International Journal of Infectious Diseases 70 (2018) 38–41

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Medical Imagery

A case-report of a pulmonary tuberculosis with lymphadenopathy mimicking a lymphoma

ARTICLE INFO

Article history:
Received 3 January 2018
Received in revised form 8 February 2018
Accepted 13 February 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

ABSTRACT

Clinical and radiological manifestations of tuberculosis (TB) are heterogeneous, and differential diagnosis can include both benign and malignant diseases (e.g., sarcoidosis, metastatic diseases, and lymphoma). Diagnostic dilemmas can delay appropriate therapy, favoring *Mycobacterium tuberculosis* transmission.

We report on a case of TB in an immunocompetent, Somalian 22-year-old boy admitted in the respiratory unit of an Italian university hospital. His symptoms and clinical signs were thoracic pain, weight loss, latero-cervical, mediastinal, and abdominal lymphadenopathy. Smear microscopy and PCR were negative for *Mycobacterium tuberculosis*. The unclear histological pattern, the unusual clinical presentation, the CT scan signs, the BAL lymphocytes suggested the suspicion a lymphoma. Culture conversion proved *Mycobacterium tuberculosis* infection.

This case report highlights the risk of misdiagnosis in patients with generalized lympho-adenopathy and pulmonary infiltrates, particularly in Africans young patients.

Introduction

Tuberculosis (TB) is one of the most important causes of morbidity and mortality worldwide. In 2016 it was estimated that 10,4 million incident cases occurred and 1.7 million died (including 374,000 people with HIV infection). The highest incidence was detected in the World Health Organization (WHO) South-East Asian and in the African Regions (45% and 25% of the total incidence, respectively).

About one third of the world's population is estimated to be latently infected by *Mycobacterium tuberculosis* (LTBI) (WHO, 2017). TB is associated with poverty and, on this basis, its epidemiological burden is heterogeneous, with high TB incidence rates mainly recorded in low income countries. During the last decade, migration flows from low- to high-income countries (e.g., those in EU/EEA) have significantly increased. Consequently, some high-income countries have shown relevant changes of their TB epidemiology (Coker et al., 2006; Davies et al., 2008). Diagnostic delay and inappropriate therapy represent the most relevant shortcomings of TB care in low TB incidence countries, frequently associated with poor physicians' knowledge on TB disease.

TB-related clinical features (Pirina et al., 2014) include cough, fatigue, fever, night sweating, chest pain, dyspnea, and hemoptysis in case of pulmonary involvement. Chest X-rays do not always show any relevant findings (high false-negative rate); however, some typical radiological patterns have been described, including parenchymal signs, hilar lymphadenopathy, pleural effusion, airway stenosis with parenchymal atelectasis, and miliary disease. Chest CT is considered the most important technique for the detection on chest x-rays of occult disease; it can detect micro nodules, infiltrations, consolidations, lymph node enlargement, and cavities. The most frequent signs of active pulmonary TB on CT scan are centrilobular nodules with branching linear opacities associated with bronchogenic dissemination, cavities, miliary micronodules resulting from hematogenous dissemination, and lymphadenopathy resulting from lymphatic spread (Ko et al., 2015; Miller et al., 2000; Rozenshtein et al., 2015; Bhalla et al., 2015; Scharer et al., 1998).

In the present manuscript we present the case of a 22-year-old Somalian HIV-negative male, with a history of chest pain, loss of appetite, and pulmonary atelectasis on chest radiography, with the clinical suspicion of lymphoma.

Case report

A 22-year-old Somalian male was referred to the Respiratory Diseases Unit of the university hospital of Sassari, Sassari, Italy, in June 2016. He complained of thoracic pain during his stay in an immigrant reception center, without reporting fever, cough, or any clinically significant comorbidities. The physical examination showed enlarged, not movable, and tender latero-cervical lymph nodes, as well as crackles in the right emi-thorax. Chest X-ray showed a right middle lobe atelectasis and increased broncho-vascular markings. Blood examinations showed a hemoglobin level of 10.6 g/dl (suspected hypochromic and microcytic anemia), a white blood cell count of 3,930 cells/mm^3

https://doi.org/10.1016/j.ijid.2018.02.011

(55% neutrophils, 25% lymphocytes, 15% monocytes, 2% eosinophils), and a platelet count of 311,000 cells/mm (Davies et al., 2008). C-reactive protein and erythrocyte sedimentation rate were elevated (6.24 mg/dl and 113 mm/h, respectively); gammaglobulins on electrophoresis were high but without any monoclonal spikes. His renal and liver function tests were within normal range. Total IgE were 4,820 IU/ml. Albumin level was below the normal values (4.00 g/dl).

A chest CT scan (Figure 1) with contrast infusion showed a generalized lymphadenopathy, particularly in the following anatomical sites: latero-cervical (sized ~25–50 mm), supraclavicular, subclavian, mediastinal, and sub-diaphragmatic. Para-tracheal, para-cardiac, and right hilar lymph nodes were confluent and enlarged (diameter size: ~30–50 mm); furthermore, a right middle lobe collapse, a tree-in bud parenchymal infiltrate, and a right shift of trachea and its bifurcation were found. Spleen showed multiple and rounded lesions.

Sputum and bronchoalveolar lavage (BAL) samples were smear- and polymerase chain reaction (PCR)-negative for *Mycobacterium tuberculosis*. Only lymphocytes (CD3+ 90%, CD4+ 68% CD8+ 17%, CD4+/CD8+ 4) were found in the BAL cellular count.

A trans-bronchial needle aspiration of the right para-tracheal lymph node was performed; however, the histological pattern was not specific (*i.e.*, non-specific chronic inflammation).

Ultrasound scans suggested a lymphoproliferative disorder based on the enlarged cervical lymph nodes, liver enlargement, and small, multiple spleen abscesses.

The patient underwent a surgical biopsy of a right supraclavicular lymph node. A chronic granulomatous inflammation with epithelioid and giant cells and central necrosis was found in the histopathological examination. Periodic acid-Schiff, Grocott, and Ziehl-Nielsen stained slides did not show any abnormal findings. Immunohistochemistry did not detect tumor cellular markers (*i.e.*, AE1/AE3, CD3, CD20).

Based on the clinical features, an empirical anti-TB treatment was started (ethambutol 1.2 g/day, isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1.5 g/day).

However, his clinical conditions rapidly worsened (abdominal pain, vomit, fever, dehydration, elevated liver transaminases levels). One week after TB treatment initiation a left pleural effusion occurred (then, classified as TB-immune reconstitution inflammatory syndrome). A sample of 2,000 ml of pleuritic liquid

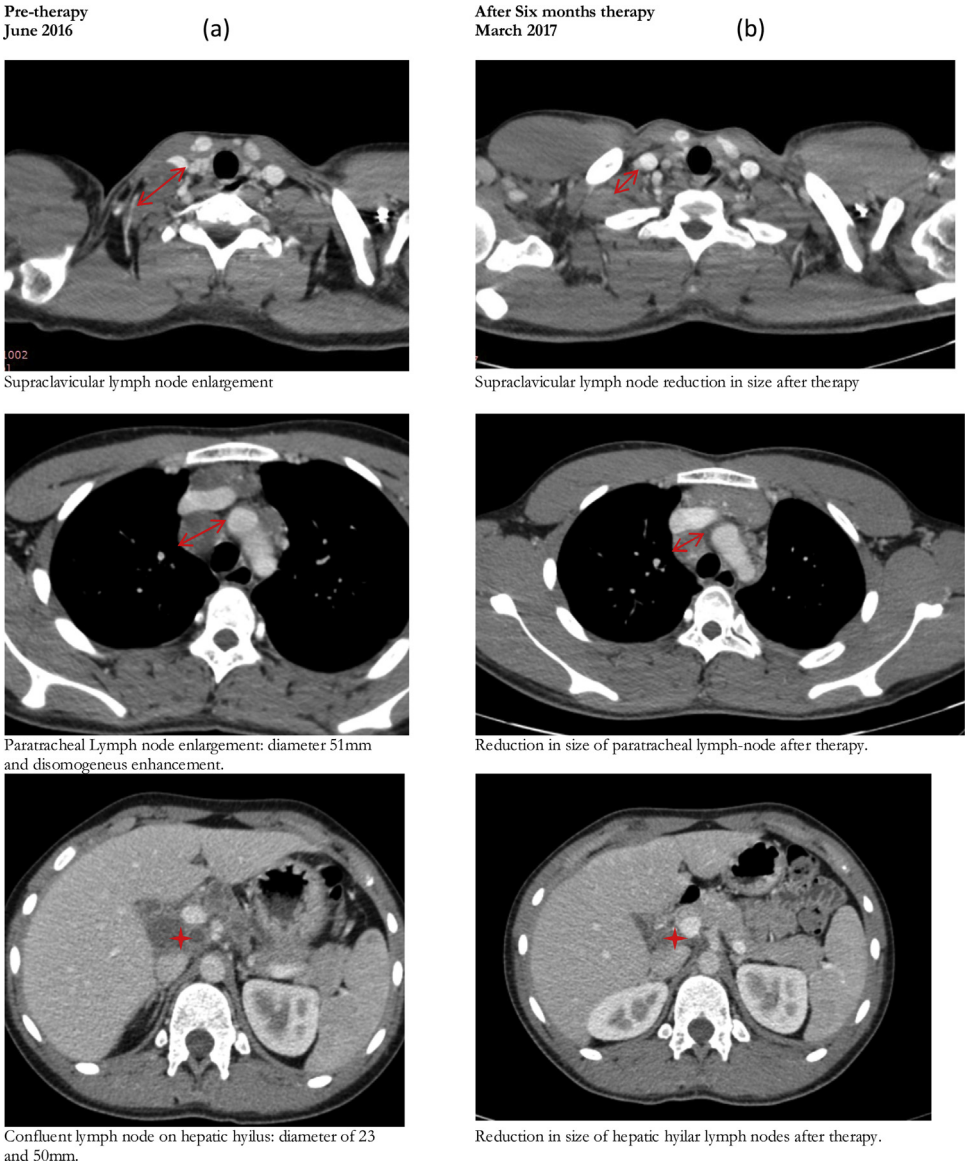

Figure 1. Pre- and post-therapy CT scan.

was collected: it was limpid yellowish, with LDH level of 369 U/L, total protein of 4.7 g/dl, glucose of 60 mg/dl, and PCR positive for *Mycobacterium tuberculosis complex*.

After 47 days, a BAL culture conversion for *Mycobacterium tuberculosis* occurred. The drug susceptibility pattern did not show any drug resistances (i.e., isolates were susceptible to isoniazid, rifampicin, pyrazinamide, and ethambutol).

Patient was discharged from hospital and underwent a new chest CT scan (Figure 1) after 6 months of treatment. It found an improvement of the atelectasis of the right middle lobe, and a decreased size of the subcarinal, right hilar, and sub-diaphragmatic lymph nodes.

Discussion

TB of the lymph nodes is the most frequent form of extra-pulmonary TB in immunocompetent African patients and its diagnosis becomes difficult to ascertain when it is smear-negative (Pirina et al., 2013; Sotgiu et al., 2017). The case report we described is very unusual for the BAL cytology (100% lymphocytes), and the negative mycobacterial sputum smear and PCR examinations. Furthermore, histopathology did not help assess the presence of a lymphoproliferative disorder. The incidence of Hodgkin and non-Hodgkin lymphomas can be relevant in HIV-infected and non-infected persons, as suggested by a recent study in Somalia (Baş et al., 2017).

Although TB lymphadenitis is more incident in children and immunocompromised (e.g., HIV-infected) patients, several reports have highlighted a high incidence in HIV-negative African and Asiatic young adults (Drake et al., 1997; Bloomberg and Dow, 1980). Culture is usually required to prove the infection and exclude other chronic diseases. Cervical and mediastinal lymph nodes are involved in 70% of the cases, followed by axillary, mesenteric, hepatic portal, peri-hepatic, and inguinal lymph nodes. In low TB incidence countries, the majority of patients with TB lymphadenitis does not show active pulmonary TB on chest x-rays (Bloomberg and Dow, 1980; Geldmacher et al., 2002; Thompson et al., 1992).

Pathogenesis of TB lymphadenitis seems to be associated with an LTBI reactivation or with a progressive primary pulmonary TB with mediastinal lymphatic dissemination.

It was demonstrated that *Mycobacterium tuberculosis* has a specific bacteriophage-type pattern when detected in African patients, causing an atypical immune reaction (Bloomberg and Dow, 1980).

Patients with mediastinal TB disease report only minor and non-specific physical complaints; in particular, fever, weight loss, loss of appetite, nocturnal sweats are frequently described (Drake et al., 1997; Bloomberg and Dow, 1980).

The present case-report showed the enlargement of intrathoracic lymph nodes associated with bronchus compression and lung atelectasis, which explained the thoracic pain. Sometimes patients can show unusual clinical findings: pulmonary artery occlusion with a lack of lung perfusion that can mimic embolism (Pirina et al., 2014) and compression of laryngeal nerve that can cause vocal cord paralysis.

Bloomberg et al. described an increased prevalence of mediastinal and cervical lymphadenitis (particularly right and left hilar, right para-tracheal lymph nodes) (Bloomberg and Dow, 1980), with or without parenchymal involvement, in non-European patients.

While rim-enhancing, central low attenuation, conglomeration or homogeneous calcifications of the lymph nodes are found in active and inactive TB forms, homogeneous enhancing lymphadenopathy without any calcifications poses a diagnostic dilemma. Viral and fungal infections are less likely to be associated with lymphadenopathy, whereas aggressive lymphomas can show similar CT features (Popescu et al., 2014).

Diagnosis of TB lymphadenitis could be performed by fine needle aspiration (FNA) or endobronchial ultrasound-guided trans bronchial needle aspiration (EBUS-TBNA), followed by microbiological and cytological examinations (sensitivity and specificity are 77% and 80%, respectively) (Boonsarngsuk et al., 2017; Fanny et al., 2012).

However, FNA and EBUS-TBNA can be helpful for Ziehl-Neelsen staining to detect acid-fast bacilli, but surgical biopsy is necessary if a lymphoma has to be excluded (Hehn et al., 2004; Göknar et al., 2015).

As reported in the scientific literature, FNA has a low sensitivity for lymphoma, is not cost-effective, and may misguide treatment (Maffessanti and Dalpiaz, 2004; Omri et al., 2015). Histologic examination of lymphoma includes an assessment of the cellular morphology, of the immune-phenotype, and of the genetic pattern. Furthermore, sensitivity of biopsy for TB in comparison with that of FNA is higher (94.2% VS. 62.5%, respectively) (Smaoui et al., 2015).

Mediastinal involvement in non-Hodgkin lymphoma cases can be seen either as the only involved site of the disease (e.g., primary mediastinal large B cell lymphoma) or as part of a systemic disease. On the other side, patients with Hodgkin's disease have a higher incidence of intrathoracic disease than those with non-Hodgkin's lymphoma (67% VS. 43%). Bulky superior mediastinal lymphadenopathy is the hallmark of Hodgkin's lymphoma. Lung involvement is more prevalent in Hodgkin's disease (11.6% VS. 3.7%) and is associated with mediastinal and/or hilar lymphadenopathy (Filly et al., 1976; Lee et al., 1992).

In our case-report histological examination showed only a granulomatous inflammation, with negative periodic acid-Schiff, Grocott and Ziehl-Nielsen staining and negative immunohistochemistry for tumor cell expression; on the other hand, histology showing granulomatous inflammation with epithelioid and giant cells and central necrosis supported the TB suspicion.

Another interesting finding was the paradoxical occurrence of a pleural effusion after the administration of the anti-TB drugs; several Authors have defined this disorder as TB-IRIS (*i.e.*, TB-immune reconstitution inflammatory syndrome) owing to an excessive immunologic reaction against mycobacterial antigens following the bactericidal effect of anti-TB drugs (Lanzafame and Vento, 2016).

Conclusion

This case report shows clinical and radiological complexity of extra-pulmonary TB. Furthermore, multi-systemic enlarged lymph nodes can pose relevant problems in terms of differential diagnosis with lymphomas (Smaoui et al., 2015; Ramírez-Lapausa et al., 2015). Comprehensive awareness and knowledge of atypical TB manifestations can help to early diagnose and start TB therapy, increasing the probability of a clinical and microbiologic cure. CT scanning and lymph node biopsy can be critical (Raniga et al., 2006). Attention should be devoted for TB diagnosis to African patients with lymph node involvement, with or without any parenchymal infiltrations.

Conflict of interest: No conflict of interest to declare.

Funding source: None.

Ethical approval: Approval was not required.

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Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Received 3 January 2018
Received in revised form 8 February 2018
Accepted 13 February 2018