Case Report

# A Diagnostic Predicament: Disseminated Coccidioidomycosis Mimics Tuberculosis

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**Abstract**

Coccidioidomycosis is a chronic granulomatous infection caused by dimorphic fungus *Coccidioides* spp. Sporadic cases of this infection have been reported globally in non-endemic regions those are primarily associated with travel to areas of high endemicity in the United States of America, Central and South America. The manifestations of coccidioidomycosis are not very different from tuberculosis (TB), and therefore, can be mis-diagnosed as TB, especially in areas with high prevalence of TB. We present a case of a middle-aged Indian male who travelled to USA and subsequently developed cough, fever, malaise, cutaneous nodules and discharging sinuses that were mis-diagnosed as TB; till a histopathological examination and fungal culture established the diagnosis of coccidioidomycosis of the lung with dissemination to the skin. He was successfully treated with oral itraconazole without any recurrence. **[Indian J Chest Dis Allied Sci 2017;59:39-42]**

**Key words:** Disseminated coccidioidomycosis, Pulmonary coccidioidomycosis, Cutaneous nodules, Tuberculosis, Spherule.

## Introduction

Coccidioidomycosis is a chronic progressive granulomatous infection of the skin, bones, lungs and other organ systems due to the highly infectious dimorphic fungus *Coccidioidesimmitis* and *C. posadasii*.[1] Conventionally, the disease is considered to be restricted to the western hemisphere and the regions of endemicity include south-western United States of America, desert region of northern Mexico and parts of Central and South America. In the United States, the region of endemicity mainly is central and southern California, southern Arizona, southern New Mexico, part of Utah and western Texas.[2] However, it is usual for cases reported from the non-endemic part of the world to have a history of travel to the afore-mentioned endemic zones.[3] Clinico-radiologically coccidioidomycosis mimics the more common mycobacterial infection tuberculosis (TB) and it is not uncommon to mis-diagnose and consequently mistreat the fungal infection using anti-tubercular therapy (ATT). The lacunae of mis-diagnosis are partly attributed to the poor recognition of the disease by clinicians and lack of well-equipped mycological diagnostic facilities. The present case of disseminated coccidioidomycosis in a male from a non-endemic region, Delhi, India who was treated with ATT till the correct diagnosis could be established is presented so that there is greater awareness among clinicians and microbiologists about this disease entity.

## Case Report

A 47-year-old male resident of Delhi, presented at chest clinic of Rajan Babu Institute of Pulmonary Medicine and Tuberculosis in April 2014 with complaints of dry cough, discharging sinuses around the neck and front of the chest, generalised malaise and weight loss of nearly 15 Kg over the past 2 years. The patient was a musician by occupation and had no history of substance abuse.

On physical examination, discharging sinuses around the midline and right side of the neck and over the sternum which exuded pus admixed with blood were observed. The skin around the sinuses revealed extensive scarring suggesting a chronic process. No lymphadenopathy, hepatosplenomegaly or bone tenderness was elicited.

Previous history revealed that he travel to Bakersfield, California, USA in November 2012 for one of his musical concerts where he has developed high-grade fever with chills, dry cough, malaise and dyspnoea. He received treatment through a private practitioner in USA and was empirically prescribed oral antibiotics for 2 weeks and was relieved of his symptoms.

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However, in July 2013 he again had similar symptoms but with associated discharging skin lesions and in December 2013 he consulted a private health facility in Delhi NCR region. His blood counts and serum biochemistry was within normal limits and antibodies for human immunodeficiency virus (HIV) were negative. Chest radiograph showed an ill-defined opacity in the right lower zone with tenting of the right hemidiaphragm. Contrast-enhanced computed tomography (CECT) of thorax revealed a necrotic right supraclavicular lymph node, sub-segmental collapse with associated fibrosis and traction bronchiectasis in the lateral segment of the right middle lobe and right-sided pleural thickening. He underwent a fine needle aspiration (FNA) from the right supraclavicular mass, which was reported to harbor numerous non-caseating granulomata with superadded acute inflammation. However, no acid-fast bacilli (AFB) were seen on smear, nor were culture positive for *Mycobacteria*. Further, interferon-gamma release assay was negative. He was prescribed ATT, comprising of daily doses of isonizid, rifampicin, ethambutol and pyrazinamide in February 2014.

He had recurrent discharging sinuses over the neck over the last one year prior to presenting to our institute at chest clinic of Rajan Babu Institute of Pulmonary Medicine and Tuberculosis for his complaints of discharging sinuses from the neck and cutaneous nodules over the neck and chest (Figure 1). Chest radiograph now revealed a fibrotic lesion in the right lower zone and associated ill-defined infiltrates with tenting of the ipsilateral hemidiaphragm. A repeat computed tomography of the thorax showed a necrotic subcutaneous mass in the right supraclavicular fossa and another heterogeneous subcutaneous nodule overlying the sternum, not in continuity with the pulmonary lesions previously described (Figure 2). An ultrasound of the abdomen did not reveal any hepatosplenoomegaly, masses, free fluid or lymph nodes.

Bacteriological analysis of pus again had no AFB and cultures were negative. The ATT was continued till January 2015. The patient refused to undergo a bronchoscopy for his pulmonary disease. Since he failed to show any signs of resolution, nucleic acid amplification techniques were employed on the discharged pus and expectorated sputum samples to assess for drug-resistant TB but the same did not reveal the presence of *Mycobacterium tuberculosis*. Surgical excision of an enlarged cervical cutaneous nodule in the pre-tracheal region was done.

The curetted samples from the base of the lesion as well as aspirates were also sent for fungal and mycobacteria other than TB (MOTT) culture. Histopathological examination of PAS stained cervical nodules showed a thick-walled spherule with multiple endospores surrounded by a mixed suppurative granulomatous reaction suggesting a diagnosis of coccidioidomycosis (Figure 3). Also, fungal culture at 28 °C grew mould colonies after 5 days of incubation that showed septate hyphae and arthroconidia in alternate hyphal cells. The isolate

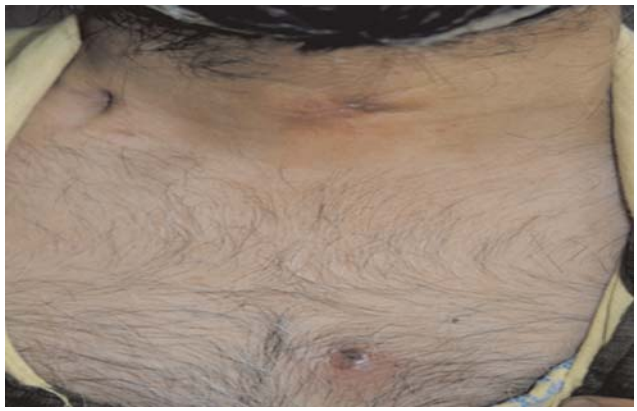

**Figure 1. Photograph showing discharging sinuses on the neck and skin nodule on the neck and chest of the patient at presentation.**

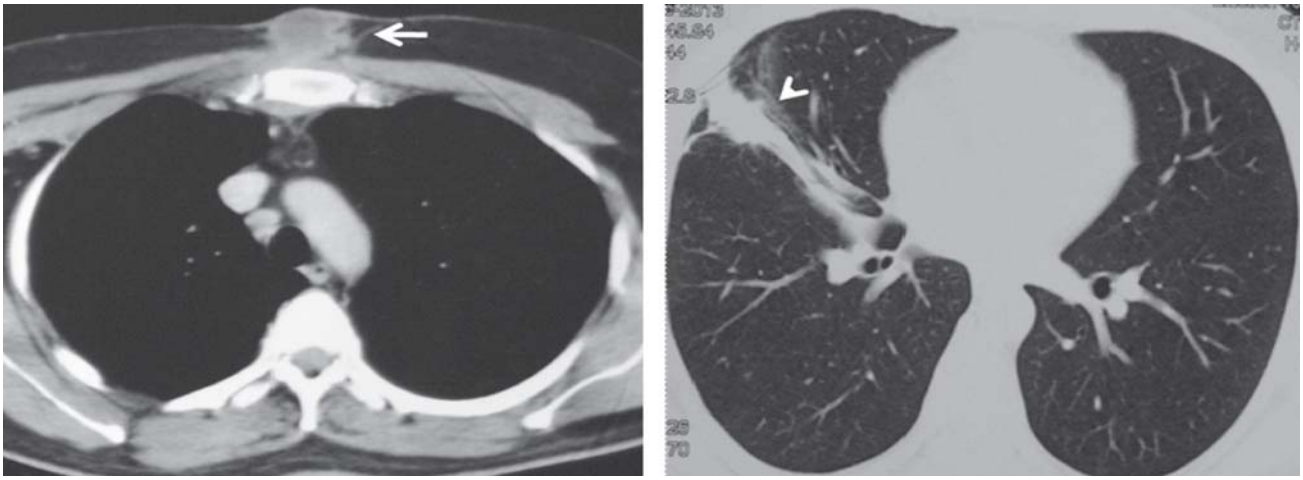

**Figure 2. Contrast enhanced computed tomography of thorax done in 2013 demonstrating median cutaneous nodule (white arrow) and infiltrates, subsegmental collapse, fibrosis and traction bronchiectasis in the lateral segment of the right middle lobe and right pleural thickening (white arrowhead).**

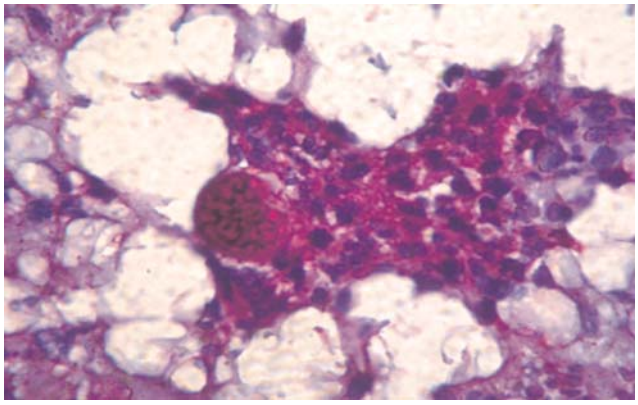

**Figure 3. Histopathology (PAS stained) section from the midline neck skin nodule showing a thick-walled spherule with multiple endospores surrounded by a mixed suppurative-granulomatous reaction (PAS × 400).**

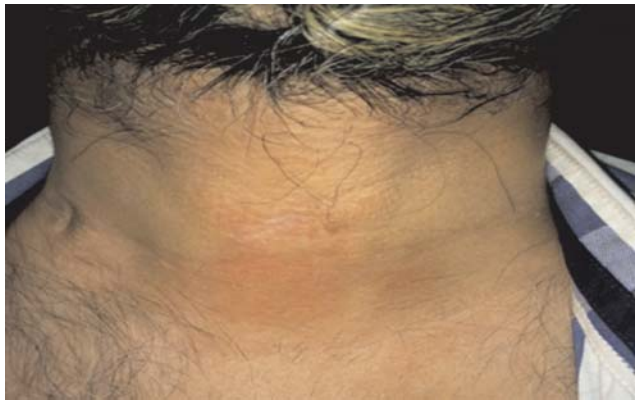

**Figure 4. Resolution of the cutaneous lesions after 6 months of therapy with itraconazole.**

was confirmed as *Coccidioidesimmitis* by sequencing of internal transcribed spacer region of the ribosomal subunit and D1/D2 region.

Treatment with oral itraconazole (400mg/day) for 6 months showed gradual resolution of the lesions. Patient was advised to stop itraconazole following complete resolution of the skin lesions (Figure 4); pulmonary complaints with a weight gain of 24 Kg. The clinical history also corroborated with the chest radiology, which showed replacement of the pulmonary and subcutaneous lesions with fibrosis (Figure 5). Thereafter, the patient continued to be well and symptom-free even after 4 months of cessation of the treatment.

## Discussion

Coccidioides species are soil-inhabiting fungus with a restricted geographical distribution, causing chronic, disfiguring, granulomatous disease. However, the geographic boundaries of the disease have begun to expand due to increasing tourist travel to areas of endemicity.[4] The Indian subcontinent is classically devoid of natural infection with the dimorphic fungus *Coccidioidisimmitisor C. posadosi*. However, it is noteworthy that all 8 cases reported from India including the present one had history of travel to endemic zones in the USA; five to Arizona, two to California and one to both the states.[3,5] Contrary to usual fungal infections, 88% of the reported cases from India occurred in immuno-competent individuals that demonstrate the primary pathogenic potential of *Coccidioidis* spp. Of the reported cases, the present case is probably the only case of imported coccidioidomycosis in Indian patient whom dissemination was noted despite lack of any immunosuppressive illness.

The fungus is usually acquired through inhalation of airborne arthroconidia and the respiratory system is the primary site of infection in up to 95% cases.[6,7] Infections are usually seen in persons involved in recreational exposure to dust and soil in endemic zones. In the present case, the patient denied any such activity, though environmental factors cannot be ruled out. The primary portal of entry in the present

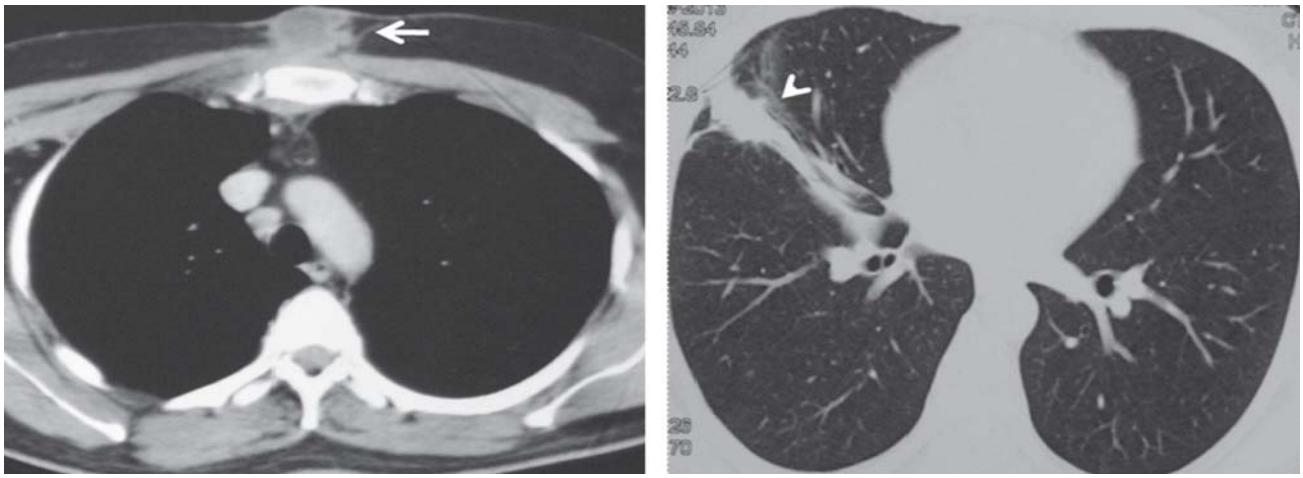

**Figure 5. Contrast enhanced computed tomography done in 2015 after 6 months of treatment showing resolution of the cutaneous nodules (white arrow) and pulmonary infiltrates (white arrowhead).**

case was the respiratory tract as apparent from his non-specific pneumonia-like initial symptoms and the consolidation on chest radiography. Given the natural history, the disease abated on its own giving the impression of a resolving bacterial pneumonia. However, over a period of time, the pulmonary disease persisted giving rise to parenchymal infiltrates, fibrosis and traction bronchiectasis. Nearly 1% patients with pulmonary coccidioidomycosis develop lymphomatous or haematogenous dissemination to other organ systems, notably the lymph nodes, integumentary, musculoskeletal and nervous systems.[4] Similarly, in the present case, dissemination occurred to the lymph nodes and skin as manifested by mediastinal lymphadenopathy on the CT, cutaneous nodules and draining sinuses. However, none of these cutaneous manifestations had any anatomical contiguity with the underlying pulmonary lesions and occurred independently of the latter, thereby indicating dissemination. Although primary infection of the skin is rare, cutaneous manifestations include papules, plaques, ulcers, draining sinuses, and subcutaneous abscesses; and punch biopsies should be obtained to establish a tissue diagnosis.[8]

In diagnosis of pulmonary coccidioidomycosis, radiology is usually non-specific and distinguishing the same from a bacterial pneumonia is usually difficult except that hilar and paratracheal adenopathy, occurs in up to 10% of primary cases of the former and rarely in other primary pneumonias. Other radiographic findings of primary pulmonary disease include infiltrates, hilar adenopathy, and pleural effusions. Presence of cavities and nodules indicates complicated or residual stage of pulmonary coccidioidomycosis. Therefore, in regions with low endemicity for coccidioidomycosis, the disease may easily be confused with TB, a more obvious cause of such radiological findings. Diagnosis of coccidioidomycosis rests on visualising the 'spherule' with the associated early or late phase reactions on tissue biopsy and or direct/indirect indicators for the presence of the fungus such as microscopy, laboratory culture, detection for anticoccidioidal antibody in the serum by enzyme liked immunosorbent assay (ELISA), immunodiffusion or by tube precipitin and complement fixation assays.[4,9]

The present case was unequivocally confirmed by isolation of the fungus in culture. Further, species were confirmed using molecular techniques. Moreover, the other diagnostic consideration such as tuberculosis/drug resistant tuberculosis or infection with MOTT was ruled out by repeated negative cultures and by molecular methods.

Treatment of primary pulmonary involvement in an immunocompetent host is usually unwarranted as the disease is self-limiting. However, treatment may be instituted for persistent and disseminated disease. Itraconazole (400mg per day) or fluconazole (800mg per day) for one year are advocated for the treatment of non-meningeal diseases; while amphotericin B is the preferred alternative agent. The patient has to be followed-up for one year to label that the disease has gone into complete remission.[9] Our patient received an adequate dose of itraconazole for 6 months and is symptom-free on regular follow-up. Antitubercular therapy on an empirical basis is common practice among high burden countries like India.[3,10]

The present case highlights the problems encountered by the clinician while dealing with the emergence of newer disease entities hitherto considered 'geographically restricted'. Such diseases are further expected to rise in the non-endemic area due to the ever-changing demographics; therefore it is important for the clinicians to be aware of epidemiology of diseases not prevalent in their countries.

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