



## Extra Pulmonary Tuberculosis- An Overview of Five Cases

Authors

**Leonidas Grigorakos<sup>1,2</sup>, Daria Lazarescu<sup>1</sup>, Dimitra Lintzeri<sup>2</sup>, Sophia Simopoulou<sup>3</sup>,  
Anna Aiginitou<sup>2</sup>, Athina Christakakou<sup>2</sup>, Vassilis Sgountzos<sup>4</sup>**

<sup>1</sup>Faculty of Nursing, National and Kapodistrian University of Athens, Greece

<sup>2</sup>Intensive Care, "KAT" Trauma Hospital of Athens, Kifissia

<sup>3</sup>Peripheral Anticancer Oncology Hospital of Athens "Agios Savvas", Athens, Greece

<sup>4</sup>Sotiria Regional Chest Diseases Hospital, Athens, Greece

Corresponding Author

**Leonidas Grigorakos**

2 Nikis St, 14561, Kifissia, Athens, Greece

Tel: +30.210.3709522, Fax: +30.210.3709520, Email: [grigorakos@parliament.gr](mailto:grigorakos@parliament.gr)

### Abstract

*Tuberculosis (TB) is commonly found in developing countries but its incidence is considerable in developed countries also. Lung is predominantly affected while extra pulmonary tuberculosis (EPTB) is rarely encountered. As the clinical features of EPTB can be non-specific and mimic other diseases, it is usually misdiagnosed. Thus, it is very important to be aware and be highly suspicious of EPTB infection in both endemic and non-endemic areas. We highlight five successfully treated cases of different sites of EPTB, which involved cervical lymph nodes, carpal joint, ocular and genitourinary/ epididymal areas. We state the significance of early diagnosis of EPTB and the crucial role played by QuantiFERON blood test, fine needle aspiration cytology and histopathological examination to support diagnosis.*

**Keywords:** *Extrapulmonary tuberculosis, lymph nodes, carpal joint, ocular TB, genitourinary TB*

### Introduction

Tuberculosis (TB), which is a common granulomatous disease caused by Mycobacterium tuberculosis, remains an important global health problem<sup>(1)</sup>. In spite of effective treatment regimen and the "End TB Strategy" which was endorsed by World Health Organization's 194 Member States during the 2014 World Health Assembly, it still counts considerable mortality and morbidity rates, especially in countries with disease's high incidence<sup>(1)</sup>. Though lung is the commonest organ affected (about 80% of cases), it also affects other

parts of the body<sup>(2,3)</sup>. More precise, extra pulmonary tuberculosis (EPTB) with no evidence of pulmonary involvement arose from 16% in 1992 to 20 - 25% of all TB cases in 2009<sup>(4)</sup>. The increase in the proportion of TB cases that are HIV co-infected has contributed to this increase in EPTB's rates<sup>(5)</sup>. The most common sites of infection are the lymph nodes (25-60% occurrence of all EPTB cases)<sup>(6,7)</sup>, but hand involvement (10% occurrence of all EPTB cases)<sup>(8)</sup> and genitourinary disease (14-41% occurrence of all EPTB cases) also occur worldwide<sup>(9)</sup>. More so, the incidence of ocular TB

varies vastly between developed and developing countries, ranging from 0.38% in the USA to 32.4% in Myanmar<sup>(10)</sup>.

The general symptoms of TB include weakness, weight loss, fever, and night sweats. Symptoms of pulmonary TB may also involve coughing, chest pain, and hemoptysis while symptoms of EPTB depend on the area affected. Many times, tuberculous affliction of atypical organs mimic other conditions and may delay diagnosis or may even lead to wrong treatment plans. Since clinical presentation is aspecific, diagnosis can be elusive<sup>(11)</sup>. Therefore, medical practitioners should: a) be aware of the extra pulmonary manifestations of TB, b) be highly suspicious of the condition while managing patients, c) confirm diagnosis by histopathology and d) institute proper treatment at the earliest.

In this study, we share our experience with five cases of different sites of EPTB, which involved cervical lymph nodes, carpal joint, ocular and genitourinary/ epididymal areas.

### Case Presentation

Patients presented to our department with various symptoms and were subjected to specific tests which led to diagnosis of EPTB (table 1).

#### Case 1

A 57-year-old woman presented with decrease of right eye's visual acuity and a medical history of right sided breast cancer a decade before. Following eye examination, patient received topical corticosteroid treatment in right eye's pupil.

Her laboratory and biochemical tests were normal while the chest X-ray was negative for active pulmonary TB. Both sputum smear using the Ziehl-Nelsen (ZN) stain and Lowenstein Jensen (LJ) medium were negative.

Chest computed tomography (CT) revealed a few fibrous fibro-anetelactic elements in both lungs, alterations of microvascular morphology without specific characteristics but with characteristic of granuloma in certain areas as well as marginal bronchiectasis. At the same time, QuantiFERON blood test was positive for TB.

#### Case 2

A 41-year-old man presented with unpainful right lymphadenitis that did not retreat with antibiotics. He was submitted to laboratory tests and chest X-ray which did not reveal any pathological findings. From the thorax CT scan resulted few fibrous fibro-anetelactic elements in both lungs, without lymph nodes while from the neck CT resulted multiple small swollen lymph nodes (up to 1,5 cm).

Sputum smear using the Ziehl-Nelsen (ZN) stain, Lowenstein Jensen (LJ) medium and the Amplified Mycobacterium tuberculosis Direct (AMTD) were negative.

The cytological features revealed polymorphous lymphatic population, numerous multi-cell additions of epithelial cells, several multi-core giant cells as well as substrate necrosis. The findings supported prolonged granulomatous lymphadenitis.

#### Case 3

A 41-year-old man presented with swelling and inflammation of the left carpal joint, was initially diagnosed with psoriatic arthritis and was administered methotrexate and prednisolone. His Mantoux test was positive with 20 mm diameter reading and was initiated anti-TB treatment (300 mg Isoniazid (INH) and 600 mg Rifampicin (RMP) administered orally). His laboratory tests were normal while chest CT revealed normal parenchyma, without lymph nodes or pleural effusions.

Sputum smear using the Ziehl-Nelsen (ZN) stain and Lowenstein Jensen (LJ) medium were negative.

Left carpal joint puncture was performed and the material was sent for gram staining and culture which proved to be negative. The pus from the puncture of the left carpal joint revealed EPTB that has been found to be sensitive to anti-tuberculosis drugs. Previous molecular method (Geno Type MTBDR) of drug susceptibility testing revealed strains of Mycobacterium tuberculosis sensitive to INH and RMP.

#### Case 4

A 73-year-old man with a medical history of papillary urothelial carcinoma (grade III) and

subsequent submission to intravesical BCG each week for 6 weeks before admission presented to our department with painful swelling of left epididymis and to a lesser extent of right epididymis with partial response to antibiotics.

Successively, he continued intravesical BCG and a re-inflammation of left epididymis and, to a lesser degree, of the right epididymis was recorded. Cystoscopy as well as removal of left epididymis were performed. Sections were sent for Ziehl-Nelsen (ZN) stain, Lowenstein Jensen (LJ) medium, Mycobacteria Growth Indicator Tube (MGIT), Amplified Mycobacterium tuberculosis Direct (AMTD) and histologic tests.

ZN, LJ, MGIT and AMTD were negative for Mycobacterium Tuberculosis while histologic results showed the presence of various granulomas sizes with wide areas of necrosis.

### Case 5

A 51-year-old man presented with lymph nodes swelling on both sides of his neck. His laboratory tests revealed normocytic anemia while the chest X-ray was negative for active pulmonary TB.

His liver – bile duct – pancreas – upper and lower abdominal ultrasound were normal while neck ultrasound revealed the presence of several pathologically expanded neck lymph nodes along the jugular chain bilaterally, with the largest being measured with a diameter of about 2.5 cm on the left side but also supraclavicular lymph nodes bilaterally, the larger on the right side of about 4x2cm.

His upper and lower abdominal CT did not reveal any pathological findings.

His Mantoux test was positive with 20 mm diameter and at the same time, QuantiFERON blood test was positive for TB.

Histologic examination revealed excessive necrosis which occupies the largest extent of lymph node parenchyma, while the DNA analysis gave a positive sample and presence of MTBC DNA.

### Treatment

Three of our five patients (patient 1, patient 2 and patient 5) were subjected to standard anti-TB

therapy, taking a two-month daily oral HRZE regime: (a) daily dosages of 300 mg Isoniazid (INH) and 600 mg Rifampicin (RMP) administered orally, (b) daily 20mg/kg PO qDay Pyrazinamide (PZA) and 2.5×500 mg of Ethambutol (EMB) in the form of Dexambutol tablets and (c) daily dosage of 20 mg B6 administered orally. After two months the optical accuracy improved (patient 1) and the lymph nodes swellings diminished (patient 2 and patient 5), both PZA and EMB were stopped while INH, RMP and B6' s administration was prolonged for four more months.

One patient (patient 3) was administered a three-month daily oral HR anti-TB treatment: a) daily dosages of 300 mg Isoniazid (INH) and 600 mg Rifampicin (RMP) administered orally. After three months of therapy, it was recorded significant improvement of both clinical and radiological image of left carpal joint. Thus, anti-TB dosage was reduced. His continuous improvement led to end of anti-TB therapy after 9 months.

One patient (patient 4) was subjected to anti-TB therapy, taking daily oral HRE regime: (a) daily dosages of 300 mg Isoniazid (INH) and 600 mg Rifampicin (RMP) administered orally, (b) 2.5×500 mg of Ethambutol (EMB) in the form of Dexambutol tablets and (c) daily dosage of 20 mg B6 administered orally. After two months his clinical image significantly improved and anti-TB therapy was prolonged for seven more months.

All patients were followed up for a period of 9 months and complete recovery, without any other complications, was recorded.

### Discussion

TB is a serious infectious disease primarily affecting the lungs. It is caused by acid-fast bacteria belonging to Mycobacterium tuberculosis complex and it accounts for millions of cases of active disease and deaths worldwide. Its epidemiology has been modified by HIV epidemic and immigration spreads TB while prevalence decreased in developed countries thanks to the introduction of effective chemotherapy<sup>(11,12,13)</sup>.

**Table 1:** Clinical features and diagnosis

Patients' characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	57	41	41	73	51
Sex	F	M	M	M	M
Symptoms at admission	Decrease of right eye's visual acuity	Neck lymphadenitis that did not retreat with antibiotics	Swelling and inflammation of the penile cartilage joint. Initial diagnosis: psoriatic arthritis	Painful swelling of left epididymis and to a lesser extent of right epididymis with partial response to antibiotics	Lymph nodes swelling
Tuberculin skin test (mm)	-	15	20	-	20
QuantiFERON	Positive	-	-	-	Positive
Chest X-ray	Normal	Normal	Normal	Normal	Normal
Chest CT	A few fibrous fibro-anetelactec elements in both lungs. Alterations of microvascul ar morphology without specific characteristics but with characteristic of granuloma in certain areas. Marginal bronchiectasis.	A few fibrous fibro-anetelactec elements in both lungs, without lymph nodes	Normal parenchyma. Without lymph nodes or pleural effusions	-	Normal
Sputum examination for Koch's bacillus	Sputum smear negative using the Ziehl-Nelseen (ZN) stain and Lowenstein Jensen (LJ) medium	Sputum smear negative using the Ziehl-Nelseen (ZN) stain, Lowenstein Jensen (LJ) medium and the Amplified Mycobacterium tuberculosis Direct (AMTD)	Sputum smear negative using the Ziehl-Nelseen (ZN) stain and Lowenstein Jensen (LJ) medium	Sputum smear negative using the Ziehl-Nelseen (ZN) stain and Lowenstein Jensen (LJ) medium	Sputum smear negative using the Ziehl-Nelseen (ZN) stain and Lowenstein Jensen (LJ) medium

Even though EPTB's incidence is rare compared to the pulmonary counterpart, its recognition may be an important public health issue and a real challenge for clinicians, as smear-negative pulmonary TB is responsible for about 17% of new pulmonary infections. It can be present despite a normal chest X-ray, even in human immunodeficiency virus (HIV)-negative patients<sup>(14)</sup>. Another challenge to the diagnosis is that extra-pulmonary specimens yield few bacilli and therefore acid-fast bacilli smear and culture have a very low sensitivity. The lack of adequate sample volumes, as was the case in our initial sputum samples, and apportioning paucibacillary samples for multiple test (e.g. acid-fast bacilli, culture), may lead to inconsistent, and often times falsely negative results. Our patients presented with different forms of EPTB<sup>(15,16)</sup>. Thus, discerning the broad differential diagnosis is another challenge.

Although the disease usually responds to standard anti-TB drug therapy, the ideal procedure and duration of treatment have not yet been established. Because smear microscopy or culture is not available to monitor patients with EPTB, clinical monitoring is the usual way to assess the response to treatment<sup>(17-18)</sup>. A paradoxical response frequently occurs during anti-TB therapy. It should be distinguished from other causes of clinical deterioration. Invasive methods are often needed to obtain samples for microbiological and histological testing while surgery is required mainly to manage complications.

Drug resistance including Multi Drug Resistant-TB was observed in a significant proportion of extrapulmonary specimens referred for drug susceptibility testing (DST). Thus, access to culture and DST for extrapulmonary specimens should be expanded. Guidelines for Multi Drug Resistant-TB management should have explicit sections on EPTB and training on laboratory techniques is required<sup>(19)</sup>. Therefore, our case report emphasizes that medical personnel should be aware of atypical and misleading presentations of EPTB, even in non-immunocompromised individuals<sup>(20)</sup> which otherwise can lead to inappropriate diagnosis and treatment for this curable disease.

### Conclusions

EPTB's occurrence shouldn't be neglected as it poses particular diagnostic challenges. It can be present with variable clinical manifestations and can mimic other entities. Therefore, it is very important to have a high index of suspiciousness and well-equipped laboratory environment to rule out EPTB, as the prompt onset of treatment leads to complete resolution of the disease. In patients with EPTB, sputum testing should be considered to detect concurrent pulmonary TB even if a chest X-ray is normal. QuantiFERON blood test, fine needle aspiration cytology and histopathological examination play a crucial role to support diagnosis.

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