Infect Dis Trop Med 2016; 2 (2): e289

Pulmonary tuberculosis sustained by *Mycobacterium bovis* in a young Italian patient

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ABSTRACT:

Historically, *Mycobacterium bovis* infection in humans was associated with consumption of unpasteurized milk and dairy products and this is still the most important route of exposure in limited-resource countries; in rich resource countries, this infection has been usually observed in elder subjects. Direct airborne transmission from animals to humans is thought to be a rare as well as an interhuman transmission. We here describe the diagnosis and clinical management of pulmonary *M. bovis* infection in a 30-year-old healthy Italian female patient. One interesting aspect of this case is the absence of identifiable risk factors including the consumption of unpasteurized diary products or animal contact. Being *M. bovis* usually resistant to pyrazinamide, it is important to understand the epidemiology of human *Mycobacterium bovis* tuberculosis in order to personalize anti tubercular treatment.

Keywords: Pulmonary tubercolosis, *Mycobacterium bovis*, Pyrazinamide resistance.

INTRODUCTION

The Mycobacterium tuberculosis complex (MTBC) includes M. tuberculosis, M. bovis, M. bovis bacillus Calmette-Guérin (BCG, the vaccine strain), M. africanum, and M. microti. *Mycobacterium tuberculosis* causes the majority of tuberculosis (TB) cases in humans; however, in several regions of the world, especially in a country with high prevalence of HIV infection, human TB caused by *M. bovis* may be common but underreported[1]. M. bovis is the main cause of tuberculosis in cattle, deer, and other mammals and human pathology is considered a zoonosis; transmission is mainly through consumption of unpasteurized dairy products, and it is less frequently attributed to inter-human transmission. The exact incidence of *M. bovis* TB is uncertain but it is considered to be uncommon in rich-resource countries; worldwide it is estimated to be responsible for approximately 3% of pulmonary tuberculosis[2].

We report the case of an Italian woman in her thirties; she reported no history of travel outside Western Europe, no contact with subjects with active pulmonary tuberculosis or chronic cough. Her past medical history included an episode of acute pyelonephritis and Gilbert's pityriasis rosea but no other significant condition or hospital admission.

She reported two weeks of night sweats, malaise and productive cough (following six months of dry cough); after the sudden onset of haemoptysis she presented to the emergency room. Chest X-ray and computerized tomography showed bilateral lung infiltrates with multiple cavitations (Figure 1) but the smear tested negative for alcohol-acid resistant bacilli. Given the high suspicion she was admitted to our Infectious Disease ward and placed in respiratory isolation with negative pressure aspiration.

Physical examination at admission was insignificant with a body temperature of 37.3 °C, blood pressure of 110/70 mmHg, a pulse rate of 74/minute and a respiratory rate of 24/min. Physical examination of the chest, head, neck, lymph nodes, heart and abdomen was normal.

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Blood chemistry was within the range of normality and HIV test, upon obtaining her consent, was negative. Quantiferon TB Gold (QIAGEN, Australia) tested positive as well as sputum samples, the latter was positive for both the Ziehl-Nielsen staining and Mycobacterium tuberculosis complex DNA (polymerase chain reaction, Cepheid, Sunnyvale, CA, USA). Directly observed weight-based four drug anti-tuberculous therapy (isoniazid 300 mg, rifampicin 600 mg, ethambutol 1200 mg and pyrazinamide 1500 mg) was started along with pyridoxine and colecalciferol. After two weeks sputum culture was positive (liquid culture) and showed the presence of *Mycobacterium bovis;* pyrazinamide administration was stopped according to the usual phenotypic resistance.

A slow clinical improvement was observed with no further hemoptysis episode after two weeks of treatment. Sputum acid-fast bacilli density slowly decreased over time with still 1-9 bacilli per microscopic field one month after antitubercular treatment initiation. At this time, she required to be discharged without physicians' consent given the presence of young children in her household. She was followed as outpatient and radiological reduction in cavitations was observed after 8 weeks of treatment. Negative sputum cultures were observed at 8 weeks and she recently completed the 7 months maintenance phase with rifampicin plus isoniazid.

The public health survey was not able to trace any contact with animals or unpasteurized diary products; however patient reported that her father-in-law had a chronic cough but he unfortunately died (a few months before the episode) due to an ischemic heart attack.

We here presented this case of a young Italian patients presenting with a rapidly evolving pulmonary disease sustained by *M. bovis:* such infection is uncommon in developed countries, where human infections have been virtually eliminated due to effective veterinary programs and the consumption of pasteurized milk.

The case here described doesn't belong to high-risk groups such as animal workers, farmers, meat packers, veterinaries and zoo keepers and no contact with infected people was found. *Mycobacterium bovis* interhuman transmission is less common than transmission from cattle but the exact incidence is unknown; the mayor pathway of disease transmission is via oral ingestion through consumption of unpasteurized dairy products or exposure to infective animals. Nowadays, the majority of the 7000 cases of human TB annually reported in the UK are due to *M. tuberculosis* acquired directly from an infectious person[3]. Among 129 cases of human *M. bovis* infection in the United Kingdom between 2005 and 2008, most patients were older than 65 years, suggesting that reactivation may have occurred following latent infection acquired prior to widespread pasteurization of milk[4]. Nevertheless one recent paper reported the diagnosis of pulmonary *M. bovis* infection in cats and humans living in the same household, in Texas, supporting the existence of non-traditional ways of transmission[5]. Worldwide *M. bovis* contribution to human tuberculosis varies widely: while <1% of human infections are caused by *M. bovis* in Spain, the prevalence in Africa ranges from 3.9% in Nigeria, up to 7% in Uganda, and even 16% in Tanzania[6-8]. A worrisome 28% prevalence was reported in Mexico[9]. It was reported that in some developing countries, *M. bovis* is responsible for 5-10% of all human TB cases and 30% of all TB cases in children[10].

M. bovis tuberculosis is hardly diagnosed because no clinical or radiological feature emerges; molecular techniques are needed to differentiate it from the one sustained by *M. tuberculosis*. M. bovis can mani-

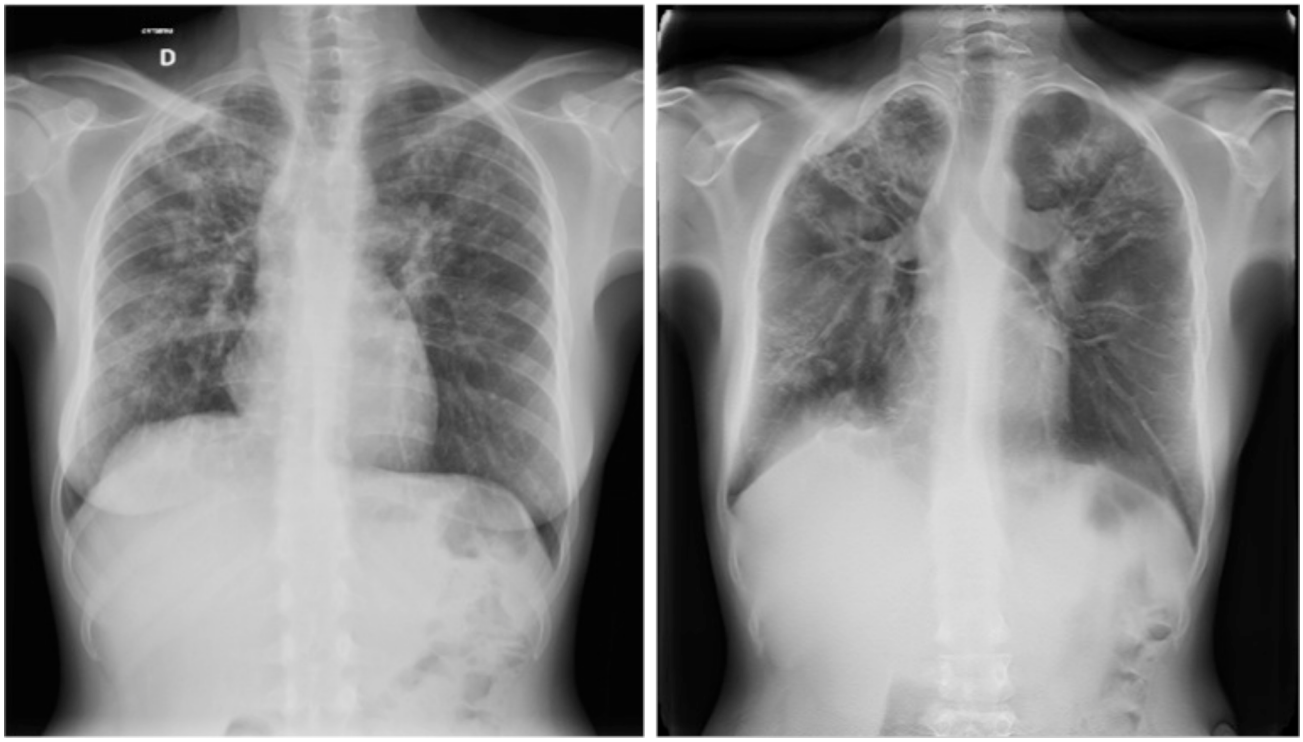

Figure 1. Chest X-ray (left) and volume-rad (right) showing diffuse involvement of both lungs with multiple apical cavitations.

fest with primary and reactivation forms; involvement may be pulmonary, extrapulmonary, or disseminated. When M. bovis is acquired via ingestion of contaminated dairy products, the extrapulmonary disease is more likely than pulmonary tuberculosis. Extrapulmonary sites of M. bovis include lymph nodes, pleural space, joints, eye, and central nervous system and they have been often observed in HIV-positive patients[11]. Strains of *M. bovis* are intrinsically resistant to pyrazinamide. Nevertheless, World Health Organization 2003 guidelines on the therapy of human bovine tuberculosis have no specific recommendations on the matter. The American Thoracic Society recommends an initial 2 months regimen of isoniazid, rifampicin and ethambutol followed by a 7-month continuation phase of isoniazid and rifampicin[12].

In a 15-year surveillance study, carried out in Mexico City, the analysis of mycobacterial isolates from human clinical samples that showed primary streptomycin resistance was higher among *M. bovis* compared with *M. tuberculosis* isolates (10.9% *vs.* 3.4%, $p<0.001$) with no difference in multidrug resistance rates (38.5% and 34.4%). Primary streptomycin resistance can be explained through the widespread use of this compound in the veterinary field[13].

Furthermore, drug-induced liver injury has been observed in 5 to 33% of patients treated with four-drug regimens and risk factors include elder age, female gender, baseline transaminase levels, viral co-infections and slow acetylator status among others[14]. The influence of pyrazinamide on TB DILI is ambiguous; some studies indicate little to no increased rate of hepatotoxicity, whereas others point to it as a contributor to increased incidence or severity of hepatotoxicity although dosing variations and patient selection biases may have contributed to these results[15]. Several cases of prolonged or severe liver damage associated with pyrazinamide have been reported[16,17].

In conclusion *M. bovis* tuberculosis should be suspected even in young and not-at-risk patients and its isolation is needed in order to avoid unnecessary exposure to pyrazinamide and the associated hepatic toxicity. Close monitoring of compliance is also warranted given the longer course of treatment and the potentially higher prevalence of streptomycin primary resistance.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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