Case Report: First Reported Australian Case of *Cladophilophora arxii*: Features Consistent with Possible Primary Pulmonary Chromoblastomycosis

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Abstract. We describe the first case of possible pulmonary chromoblastomycosis in the absence of any identified cutaneous lesions in a relatively immunosuppressed man. The causative organism was *Cladophilophora arxii*, which is a rare pathogen that has only been described as causing human disease two times previously.

INTRODUCTION

Chromoblastomycosis, a localized chronic cutaneous and subcutaneous infection of the skin caused by pigmented fungi, is most common in the world's tropical and subtropical zones.^{1,2} The condition rarely occurs in Australia, although six cases of chromoblastomycosis were seen at the Royal Darwin Hospital, Northern Territory from 1989 to 1994.³ The pathognomonic finding is the presence of brown spores or sclerotic bodies within granulomata or microabscesses in the skin.¹ We present the third possible case, to our knowledge, of chromoblastomycosis involving the lung in a relatively immunosuppressed patient. The causative organism in this patient (*Cladophilophora arxii*), while producing characteristic histological features, is also a rarely identified and recently characterized pathogen. This is only the third reporting of this fungus causing disease in humans.

CASE REPORT

A 67-year-old man was undergoing radiographic computed tomography (CT) surveillance at the Hematology Clinic of Royal Darwin Hospital for diffuse large-cell B-cell lymphoma (DLCL) in remission. He was found to have developed a right upper lobe irregular lesion in October of 2012. Differential diagnosis for the lesion included infective change or recurrent lymphoma. This was on a background history of diagnosis with DLCL in 2008. He was treated soon afterward 14 times with six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) among other therapy. Relevant past medical history included Hodgkin's lymphoma in 1971 (treated with radiotherapy and splenectomy) and metal aortic valve replacement for aortic regurgitation in 2006. He was asymptomatic from the lesion apart from some mild worsening of shortness of breath on exertion.

Over 4 months, the nodular density increased in size from 17 × 11 to 17 × 14 mm. He underwent a bronchoscopy with negative mycobacterial, *Nocardia*, fungal, and bacterial cultures and negative human immunodeficiency virus (HIV) testing. A CT-guided biopsy was attempted but unsuccessful, and a Positron emission tomography (PET) scan showed no avid

fluorodeoxyglucose (FDG) uptake. A decision was made to perform a video-assisted thoracoscopic surgery (VATS) right wedge resection of the lesion with an intraoperative frozen section in July of 2013. An intraoperative frozen section revealed brown-pigmented cells resembling muriform cells (or medlar bodies), consistent with a diagnosis of chromoblastomycosis.

Histopathology examination of the resected right lung tissue revealed nodular areas of pneumonitis with focal areas of chronically inflamed fibrosis containing aggregates of brown-pigmented fungal hyphae and fungal cells engulfed in brown-pigmented macrophages (Figure 1). The features were consistent with chromoblastomycosis.

C. arxii was grown from lung tissue and sent to the National Mycology Reference Center (NMRC), SA Pathology, Adelaide for identification and susceptibility testing. This fungus was slow growing at 35°C and eventually produced a dark, olivaceous, grey felt-textured colony with dark reverse. Darkly pigmented hyphae were observed in highly branched chains of brown, smooth-walled, lemon-shaped conidia. Identification was confirmed by DNA sequencing of the internal transcribed spacer (ITS) regions,⁴ with 98–99% sequence identity to other quality-controlled *C. arxii* sequences in the Centre for Biological Sequence Analysis (CBS) and Genbank databases. The isolate is stored in the NMRC culture collection, and the ITS sequence was submitted to the Genbank database (accession no. KP223283).

Antifungal susceptibility testing was performed using the CLSI M38 A2 standard.⁵ Minimum inhibitory concentrations (MICs) were as follows: amphotericin B, 2 µg/mL; 5-flucytosine, 32 µg/mL; fluconazole, 64 µg/mL; itraconazole, 0.12 µg/mL; voriconazole, 0.06 µg/mL; posaconazole, 0.03 µg/mL; caspofungin, 2 µg/mL; anidulafungin, 2 µg/mL; and micafungin, 2 µg/mL. Although there are no interpretive breakpoints currently accepted for any drug against this species, the triazole drug MICs would generally be considered low and indicative of *in vitro* sensitivity.

No cutaneous lesions of chromoblastomycosis were found after careful examination. The patient was initially treated with oral fluconazole at 400 mg daily. This was ceased after 2 weeks because of raised liver enzymes, with a peak alanine transaminase (ALT) of 143 IU/L. It was decided by the infectious diseases team to monitor the patient rather than treat with an antifungal, because the lesion appeared to have been completely excised, and there were issues with azole side effects.

The patient was reviewed regularly in the infectious diseases outpatient clinic. A repeat CT scan performed 4 months post-surgery showed no recurrence of the pulmonary lesion. He was feeling fit and well, with a return of his exercise tolerance.

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FIGURE 1. (A) Right lung microscopy showing nodular areas of pneumonitis. There are focal areas of chronically inflamed fibrosis containing aggregates of brown pigmented fungal hyphae and fungal cells (arrow), which are sometimes engulfed in brown-pigmented macrophages. (B) Periodic acid-Schiff stain of right lung tissue showing fungal cells and hyphae (arrow) within areas of pneumonitis. (C) Lactophenol cotton blue stain from plate culture of the fungus showing erect, partially apically branched, elongated conidiophores producing acropetal chains of smooth-walled conidia of *C. arxii*. The conidia are limoniform to fusiform (2.0–4.0 µm in size).

He was last reviewed 1-year post-removal of the lesion, and he had a normal chest X-ray and remained asymptomatic.

DISCUSSION

Chromoblastomycosis refers to cutaneous or subcutaneous lesions caused by melanized fungi. Pathognomonic of this condition is the presence of muriform cells on histology, which are round, brown sclerotic cells seen on direct microscopy.^{1,2,6} The conditions under which these bodies form and how they do it is not completely understood.⁷ The most common causative agents are *Fonsecaea pedrosoi*, which is generally seen in humid environments, and *Cladophialophora carrionii*, which is the most common causative agent seen in Australia.³ It is usually seen in otherwise healthy individuals, and extradermal spread is extremely rare. Cases have been described in the cornea,⁸ liver,⁹ lymph nodes,¹⁰ and recently, lung¹¹ but usually, they are in the presence of skin lesions.

Phaeohyphomycosis refers to clinical syndromes caused by melanized fungi that are not classified as eumycetoma or chromoblastomycosis.⁷ Eumycetoma is characterized by the presence of grains or sclerotia on histopathological examination, and chromoblastomycosis must have the presence of the pathognomonic muriform cells. Phaeohyphomycosis, therefore, shows dark fungal hyphae on histopathological examination without the presence of muriform cells or sclerotia.² Clinical syndromes classified as phaeohyphomycosis include allergic disease, deep-seated infections, deep local infections, pulmonary and central nervous system infections, and disseminated disease.⁷

We report a case of a dematiaceous fungal infection of the lung with muriform cells seen on histology. No skin lesions were found. The presence of these muriform cells is pathognomonic for chromoblastomycosis, indicating that this could be a case of primary chromoblastomycosis of the lung rather than phaeohyphomycosis.

Only two other cases of pulmonary chromoblastomycosis are reported in the literature.^{11,12} The most recent case describes a malnourished, otherwise healthy man with both skin and pulmonary lesions positive for muriform cells on histological examination. Fungal culture was positive for *F. pedrosoi*, a known causative agent of chromoblastomycosis.¹¹ Our case did not have any cutaneous lesions but did show the characteristic muriform bodies on histology. Our patient was

also relatively immunosuppressed, having received chemotherapy for DLCL a few years previously. This relative immunosuppression may account for the unusual presentation of a primary pulmonary presentation of chromoblastomycosis. The only other reported case of chromoblastomycosis involving the lung was in a 40-year-old male in Kenya with associated cutaneous lesions on the legs. The causative organism was *Cladosporium trichoides*.¹²

The causative agent in our case was *C. arxii*, which is a rare, recently identified dematiaceous fungus. It was first identified as a new member of the genus *Cladophialophora* in 1991.¹³ The clinical case described an otherwise well 22-year-old woman with a 5-cm granulomatous pulmonary lesion. This was surgically excised and incorrectly identified as sarcoidosis. Two years later, recurrent lesions were found on the trachea and intra-abdominally. These grew the new species of *Cladophialophora C. arxii*. Muriform bodies, similar to those described in our case, were found on histological examination of all of the lesions. After surgical excision of the lesions, the patient was treated with 6 weeks of flucytosine and itraconazole and then continued on itraconazole alone for 12 months. She was free of symptoms at 2 years post-therapy. To the best of our knowledge, the only other case of *C. arxii* infection in humans was a case of femoral osteomyelitis in a patient with chronic granulomatous disease.¹⁴

Both surgical and medical treatments of chromoblastomycosis are usually recommended because of the high rates of recurrence of this disease.^{1,6,7} Duration depends on clinical progress, and itraconazole and terbinafine are the usual antifungal agents of choice.² In our case, surgical management alone was used because of side effects from the medication initially trialed. At 1 year, there was no evidence of recurrence. The other case of pulmonary infection with *C. arxii* resulted in recurrence of disease after surgical management was used alone, although that lung lesion was significantly larger than the one seen in our case.¹³

In conclusion, we present the third possible case of chromoblastomycosis involving the lung and the first case with no primary skin lesion. Although some may classify this as phaeohyphomycosis rather than chromoblastomycosis given the absence of cutaneous or subcutaneous lesions, it meets the diagnostic criteria for chromoblastomycosis, because muriform cells were identified and a dematiaceous fungus was grown. It is also only the third known case of human infection with *C. arxii* and the first case in Australia.

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