Case Report

Chest tuberculosis with mediastinal asymptomatic lymphadenitis without lung involvement in an immunocompetent patient

Pietro Pirina[1], Valentina Spada[1], Luigi Santoru[1], Maria Francesca Polo[1], Paola Molicotti[2], Vincenzo Marras[1], Paolo Cossu Rocca[1], Sara Canu[1], Stefania Zanetti[2], Alessandro Giuseppe Fois[1]

[1]*Department of Clinical and Experimental Medicine, University of Sassari, Sassari Italy*
[2]*Department of Biomedical Sciences, University of Sassari, Sassari, Italy*

Abstract

Tuberculosis remains the major cause of morbidity and mortality by a single infectious agent, particularly in developing countries. In recent years, we have witnessed the emergence of uncommon radiographic patterns of chest tuberculosis. Lymphadenitis is the most common extrapulmonary tuberculosis (TB) manifestation which, in developed countries, occurs more frequently in childhood, but also among adult immigrants from endemic countries and in HIV-infected people. Isolated and asymptomatic mediastinal lymphadenitis is uncommon in immunocompetent adults.

We report a case of a young adult man from Senegal affected by sovraclavear and mediastinal TB lymphadenitis, which contains some uncommon elements: no compromised immunity, especially no HIV-infection, no lung lesions, no symptoms of infection or of mediastinum involvement, and rapid response to therapy in terms of mass size reduction. Examination of extra-thoracic lymph nodes and the patient's characteristics guided our diagnostic process to suspect TB. Surgical biopsy and subsequent histopathological and microbiological examinations of lymph material, first by Lowestein-Jensen and BACTEC cultures that remain the gold standard of diagnosis, confirmed the diagnosis. Chest X-ray was inconclusive; however, CT played an important role in the diagnostic course and in the management of the patient, particularly in determining disease activity, offering mediastinum and parenchymal details, as well as in identifying typical features of tuberculous lymph nodes and also of active/non active disease. Six months of antimycobacterial regimen is the recommended treatment in TB lymphadenitis of HIV-negative adults.

Key words: tuberculosis; lymphadenitis; CT features; HIV seronegativity

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Introduction

The incidence rate of tuberculosis (TB) is almost stably high in people with human immunodeficiency virus (HIV) infection and among people from countries characterized by high TB endemicity [1-3]. In recent years, we have witnessed the emergence of uncommon radiographic patterns of chest tuberculosis in adults, probably due to the progress in radiological supports such as computerized tomography (CT) and high resolution computerized tomography (HRCT) scans, with particular reference to isolated hilar or mediastinal lymphadenopathies, multiple cavities, basilar infiltrates, centrilobular nodules, tree in bud appearance, bilateral patchy infiltration, ground glass attenuation, miliary tuberculosis, and isolated pleural effusion [4,5]. These radiologic features were typically associated with defects in cell-mediated immunity; some were seen almost exclusive of interstitial lung diseases [6] and they were rarely seen in people indigenous from low-TB incidence areas, if we exclude the HIV-positive hosts. The sensitivity, specificity, positive predictive value, and negative predictive values of thorax HRCT in determining the activity of pulmonary tuberculosis reported in a recent study were 97%, 86,7%, 94,2% and 92,9% respectively [6]. Furthermore, chest CT and particularly HRCT scanning clearly differentiate old fibrotic lesions from new active lesions, which is crucial in terms of management and early treatment, especially in smear- and culture-negative TB with high clinical suspicion of disease [5,7].

In Italy, 43% of total TB cases are among immigrants, first in Romanians, second in people from Morocco, third in people from Senegal (2): in these subpopulations the main clinical localizations are lung (66%), lymph nodes (15.3%) and bone (5.3%), with 16% of drug resistance (of which 9% are multidrug resistant (MDR) –TB [8].

Lymphadenitis is the main extrapulmonary manifestation of tuberculosis accounting for 35% of cases [1-3]; it is more frequent in children and in females, with peak age of onset in adults between 20 to 40 years. In childhood, TB lymphadenitis is the most common single manifestation of primary tuberculosis (96% to 100% of cases), generally characterized by conglomerates, localized in multiple sites (mostly in the right paratracheal, hilar and subcarinal areas), with an inhomogeneous CT enhancement pattern and associated with lung infiltrate in 90% of cases [9]. In adults, lymphadenopathy without a parenchymal infiltrate is unusual and very rare and has been observed in patients with acquired immune deficiency syndrome (AIDS) [10]; moreover, TB disease is strongly suggested when a hilar or mediastinal lymph node enlargement is associated with lobar pneumonia.

The SIMIT (Italian Society of Infectious and Tropical Diseases) study (2008) showed that, in African people, 21% of tubercular lymphadenitis patients had concomitant HIV infection, and among 50% of the HIV-positive patients, extra-pulmonary TB manifested as lymph nodal forms [11]. Another Italian study also revealed that nodal localization without lung involvement was infrequent in Italian people but was observed almost exclusively in foreigners from endemic countries, especially in HIV-infected patients [8]. Furthermore, the HIV-infected patients were more likely than the HIV-negative subjects to have either disseminated, genitourinary, intra-abdominal, mediastinal, or concurrent pulmonary TB [12,13].

The epidemiological study of Codecasa *et al*., which evaluated retrospectively a group of HIV-negative adult patients with hilar and/or mediastinal TB adenopathy, concluded that when HIV-positive people are excluded, this TB localization occurs more frequently in immigrants than in the indigenous Italian population (7.0 versus 0.3%, $p < 0.001$), and mostly in people from India and Senegal [14].

We report a case of sovraclavear and mediastinal TB lymphadenitis without lung localizations in a young Senegalese hawker, an immigrant in Sardinia (Italy), about two years before diagnosis.

Case report

A 29-year-old immunocompetent man from Senegal was admitted in the hematology department with lymphoma suspicion, presenting a lymph node swelling of approximately four centimeters in diameter, situated in the right sovraclavear district. It appeared painful and tender, adherent to the deep tissues and hard in consistency. The chest X-ray was negative; only a slight right mediastinum flare was described.

He was in discrete health condition; particularly, he had no fever, weight loss, night sweat or other symptoms and signs of infection. Moreover, he denied previous diagnosis of tuberculosis as well as TB cases in his family or other close contacts.

Blood tests for blood count, hepatic and renal function, coagulation profile, markers of HIV, Hepatitis C virus (HCV), Hepatitis B virus (HBV) and Epstein-Barr Virus (EBV) infections were normal; only a mild leukopenia with lymphocytosis and a reduction of folic acid and beta 2 microglobulin were detected.

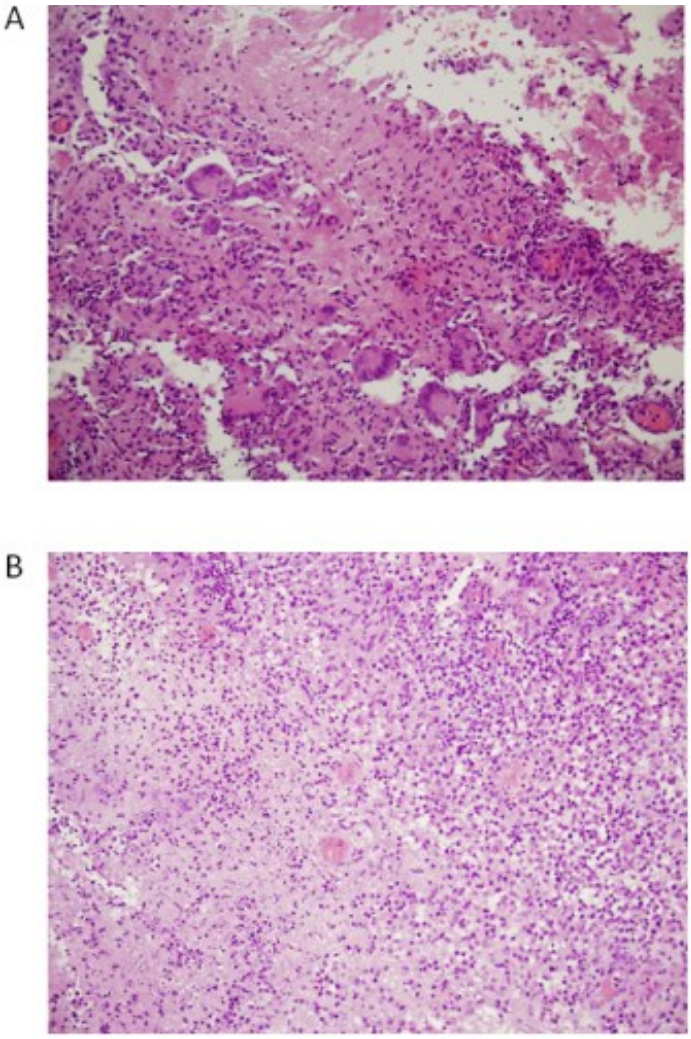
To exclude TB suspicion, the patient was transferred to isolation rooms of our respiratory diseases department, where other diagnostic tests were performed. The sonographic features of the sovraclavear nodal swelling were compatible with a pathological process: the echotexture was solid and inhomogeneous, with slight vascularization and with dimensions of 41 by 25 by 33 millimeters. The laterocervical ultrasonography also showed three other lymph nodes of 11, 15, and 20 millimeters in diameter respectively, without liquation signs and therefore compatible with reactive lymphadenitis.

Surgical biopsy of the sovraclavear lymphadenopathy was performed and subsequent histological examination showed chronic granulomatous inflammation characterized by epithelioid and giant cells with foci of central necrosis whereas Periodic acid-Schiff, Grocott and Ziehl-Nielsen stained slides were negative (Figure1).

Microscopic examination of the lymph node liquid (caseum material), which was collected during the surgical biopsy, was negative for the Koch's Bacillus detection, but subsequent culture on Lownstein-Jensen medium and Bactec 460 TB – MGIT 960 TB (Mycobacterial Detection System, Becton Dickinson, Franklin Lakes, NJ, USA), polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* complex, adenosine deaminase assay (ADA), all performed on the same biological material, were positive. Mantoux test and Quantiferon-TB immunoassay were also used to confirm the results. However, sputum smears and cultures failed to grow acid-fast bacilli.

Meanwhile, we also performed a total body CT scan with contrast infusion that pointed out a right paratracheal lymph node package measuring 44 by 32 millimeters, characterized by widespread necrosis

Figure 1. Histological examination of surgical biopsy material



Chronic granulomatous inflammation characterized by epithelioid and giant cells with foci of central necrosis.
Details: A. Giant cells; B: necrosis surrounded by histiocytic granulomatous reaction

areas, as well as another lymph package of 63 by 19 millimeters with the same radiologic features, situated below the carina (Figure 2). These nodal finds were not associated with lung lesions but they were compatible with other characteristic signs of active TB such as nodal enlargement and conglomeration, involvement of multiple and typical sites, inhomogeneous enhancement. Nothing of significance was reported in other areas of the body.

Accordingly, we prescribed an antimycobacterial therapy: two months of rifampicin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 1500 mg/day and ethambutol 1200 mg/die, followed by four months of rifampicin and isoniazid. The sensitivity test did not find any antibiotic resistance.

The patient continued therapy for six months, with a relatively rapid reduction in the size of the nodes and positive results seen during the first eight weeks of treatment (Figure 2).

Discussion

In the literature there are no case reports of TB lymphadenitis without lung involvement and without symptoms in people indigenous to areas with low TB and AIDS incidence, particularly in immunocompetent patients [15-17]. In general, tuberculous and non-tuberculous adenitis are associated with advanced immunosuppression [13]. Also, in children, almost all the TB cases are associated with lung parenchyma abnormalities [9].

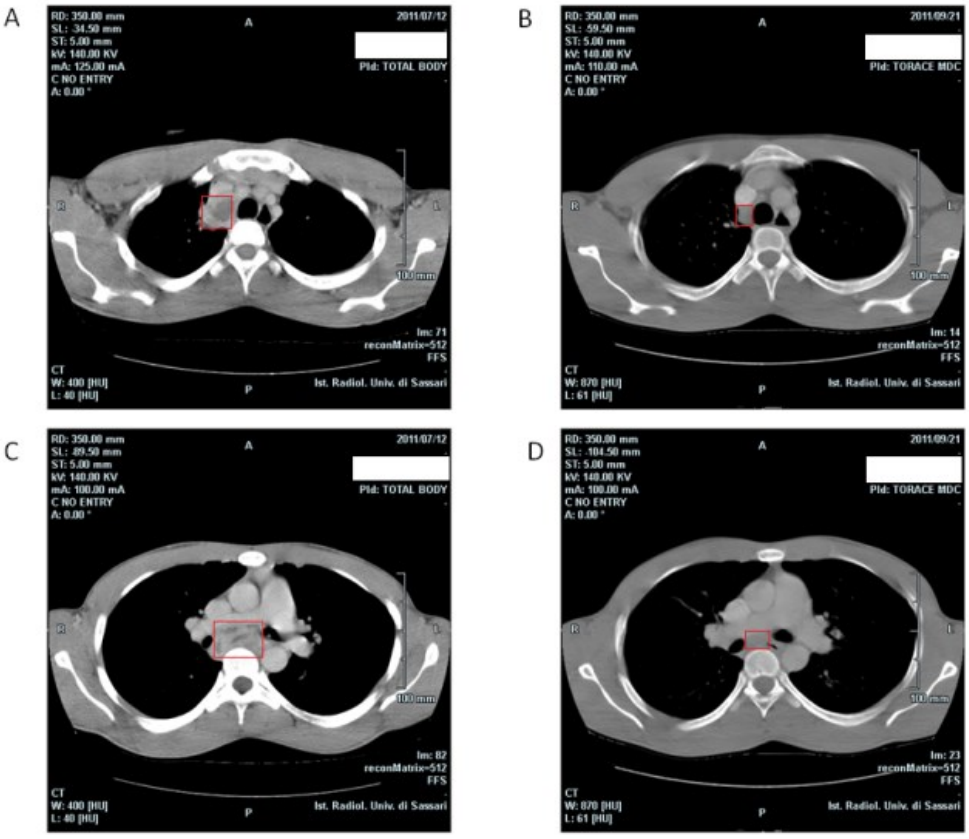
Our peculiar case demonstrates and confirms that this form of extrapulmonary TB, when it occurs in HIV-negative people, is seen almost exclusively in immigrants from countries with high TB endemicity.

Moreover, while TB lymphadenitis is more frequently a clinical sign of disseminated diseases or of latent TB reactivation [2,18], in this rare case the sovraclavear and mediastinal TB lymphadenitis was not associated with other areas in the body, and , particularly not to lung lesions which is more commonly seen in HIV-positive patients [13]. In the case of isolated adenopathies, after exclusion of malignant causes, TB diagnosis should always be considered, especially in people from developing countries, and confirmed by microbiological examination, first by culture.

Unlike the usual cases of mediastinal masses with considerable size, our patient did not present symptoms related to the involvement of adjacent structures, such as dysphagia [19], esophageal perforation [20] or pulmonary artery occlusion mimicking pulmonary embolism [21]. In our case, the mediastinal adenopathies were discovered after the examination of extra-thoracic lymph nodes, when we continued the TB diagnostic process using CT scan, which plays an important role in the characterization of lymph nodes and in the determination of active/non-active disease.

The differential diagnosis included malignancy (Hodgkin and non-Hodgkin lymphomas, metastatic lymph nodes), sarcoidosis and other infections (*eg*., nontuberculous mycobacteria, cat scratch disease, fungal infection, bacterial adenitis). The patient's age, country of origin, and sonographic and CT scan features effectively guided our diagnostic suspicions.

Figure 2. CT scan images of right paratracheal lymphadenopathy and subcarinal lymphadenopathy



-Paratracheal lymphadenopathy pre-treatment (A) and during treatment (B)
-Subcarinal lymphadenopathy pre-treatment (C) and during treatment (D)

In effect, there were many CT features of tuberculous lymph nodes, including multiple site involvement (in particular, the right paratracheal and subcarinal, considered also the typical largest lymph node sites); inhomogeneous enhancement patterns; and classical determinant of disease activity, such as nodal enlargement and conglomeration.

TB clinical-ultrasound-radiological suspicions were confirmed by histopathological examination, obtained by excisional biopsy of the sovraclavear lymph node, and also by culture and polymerase chain reaction (PCR), recommended as the gold standards for TB lymphadenopathy diagnosis [18,22]. The diagnosis was also supported by ADA and Quantiferon-Tb assays. For initial evaluation of TB lymphadenopathy, data from the literature recommended fine needle aspiration cytology (FNAC), which demonstrated a good sensitivity and specificity (77% and 93% respectively); however, when it is not diagnostic, surgical biopsy for histopathologic and microbiological evaluations, which provides the highest diagnostic yield can be used [2,23,24]. The Transbronchial Needle Aspiration guided by Endobronchial Ultrasound (EBUS-TBNA) is advised in cases of isolated intrathoracic lymphadenopathy [25-27]. However, a prospective longitudinal cohort study of 34 consecutive patients, who presented with isolated mediastinal lymphadenopathy, concluded that bronchoscopy has a low diagnostic yield in mediastinal tuberculous lymphadenopathy in the absence of a parenchymal lesion, while mediastinoscopy, although invasive, is a safe procedure and provides a tissue diagnosis in most cases [28].

Regarding the treatment, we followed the international recommendations for HIV seronegative adults [29], which consists of two months of rifampicin, ethambutol, isoniazid and pyrazinamide, followed by four months of rifampicin and isoniazid; no differences have been reported in comparison to a nine-month regimen [30].

The patient responded successfully to the therapy and did not present the paradoxical reaction or the

increase in lymph node size or the enlargement of additional lymph nodes during or after treatment cessation; these results agree with those described in 23% of HIV-negative TB cases [31]. Interestingly, while the literature reports a slow response of TB lymphadenitis to the treatment [22], CT scans performed after the first two months of chemotherapy showed the halving of sovraclavear and mediastinal (paratracheal and subcarinal) masses, which measured 20, 18 and 18 millimeters respectively.

Conclusion

Our case demonstrates that, in adults, we should always consider tuberculosis as a possible etiology of mediastinal lymphadenitis in the absence of lung parenchyma involvement, even if the patient is not HIV infected or not symptomatic. While this scenario is uncommon, we have shown that it exists. Isolated TB lymphadenopathy is one of the emerging patterns of chest tuberculosis; few cases are reported in the literature, and those all date back to the preCT era. A chest CT scan in conjunction with a preliminary chest X-ray shows mediastinum details, especially the features of tuberculous lymph nodes such as the presence of nodal enlargement in multiple sites (typically in the right paratracheal and subcarinal locations), conglomeration, and inhomogeneous enhancement patterns, as reported in our case.

The gold standard in the diagnosis of TB lymphadenitis is the histo-cyto-pathological and cultural examination of lymph material obtained by FNAC and EBUS-TBNA in case of isolated intrathoracic lymphadenopathy, or by surgical biopsy, which still has a good diagnostic yield.

Finally, the effective therapeutic protocol to treat TB lymphadenitis in HIV-seronegative adults remains a six-month regimen with antimycobacterial antibiotics.

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Corresponding author

Pirina Pietro
Department of Clinical and Experimental Medicine
Viale San Pietro (nuovo edificio, scala A, I° piano)
07100 Sassari, Italy
Email: pirina@uniss.it

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