diverse morphologies demonstrated by *Coccidioides* spp. and should be aware of this organism in their differential diagnosis, even in patients seeming lacking in pertinent risk factors.

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Compliance with Ethical Standards

Conflict of interest None.

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