

**REVIEW ARTICLE**

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## **Extra-pulmonary tuberculosis in immunocompetent patients: Case series and mini review of the literature**

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**Abstract:** *Introduction: Tuberculosis (TB) is still one of the most frequent infectious diseases, causing 2 million deaths a year worldwide. The prevalence of TB has increased in both immunocompetent and immunocompromised and virtually, it can affect any organ. Up to 25% of tuberculosis cases present extra-pulmonary involvement. The diagnosis of extra-pulmonary TB (EPTB) is difficult, often requiring biopsy.*

**Material and methods:** *We present two cases of EPTB in immunocompetent young women. The first case is about a 15-years old female who presented with persistent high fever, ascites and an increased CA-125 serum level. Biochemical analysis of ascites fluid revealed a high value of adenosine deaminase (ADA), negative Ziehl-Neelsen stain and undetectable Mycobacterium tuberculosis at PCR assay. The peritoneal biopsy confirmed the diagnosis of peritoneal TB. The second case, a 29-years old female with a seven-month history of cervical lymph nodes swelling, with drainage and excision biopsy performed, misdiagnosed as cats-scratch disease based on the histological description as granulomatous lymphadenitis, which turned out to be tuberculous lymphadenitis at the second histopathological opinion.*

*In conclusion, these cases highlight the need for tuberculosis consideration in the differential diagnosis of extra-pulmonary involvement, even in immunocompetent individuals, in order to decrease the misdiagnoses and complications rates.*

**Keywords:** extra-pulmonary tuberculosis, immunocompetent, peritoneal tuberculosis, lymphadenitis, challenging diagnosis

### **INTRODUCTION**

Tuberculosis (TB) can be considered an ancient disease which is still causing 2 million deaths a year worldwide. According to global statistics, one person is newly infected with TB bacilli every second world-wide and one third of the global population is currently infected with TB. TB ranks alongside HIV as a leading cause of death from an infectious disease. The prevalence of TB has increased in both immunocompetent and immunocompromised and virtually, it can affect any organ.

It is now seen that extra-pulmonary presentations form a major proportion of new cases. Between 2002 and 2011, extra-pulmonary TB (EPTB) accounted for 19.3% of all TB cases throughout Europe. EPTB is more common in children, women and minorities. Based on Romanian Tuberculosis Notification Data,

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12,498 new TB cases (a rate of 6.4 cases per 100,000 individuals) were registered in our country during 2014, which is higher compared with a rate of 5.2 cases per 100,000 individuals throughout Europe. Extra-pulmonary involvement occurred in 8% of the new cases. Among the extra-pulmonary TB (EPTB) cases, 30.1% were lymph node TB, 13.3 % osteo-articular TB, 6.3% genitourinary TB and 47.3% in other anatomical sites.

Lymphadenitis is the most common extra-pulmonary presentation of TB. Abdominal TB is also one of the most prevalent forms of EPTB. In particular, peritoneal TB is the sixth most common location of EPTB, with an incidence between 0.1% and 0.7% of all TB cases worldwide.

In EPTB, the diagnosis is challenging because of nonspecific symptoms and low sensitivity of classical diagnostic methods, such as microscopy and culture and it is often requiring biopsy. Delay in diagnosis and treatment initiations lead to poor prognosis and sequelae in up to 25% of cases.

## MATERIAL AND METHOD

### Case 1

A 15-year-old young female patient presented at the territorial hospital with abdominal distension, low abdominal pain, fever (40 degrees) with shiver, excessive sweating and loss of appetite. No other previous health problems were reported. All vaccines provided in universal vaccination schedule were performed. She denied smoking, drug use or alcohol consumption, and she was sexually inactive. The tests performed led to the diagnosis of ascites of unknown etiology. Despite the empirical antibiotic treatment with ceftriaxone, she continued to present fever, being subsequently referred to our clinic for further investigations.

At admission, the clinical status of the patient revealed a relatively good general condition, without fever, no abnormalities on pulmonary examination and normal vital signs. The abdomen was enlarged, with shifting dullness and positive ascitic wave, diffuse pain on palpation, without signs of peritoneal irritation. No masses or organomegaly were present on clinical

examination. Blood tests showed lymphopenia ( $880/\text{mm}^3$ ), mild microcytic anemia, elevated inflammatory markers (erythrocyte sedimentation rate of 58 mm/1h, Fibrinogen of 709 mg/dl, C-reactive protein of 112 mg/dl) with negative procalcitonin and normal biochemistry. Chest X-ray did not reveal any infiltrates. Abdominal ultrasonography showed the ascites in large quantity. Transthoracic echocardiography described minimal pericardial effusion (20-30 millimeters).

Further immunology and virology lab tests [rheumatoid factor, antinuclear antibodies, anti-double stranded DNA antibodies (Ab), complement fractions C3, C4, hepatitis B surface antigen, hepatitis C virus Ab, and Human Immunodeficiency Virus 1 and 2 Ab] were negative. The patient underwent paracentesis with ascitic fluid analysis. The gross appearance of the fluid was pale yellow, with exudative features, based on the biochemistry, a total nucleated cell count of  $600/\text{mm}^3$  with predominance of polymorphic lymphocytes (72%). The ascites fluid ADA level reached a high value of 140 IU/l, normal value being <33 IU/L. The microscopy for non-specific bacteria and acid fast bacilli, using Gram and Ziehl-Neelsen stains, was negative. Moreover, we performed a broad-spectrum molecular microbial identification from the ascites (IRIDICA BAC BSI® Assay platform for bacteria and fungi) and MTB-DNA amplification (GeneXpert® platform), both of them being undetectable. The serum tumor markers such as CEA, CA19-9 and CA15-3 were within normal limits, apart from CA 125, which was significantly higher (189.5 IU/ml). Serum gamma-interferon specific to MTB antigens produced by T cells (QuantiFERON®-TB Gold) was positive.

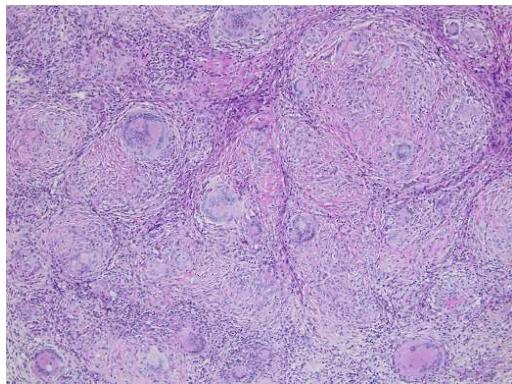
In the meantime, we started empiric antibiotic treatment based on oral clarithromycin 1g/day for 3 days, with fever persistence. Then we switched to intravenous (iv) ertapenem 1g/day. After 5 days of ertapenem treatment, the fever has disappeared, with minimal ascites fluid regression. Abdominal and pelvic magnetic resonance imaging (MRI) showed the presence of ascites and described irregular masses with peripheral contrast enhancement near the ovarian fossa, similarly to epiploic fringes.

The patient was transferred to a pediatric general surgery department for exploratory laparoscopy and peritoneal biopsy. The laparoscopic findings described thickened peritoneum with disseminated miliary white nodules on the surface and intestinal wall congestion, being highly suggestive of PTB (Figure 1).

**Figure 1.** Laparoscopic findings with thickened peritoneum, diffuse congestion, disseminated miliary white nodules on the surface of peritoneum highly suggestive for TB.



**Figure 2.** Multiple foci of granulomatous inflammation with multinucleated giant cells, epithelioid histiocytic cells and peripheral lymphocytes are seen on Periodic acid-Schiff (PAS) staining (100X).



Multiple tissue biopsies were collected. Based on clinical and biological features, along with laparoscopic findings, we decided to start antituberculous therapy with isoniazid 200 mg, rifampicin 450 mg, pyrazinamide 1,500 mg, ethambutol 1,200 mg daily, and oral pyridoxine vitamin 250 mg/day. After 10 days of antituberculous treatment, the symptoms of the patient have regressed, serum C-reactive protein level decreased from 153 mg/dl to 8.6 mg/dl, with no ascites presence

at the abdominal ultrasound.

The histopathological results confirmed the diagnosis of peritoneal tuberculosis (Figure 2). In addition, MTB-DNA from the biopsy sample was detected, with no detection of genetic mutations associated with rifampicin resistance.

## Case 2

A previously healthy, 30 year-old Caucasian female, smoker (10 pack/year), presented to our department for laterocervical and supraclavicular lymph nodes enlargement, slightly painful on palpation. She also complained of fatigue and dry cough. She was not on any medication, no histories of allergies, all vaccines provided in universal vaccination schedule were performed and she has not travelled during the past year outside of Romania. She has a cat which is an indoor pet.

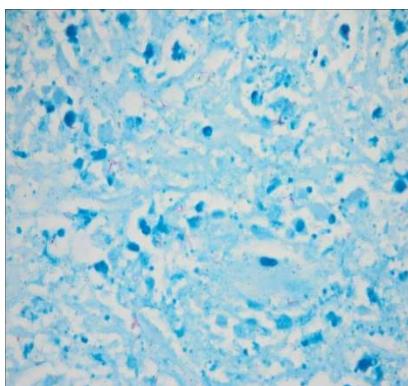
The symptoms began about 7 months ago with a red, painful swelling of about 4-5 cm, in her left laterocervical region, which she noticed several weeks ago and continued to enlarge. She went to the surgical department where was performed the incision of the lymph node with drainage and lavage. The cultures provided from the procedure were sterile at 48 hours.

5 months later, she presented to the thoracic surgery department with suppurated supraclavicular lymph nodes. All the laboratory tests performed were normal (blood count, coagulation, biochemistry (glucose, creatinine, ALT, AST, GGT, Alkaline phosphatase, sodium, potassium). The patient was evaluated by cervical and thoraco-abdominal CT and the images showed multiple extended outbreaks of pulmonary infiltrates with tree in bud pattern in the apical-dorsal segment of the superior left lobe and in the dorsal segment of the superior right lobe and some isolated centimeter nodal images and mediastinal, supraclavicular, and bilateral laterocervical lymph nodes. They continued the investigations with bronchoscopy with GenExpert test, direct microscopic examination and culture for acid fast bacilli in bronchial aspiration and sputum. They performed an excision biopsy of the supraclavicular lymph node and the histopathological findings described as confluent epithelioid granulomas

with central clotting necrosis have been interpreted as specific lesions for cat scratch disease. The patient was referred to a department of infectious diseases for additional investigations and specific treatment. Meanwhile, the GenExpert test and the direct microscopic examination for acid fast bacilli were negative with cultures in progress.

When she came in our department, she had good general state. On physical examination we noticed in the left laterocervical area two scars with redness surrounding and several firm, tender, lymph nodes about 1 to 3 cm in diameter, palpable in the left laterocervical and supraclavicular area. The initial laboratory tests were normal, the test for antibody to human immunodeficiency virus (HIV) was also normal, with no other immunity issue found. The serology for *Bartonella henselae* infection was negative for both antibodies Ig M and Ig G. The patient was referred to the National Institute of Pneumophtisiology for reevaluation. Based on the high clinical and histopathological suspicion of tuberculosis, the biopsy blades were re-analyzed and by performing Ziehl-Neelsen coloration, were discovered few acid-fast bacilli (Figure 3). The histopathological description with necrotizing granulomatous epithelioid inflammation was also pathognomonic for tuberculosis.

**Figure 3.** Acid-fast bacilli on Ziehl–Neelsen smear (100X)



The patient was put on anti-tubercular drugs with good evolution. The cultures for mycobacterium tuberculosis read at 2 months were positive.

## DISCUSSIONS

TB is still one of the most frequent infectious disease and worldwide strategies to eradicate it have met only with partial success. According to global tuberculosis report, in 2015, there were an estimated 10.4 million new TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. People living with HIV accounted for 1.2 million (11%) of all new TB cases. There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people with HIV. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015.

Although it is well known that TB occurs mainly in immunocompromised host, it seems that the prevalence of TB has increased both in immune-competent and immunocompromised patients. Nowadays extra-pulmonary presentations form a major proportion of new cases of TB. Among them, lymphadenitis is the most common clinical presentation, with a major predilection for cervical lymph nodes.

Abdominal TB is also one of the most prevalent forms of EPTB and the peritoneal involvement has been observed in about 1-2% of all cases of TB. Pelvic TB is common in developing countries, mainly in young, fertile women aged between 15 to 25 years old. The common clinical features include ascites, fever, diffuse abdominal pain and weight loss. Therefore, peritoneal TB is often misdiagnosed, usually as carcinomatous peritonitis. The lacking of medical awareness of pelvic TB could lead to mutilating surgical treatment like adnexitomy for many young, fertile, women.

Our patient presented with a clinical picture highly compatible with peritoneal TB. However, we had to continue the investigations because the conventional methods, like microscopy and MTB-DNA amplification from ascitic fluid, failed to establish the positive diagnosis. In addition to clinic-biological findings and radiological characteristics, the accuracy of early diagnosis was increased by measuring the ascites ADA and serum CA125 levels.

The studies showed a significant correlation between

ADA and CA-125 in patients with peritoneal TB. The tests are simple, non-invasive, cheap, and it seems to have enough power to confirm or exclude the diagnosis of peritoneal tuberculosis and it is a good approach to begin the empirical treatment while waiting for the histopathological result or cultures.

The diagnosis of peritoneal TB can also be suggested by characteristics findings at laparoscopy or laparotomy; however, these are invasive examination methods and should be recommended with caution in clinical practice.

Lymphadenitis is the most common extra-pulmonary presentation of TB. It is seen in nearly 35 per cent of extra-pulmonary TB which constituted about 15 to 20 per cent of all cases of TB. Although previously considered a childhood disease, lymphadenitis has a peak age of onset of 20-40 years. The most common site of involvement is represented by cervical lymph nodes, reported in 60% to 90% patients, followed by mediastinal and axillary lymph nodes<sup>6</sup>.

Cervical lymph nodes can be involved via various pathological processes, including inflammatory diseases, lymphomas and even metastases. It is important that a high index of suspicion for tuberculous lymphadenopathy should be kept in mind because it mimics other pathologic processes and yields inconsistent physical and laboratory findings.

TB lymphadenitis usually presents with gradually painless swelling of one or more lymph nodes. Initially the nodes are firm, mobile, later they become matted with inflamed overlying skin and with abscesses formation in the advanced stages. Some patients may associate systemic symptoms such as fever, weight loss, fatigue, dry cough.

In our case, the patient had a seven-month history of cervical lymph nodes gradually swelling, which become matted with redness of the overlying skin. She also associated systemic symptoms represented by dry cough and fatigue.

The diagnosis of tuberculous lymphadenitis is difficult due to low sensitivity of mycobacterial isolation, prolonged time of the isolation process and multiple differential diagnosis that need to be ruled out. In

endemic areas, for faster diagnosis, has been used fine-needle aspiration cytology (FNAC), combined with polymerase chain reaction for detecting *Mycobacterium tuberculosis*, in the absence of compatible cytological findings or negative acid-fast bacilli smears. Acid fast bacilli may be present in 25-50% of smears and the mycobacterium may be isolated in up to 70% of cases where there is a high suspicion of tuberculosis. Caseating granulomas are seen in almost all the biopsies and in 77% cases of the FNAC's. Typically, epithelioid cell granulomas, multinucleated giant cells and caseation necrosis are features of tuberculous lymphadenitis but these are neither specific nor sensitive and the diagnosis remains a challenge, necessitating a high index of suspicion, since granulomatous lymphadenopathy has an extensive differential diagnosis [13].

Cat scratch disease (CSD) is an infectious disease caused by gram-negative bacteria *Bartonella henselae* (*B. henselae*) and/or *Bartonella quintana*. It is represented by regional suppurated lymphadenitis, the lymph nodes affected are cervical (33%), axillary (27%) and inguinal (18%). The disease affects children and youths under 18 years old. Epidemiologic studies from the United States, Europe, Israel, Australia, and Japan, suggest that CSD has a worldwide distribution. In the United States, a retrospective study of patients younger than 65 years of age identified 13,273 patients with a diagnosis of CSD from 2005 to 2013. The diagnosis is based on the following: a) history of contact with a cat; b) checking of injury sites; c) regional lymph node swelling; d) characteristic histology of lymph node; e) skin test for CSD, replaced in the last years by immunohistochemically staining with antibodies to *B. henselae* in formalin-fixed paraffin-embedded tissue sections and polymerase chain reaction.

The histopathologic findings are nonspecific and depend upon the stage of the disease. Lymphoid hyperplasia is present initially, followed by the development of stellate granulomas. The centers are acellular and necrotic with histiocytes and peripheral lymphocytes surrounding these areas. Microabscesses develop and may become confluent at a later stage. Although these findings support a diagnosis of CSD,

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they should not be considered definitive.

Based on the granulomas found on the histological examination, our patient was first misdiagnosed as cat scratch disease without staining for acid-fast bacilli or PCR identification for *Mycobacterium tuberculosis* on the biopsy specimens.

## CONCLUSIONS

Tuberculosis still remains a worldwide public health issue. It is still a common disease in developing countries, even in immunocompetent individuals. It should be kept in mind in the differential diagnosis of extra-pulmonary manifestations in order to avoid misdiagnosing and further complications. Surgical

biopsy leaves unwanted scars, causing esthetic problems and also the possibility of long-term drainage problems through the incision line.

In young, fertile, women, presenting with febrile ascites, often mimicking adnexal malignancy, surgeons should be aware of peritoneal TB, avoiding unnecessary mutilating surgery leading to increase complications, such as infertility.

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**Conflicts of interest:** All authors – none to declare

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