Case Report

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Pulmonary *Coccidioides* nodule in a Swiss patient with chronic lymphatic leukaemia

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The dimorphic fungus *Coccidioides immitis*, causative agent of coccidioidomycosis, is endemic in semi-arid regions of the Americas. The disease is rarely encountered in Europe. We describe the case of a 61-year-old Swiss patient with chronic lymphatic leukaemia who was eventually diagnosed with an initially unnoticed pulmonary coccidioidomycosis.

Case report

A 61-year-old Swiss patient was diagnosed with chronic lymphatic leukaemia (CLL) in 1999. No specific therapy had been initiated at that time, but the patient stopped smoking. In December 2002, the patient presented to his general practitioner with fever, cough and general weakness. A chest X-ray (Fig. 1a) showed a pneumonic infiltrate in the middle lobe. Pneumonia was suspected and antibiotic therapy was initiated with clarithromycin, but the patient showed an incomplete clinical response. Bronchitic symptoms persisted; episodes of amelioration alternated with deterioration of the patient's general condition. Another chest X-ray showed a reduced middle lobe infiltrate but a new pulmonary nodule in the left lower lobe (Fig. 1b). Symptoms improved again under clarithromycin to some extent, but the pulmonary nodule in the left lower lobe persisted on a follow-up chest X-ray (not shown). Because of the primary disease, the patient was referred to a pulmonologist. A computed tomography scan of the chest showed complete regressive pneumonia but a persisting pulmonary nodule in the left lower lobe of 13 mm in diameter (Fig. 2). During radiological surveillance over the next 12 weeks the nodule remained unchanged. Bronchitic symptoms gradually continued to improve. Additionally, a bronchoscopy with multiple mucosal biopsies and subcarinal fine needle aspirations was done in January 2003. The pulmonary nodule was not accessible by bronchoscopy. Histology and bacteriology did not reveal new findings either. To exclude a malignant process, the patient was referred to the Department of Thoracic Surgery of our hospital.

On admission, the patient presented in good general condition without weight loss, night sweats, fatigue or cough. Physical examination showed no pathological findings. All laboratory values were normal, except for an elevated white blood cell count of $34 \times 10^9 \text{ l}^{-1}$ ascribed to the CLL. The pulmonary nodule was still present upon chest X-ray.

A wedge resection was performed in the area of the left lower lobe in May 2003. Histology showed a homogeneous lymphocytic infiltrate which originated from the known CLL. Grocott–Gomori and periodic acid–Schiff staining initially showed necrosis with peripheral reactive zones but no fungus was seen. Hence symptoms were considered to be complications of the CLL.

As tuberculosis was still considered part of the differential diagnosis, tissue was sent to the clinical mycobacteriology laboratory. Smear was negative for acid-fast bacilli. PCR for the *Mycobacterium tuberculosis* complex (COBAS Amplicor MTB PCR assay; Roche Diagnostics) was negative as well. To check for sterility, the homogenized tissue suspension was inoculated on a chocolate agar plate prior to inoculating the mycobacterial culture media [Löwenstein–Jensen medium, Middlebrook 7H10/7H11 selective agar bipate (Becton Dickinson) and BBL MGIT tube (Becton Dickinson)].

After 7 days, a white fungal mycelium was detected exclusively on the chocolate agar plate, while the mycobacterial media remained negative after 8 weeks. Based on microscopic and cultural aspects the fungus was identified as *Coccidioides immitis*. Colony morphology of *C. immitis* at 25–30 °C ranges from greyish to white, floccose colonies. Microscopic features include thin, septated hyphae and one-celled, short cylindrical arthroconidia. Since mycobacteriological analyses were done, all media were kept in the P3 facility and the fungus was followed up at the appropriate containment right from the beginning.

In a histological reassessment using silver staining, a few spherules were observed confirming coccidioidomycosis. Once the clinical diagnosis had been made, the patient reported travelling to Arizona for 2 weeks prior to the onset of symptoms. No specific therapy was initiated since the patient was in good general condition again.

Abbreviation: CLL, chronic lymphatic leukaemia.

Fig. 1. (a) Initial chest X-ray from 18 January 2003, showing a pneumonic infiltrate in the middle lobe (asterisk). (b) Follow-up chest X-ray under therapy with clarithromycin from 25 January 2003, with a reduced middle lobe infiltrate (asterisk) but a new pulmonary nodule in the left lower lobe (arrows).

Discussion

C. immitis is a dimorphic fungus endemic in the south-west of the USA and South America. A few cases associated with travel to endemic areas have been reported in

European patients, most of them, however, before 1980 (Alanko *et al.*, 1975; Holemans *et al.*, 2000; Kreml-Lamprecht, 1978). Since coccidioidomycosis is rarely seen in Europe and therefore will not often be suspected, it is

Fig. 2. Computed tomography of the chest with a persisting pulmonary nodule in the left lower lobe of 13 mm in diameter (arrow).

important that physicians recognize infections with this pathogen worldwide, in particular with respect to the generally observed increase in mobility. As a consequence, it should be part of the differential diagnosis. Even in countries with a high incidence of the disease, e.g. the USA, diagnosis is frequently missed or delayed if the patient lives in a non-endemic area (Desai *et al.*, 2001). In Europe, patients are rather checked for malignancies or tuberculosis and not for diseases caused by endemic dimorphic fungi. Hence the first differential diagnosis in this case was a malignant process in conjunction with the patient's primary disease. Finding the appropriate diagnosis was complicated by the fact that chronic nodules may form after coccidioidomycosis which can mimic lung cancer (Petrini *et al.*, 2003). Such nodules develop from weeks to months after infection and usually remain stable for long periods of time. Microscopic, cultural and serological methods are available for diagnosis of coccidioidomycosis. Nucleic acid amplification tests have been developed as well, but are not on the market yet (Saubolle, 2007; Saubolle *et al.*, 2007). However, serological tests for *C. immitis* are uncommon in Europe. Positive serologies can be helpful in the diagnosis, but negative tests should not be used to rule out the disease (Saubolle, 2007; Saubolle *et al.*, 2007). In this case, no serological testing was ordered, because the disease was not suspected until the cultures became positive. Immunocompromised conditions such as diabetes, HIV infection, lymphoma or a history of smoking are known risk factors not only for coccidioidomycosis (Blair *et al.*, 2005; Laniado-Laborin, 2007; Rosenstein *et al.*, 2001) but also for tuberculosis (Maartens & Wilkinson, 2007). In low-incidence countries for *C. immitis*, clinicians will evidently rule out tuberculosis by requesting mycobacterial analyses. Today's changes in travelling behaviour may increasingly lead to infections with organisms that are uncommon in the travellers' home countries and consequently be mis- or underdiagnosed.

It remains unclear why the fungus was missed initially upon histology and only detected in a histological reassessment. Smears and histopathology are less sensitive than culture, which remains the gold standard (Binnicker *et al.*, 2007). Unlike culture, microscopical methods largely depend on the skills of the laboratory personnel. In our case, lack of experience with dimorphic fungi may explain why *C. immitis* was initially overlooked. Remarkably, *C. immitis* was only detected because mycobacterial cultures were requested by the clinicians. In our mycobacteriological laboratory, specimens from normally sterile body sites are first inoculated on chocolate agar to check for contaminants. If contaminants can be excluded, specimens are directly inoculated on mycobacterial media without pre-treatment. Chocolate agar plates are kept for 8 weeks and thereby allow the detection of fastidious organisms such as *Mycobacterium haemophilum*. Without the inoculation of a chocolate agar plate, *C. immitis* would have been missed. This case report demonstrates that cultures from patients at risk for endemic fungal infections should be

handled with special care. Clinicians should immediately inform the laboratory if endemic fungi are part of the differential diagnosis. Since all dimorphic fungi are class 3 organisms, such specimens should be processed in biosafety cabinets (class II) or, more appropriately, in a biosafety level 3 containment.

Despite the CLL, no antifungal therapy was initiated because the clinical condition of the patient improved spontaneously. Also, there had been no need for therapy for the CLL by the time of admission. However, it cannot safely be excluded that a patient with CLL will need corticosteroids or other chemotherapy during the course of the disease. Hence such a patient may become immunocompromised either pharmacologically or during the natural course of leukaemia. To prevent reactivation of the disease, a prophylactic therapy, e.g. with fluconazole or itraconazole, may be indicated. It has to be emphasized, however, that in acute disease in an already immunocompromised host, antifungal therapy is generally indicated (Lortholary *et al.*, 1999; Yamada *et al.*, 2003).

Retrospectively, our patient had several risk factors that would have pointed to coccidioidomycosis: (1) he was potentially immunocompromised because of CLL; (2) he had a history of smoking; (3) there was a history of travelling to an endemic area which was unknown to the clinicians; (4) he had a pulmonary nodule after a prolonged course of pneumonia that did not fully respond to antimicrobial agents.

Hence, in patients with risk factors for coccidioidomycosis, special emphasis is mandatory in order to elicit history of travel to endemic areas. Most importantly, physicians in non-endemic areas should be aware of the possibility of infections with foreign endemic pathogens. In parallel, techniques such as an additional chocolate agar plate allowing laboratories to detect uncommon fungi should be used.

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