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First imported coccidioidomycosis in Turkey: A potential health risk for laboratory workers outside endemic areas

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ABSTRACT

Coccidioidomycosis caused by *Coccidioides immitis* or *Coccidioides posadasii* is endemic in arid climate zones in America, travel-related cases have been reported. We report the first documented case of coccidioidomycosis in Turkey, overviewing reported cases in Europe and underlying difficulties of differential diagnosis outside endemic regions. The patient was an otherwise healthy 41-year-old man who travelled endemic areas. Laboratory diagnosis was based on direct microscopy of two subsequent subcutaneous biopsy specimens and culture and confirmed molecularly. Laboratory personnel should become aware that BioSafety Level-3 organisms may become more frequent and widespread.

1. Introduction

Coccidioidomycosis is an endemic disease of arid and semi-arid regions of northern and southern America caused by *Coccidioides posadasii* and *Coccidioides immitis*, which can only be separated by DNA sequencing. Travellers to endemic areas are at risk of developing coccidioidomycoses through inhalation of airborne conidia. A history of travel to endemic areas as well as a high index of suspicion is imperative for timely and accurate diagnosis [1]. In order to differentiate this infection from other systemic mycoses, diagnostic spherules should be observed in clinical samples, and/or typical barrel shaped arthroconidia in culture. The present case is the first report of proven, imported coccidioidomycosis in Turkey. Unfamiliarity with the disease might present a severe biohazard to laboratory personnel.

2. Case

On June 2011, a 41-year-old, otherwise healthy, Turkish man travelled toTexas for 2 months where he spent his spare time in walking through the forests, and then took 1 month trip by car to Grand Canyon, Las Vegas and San Francisco during which he fasted in accordance with Ramadan, but felt unusually weak and lost weight. On his 80th day in the USA, he felt very ill near Niagara Falls and laid down on the grass, suffered from chest pain and severe sweating. Ten days later, he was admitted to an hospital in Texas with coughing, fever, vomiting and loss of appetite (day 0). He was diagnosed with pneumonia and given 400 mg/day moxifloxacin. The next day he returned to Batman, Turkey and attended University Hospital with nausea, vomiting, weakness, sweating, productive coughing and fever (day +1). Serologic assays for IgM levels of CMV, Herpes type II, Rubella, Parvovirus B19, and EBV EBNA were all negative. CRP was 30.7 mg/L and increased to 42.5 mg/L (day +4). Sputum, throat, urine cultures and haemoculture as well as stains for acid-fast bacteria and mycobacterial cultures were also negative while moxifloxacin was continued. Chest X-rays were normal but chest CT scan revealed a 18 mm nodule on the left upper lobe with suspected histoplasmosis. Bronchoscopy showed white mucosal nodularity and a biopsy was performed. Fungal cultures of the biopsy specimen were

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negative. A blood sample gave negative result for Histoplasma DNA identification by PCR. Abdominal ultrasound and a cranial CT scan were normal. Due to persistent fever up to 40 °C and night sweat, patient was switched to imipenem and clarithromycin. He refused pulmonary biopsy and left hospital (day +11). Following the development of a cutaneous lesion of about 1 cm diameter on his neck (day +38), he attended University Hospital in Ankara and was hospitalised. CRP level was 15.8 mg/L and increased to 22.5 mg/L (day +42). Routine clinical laboratory data were unremarkable. Cytology and stains for acid-fast bacteria, as well as fungal and mycobacterial microscopy and cultures of two subsequent bronchoalveolar lavage (BAL) samples and a lymph node biopsy specimen were all negative. For his neck lesion, amoxicillin-clavulanic acid, 1000 mg, t.i.d. and a topical fusidic acid cream were started and then he was discharged (day +46).

He attended Batman State hospital with severe chest pain, lack of appetite, the persistent lesion on the neck and an additional small papule in the left palm (day +47). An abdominal CT scan revealed ascites, and the cytology of aspirated peritoneal fluid showed numerous lymphocytes, neutrophils, eosinophils and histiocytes.

He was admitted to another hospital and a chest CT scan revealed a nodule of about 18 mm on the left upper lobe and oedema (day +54). Pathological examination of a punch biopsy of his neck lesion revealed pseudoepitheliomatous hyperplasia-like verrucose proliferation and neutrophils in the epidermis. A dense infiltrate of neutrophils, lymphocytes, plasma cells, histiocytes and eosinophils invading epithelia were present in the dermis. Langerhans-like multi-nuclear giant cells and granuloma formations were also observed. PAS-positive, round, thick-walled fungal elements were observed in the cytoplasm of the giant cells in neutrophilic abscesses. North American blastomycosis was suspected. Stains for acid-fast bacteria and mycobacterial cultures were negative. Histopathological preparations sent for consultation were reported as being fungal dermatitis. Itraconazole (ITZ) 100 mg b.i.d. was prescripted for 6 months.

When he was admitted to a university hospital in Ankara (day +164), CRP level was 1.74 mg/L. A chest CT scan revealed additional lymph nodes with an infectious appearance in the left lung. Parenchymal lesions were smaller than they were on the day +4. No ascites was detected on abdominal CT scan. He was free of pain. ITZ treatment was continued. A chest CT scan made in Batman (day +308) showed micronodules in the left lung and left hilar lymphadenopathy of a "tree-in-bud" appearance with some regression when compared with the CT scans of day +2. His palm lesion was healed but lung lesions were sustained after having been treated with ITZ 200 mg/day for 6 months. On follow-up visit (day +363), because of his persisted neck lesion despite ITZ treatment, the patient was transferred to a Research Hospital in Istanbul for further evaluation for suspected blastomycosis and its treatment with amphotericin B (AMB).

When he admitted to the dermatology department (day +368), he was concious, cooperative and oriented with normal physical examination. He had an erythematous, slightly elevated atrophic lesion on his neck of about 4.3 cm and brightly coloured peripheric minor papules. Serology for HBsAg, Anti HBs, Anti HCV and Anti-HIV were all negative. Neck ultrasonography revealed several lymph nodes having a reactive appearance, smaller than 12 mm in diameter. Abdominal magnetic resonance imaging (MRI), cranial CT scans and a whole body bone scintigram were normal (day +373). Pulmonary radiological scans were thought compatible with blastomycosis.

Two subsequent punch biopsies of 5 mm were carried out (days +368 and +379) and sent to Cerrahpasa Medical Faculty (CMF), Deep Mycoses Laboratory (DML), with clinical suspicion of North American blastomycosis and the patient was discharged at his own request. Previous histopathological sections were requested from the laboratory for mycological re-examination. *Coccidioides* sp. was identified by microscopy and two subsequent biopsy samples were cultured. Treatment was continued with ITZ 200 mg/day for 3 months.

When the patient was seen on day+465, his neck lesion was healed and his physical examination and routine clinical laboratory data were unremarkable. On the chest CT scan parenchymal miliary lesions were resolved, lesions defined on the left lung and mediastinal windows showed no significant differences with those of the previous years, but there was a significant reduction of the diameter of the left axillary and mediastinal lymph nodes. Nodullary consolidation documented on the left lung altered to granuloma-like configuration (Fig. 1). A nasal endoscopy was carried out. A previous sinoorbital MRI was reviewed but revealed no abnormality except

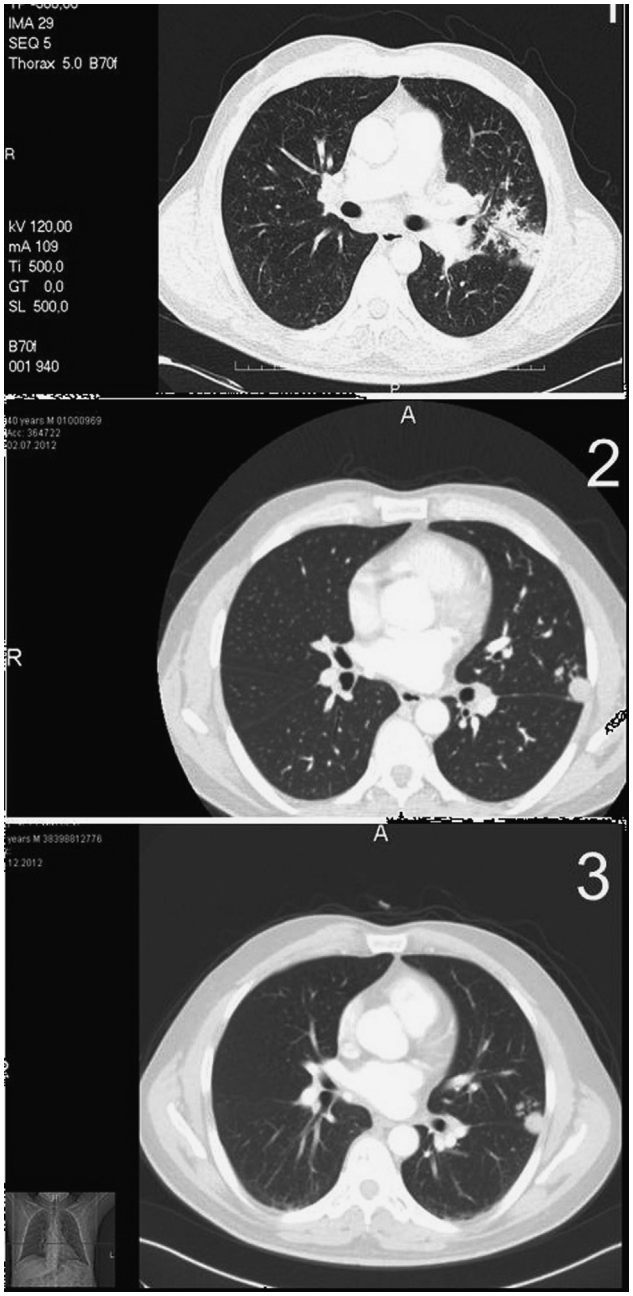

Fig. 1. Chest images. (1) MRI on September 2011 showing pneumonic infiltration and nodular appearance also suggestive for fungal infection in the middle lob. (2) MRI on July 2012 showing micronodules in the left lung and left hilar lymphadenopathy of "tree-in-bud" appearance. (3) CT image on December 2012, there was no significant differences with that of July 2012 and was interpreted as a sequelae.