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Pneumologia

Extrapulmonary Tuberculosis: Challenges in Diagnosis and Treatment - Case series

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Abstract

English:

Extrapulmonary tuberculosis (TB) accounts for 10%–15% of all the TB cases worldwide, as reported by WHO. Due to the diverse presentations of extrapulmonary TB, diagnosis is frequently challenging. This challenge is further compounded by the difficulty in obtaining adequate diagnostic samples and the low concentration of Koch's bacilli. In this study, we discuss cases of patients aged between 32 years and 72 years with negative HIV serology, but with other risk factors that trigger extrapulmonary TB, including chronic inflammatory disease under treatment with monoclonal antibodies or corticosteroids, cancer, chronic obstructive pulmonary disease, or chronic kidney disease stage V. The patients had miliary, bone, and lymph node extrapulmonary TB, and their diagnostic methods, duration, and type of treatment varied based on their tolerance and response to treatment. In conclusion, our study highlights the challenges in diagnosing extrapulmonary TB, resulting from the diverse clinical presentations of the disease and difficulties in obtaining adequate diagnostic samples. Our findings provide potential solutions to these issues.

Keywords

extrapulmonary tuberculosis • TB risk factors • miliary • TB bone • TB lymph node

Tuberculoza extrapulmonară: provocări de diagnostic și tratament – Serie de cazuri

Rezumat

Romanian:

Tuberculoza extrapulmonară reprezintă aproximativ 10%–15% din totalitatea cazurilor de tuberculoză la nivel mondial, conform datelor publicate de OMS. Diagnosticul tuberculozei extrapulmonare este unul dificil datorită nespecificității tabloului clinic. Provocarea diagnostică este completată de dificultatea de prelevare a probelor care ar putea confirma diagnosticul, dar și de concentrația scăzută a bacilului Koch din acestea. În acest studiu vom prezenta cazurile unor pacienți cu vârsta cuprinsă între 32 și 72 de ani, cu serologie HIV negativă, dar cu alți factori de risc pentru tuberculoza extrapulmonară, cum ar fi tratamentul cu anticorpi monoclonali sau corticosteroizi, cancerul, bronhopneumopatia obstructivă cronică sau boala cronică de rinichi stadiu V. Pacienții au prezentat forme de tuberculoză pulmonară miliară, osoasă și ganglionară, metodele diagnostice fiind diferite, la fel și durata și tipul de tratament, personalizat în funcție de toleranță și răspuns. Studiul nostru subliniază provocările diagnostice ale tuberculozei extrapulmonare și prezintă eventuale soluții în cazul unor asemenea pacienți.

Cuvinte-cheie

tuberculoză extrapulmonară • factori de risc TB • miliară • TB osos • TB ganglionar

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Case Reports

Introduction

Tuberculosis (TB) is caused by the *Mycobacterium tuberculosis* complex and is a significant cause of mortality worldwide. It can be classified as pulmonary or extrapulmonary, with the latter being less common, representing only 10%–15% of TB cases, but rising to 50% in patients co-infected with HIV (1). Confirming the diagnosis of extrapulmonary TB is often challenging and poses a significant clinical problem. Here, we discuss six cases of extrapulmonary TB in patients with negative HIV serology but with other predisposing risk factors. Diagnosis varied across the cases, from detecting *Mycobacterium tuberculosis* DNA in sputum or in bronchial aspirate to histopathological examination of an anterior cervical lymph node or bacillary DNA detection in secretion from a lymphatic fistula. The duration and type of treatment were tailored to each patient based on their individual response and tolerance to treatment. GeneXpert tests were utilized to detect *M. tuberculosis* DNA and rifampicin resistance (4).

Case 1

A 32-year-old woman having systemic lupus erythematosus (SLE) and treated with corticosteroids at home presented with dry cough, dyspnea, fatigue, and progressively worsening lumbar pain with left thigh radiation over the past 3 months. Three months prior, the patient discontinued biological treatment with belimumab as directed by the rheumatologist and had a normal chest X-ray.

On presentation, the patient was afebrile. Imaging studies revealed micronodules with a tree-in-bud appearance bilaterally (Figure 1) and osteolytic lesions at L5, S1 (Figure 2), and left acetabulum.

A bronchoscopy with bronchoalveolar lavage and bronchial aspirate was performed. The analysis of the bronchoalveolar lavage did not detect cancer cells, but revealed acid fast bacilli (AFB), as well as bacillary DNA (GeneXpert positive without rifampicin resistance), which confirmed the diagnosis of miliary TB. The patient was started on anti-TB treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide according to the Romanian protocol, resulting in good tolerance and improvement of respiratory symptoms after about 1 month.

Unfortunately, lumbar and left lower limb pain intensified, leading to functional impotence and wheelchair immobilization. A bone biopsy of the sacral vertebra S1 confirmed the diagnosis of bone TB with the detection of bacillary DNA. Given the confirmation of bone TB and worsening symptoms, the intensive phase of the anti-TB treatment was extended to 3 months, and the continuation phase with isoniazid and rifampicin was extended to 12 months.

At the 9-month follow-up, the patient was asymptomatic from a respiratory point of view, had less significant lumbar pain, successfully mobilized herself, and had much improved chest CT scan images (Figure 3). The patient continued corticosteroid treatment for SLE as directed by the rheumatologist.

Conclusion

In conclusion, this case report describes a 32-year-old woman with SLE, who presented with respiratory and musculoskeletal symptoms, eventually leading to the diagnosis of miliary and bone TB. The discontinuation of biological treatment with belimumab may have contributed to the reactivation of TB in this patient.

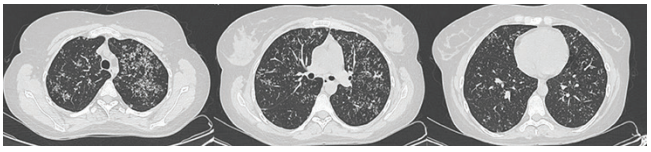

Figure 1. Thoracic CT transversal sections showing pulmonary micronodules with tree-in-bud appearance in both lungs.

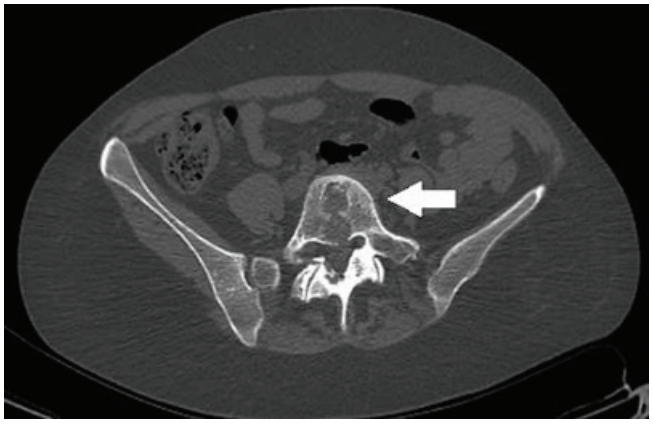

Figure 2. Pelvic CT transversal section revealing osteolytic lesion in S1 (white arrow).

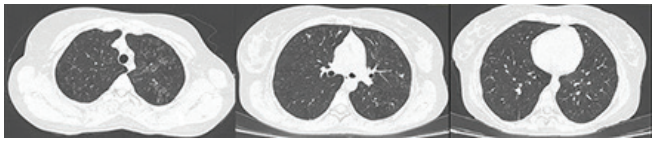

Figure 3. Thoracic CT transversal sections at the 9-month follow-up showing less pulmonary micronodules compared with Figure 1.

This case highlights the importance of considering TB in the differential diagnosis of respiratory symptoms in immunocompromised patients and the need for prompt treatment to prevent further complications.

SLE patients are at an increased risk for TB compared to the general population, with a higher relapse rate and a higher likelihood of developing TB at multiple extrapulmonary sites (5). Extrapulmonary TB with musculoskeletal involvement is often a difficult diagnosis, as the disease can mimic infection or metastases (6). The use of corticosteroids and biologic agents increases the risk of TB (7). The duration of anti-TB treatment varies between 6 months and 12 months, depending on the patient's clinical and imaging response (8). In this case, the patient was treated for 12 months.

Case 2

A 42-year-old man with ankylosing spondylosis, HLA B24 positivity, and a 25 pack-year smoking history had been undergoing treatment with adalimumab for 1 year when he presented with a persistent fever (40°C), night sweats, fatigue, significant weight loss, and a dry cough. Despite being treated with levofloxacin for 7 days, the patient's symptoms did not improve. He reported experiencing febrile states predominantly at night for 3 months before his presentation.

During treatment with adalimumab, the patient had multiple dental cavities with infections, an episode of pneumonia, and an altered general condition. The chest X-ray was normal before starting adalimumab.

On admission, the patient was febrile (38°C) with altered general condition, and the chest X-ray showed micronodular opacities arranged diffusely bilaterally (Figure 4).

The patient tested positive for SARS-CoV-2 via an RT-PCR test and underwent a chest CT scan, which revealed numerous diffuse micronodules bilaterally, a thin line of pericardial fluid, bilateral minimal pleurisy, and small areas of ground glass in the upper lobes. The ground glass areas were interpreted as being indicative of a viral infection (Figure 5).

The biological results showed a significant inflammatory syndrome and the transaminase levels as being at the upper limit of normal. Sputum examination revealed the presence of AFB and *M. tuberculosis* DNA, leading to a diagnosis of miliary TB.

The patient's adalimumab treatment was discontinued, and anti-TB treatment with the four first-line drugs, isoniazid, rifampicin, ethambutol, and pyrazinamide, was initiated.

After 4 days, the patient developed diarrhea, and a diagnosis of *Clostridium difficile* infection (CDI) was made, leading to the discontinuation of anti-TB treatment. Vancomycin was administered, and the patient's digestive symptoms remitted within a week. Isoniazid and ethambutol were resumed 4 days later, with the gradual introduction of pyrazinamide and rifampicin. One week after resuming treatment, the patient's condition worsened, and he experienced nausea, vomiting, and a loss of appetite. There was a significant increase in transaminases and total and direct bilirubin levels, so anti-TB treatment was discontinued due to acute drug-induced liver injury. The patient was stabilized both clinically and hemodynamically.

After 10 days, anti-TB treatment was gradually reintroduced, starting with ethambutol in a therapeutic dose, followed by isoniazid with doses increasing every 3 days until the

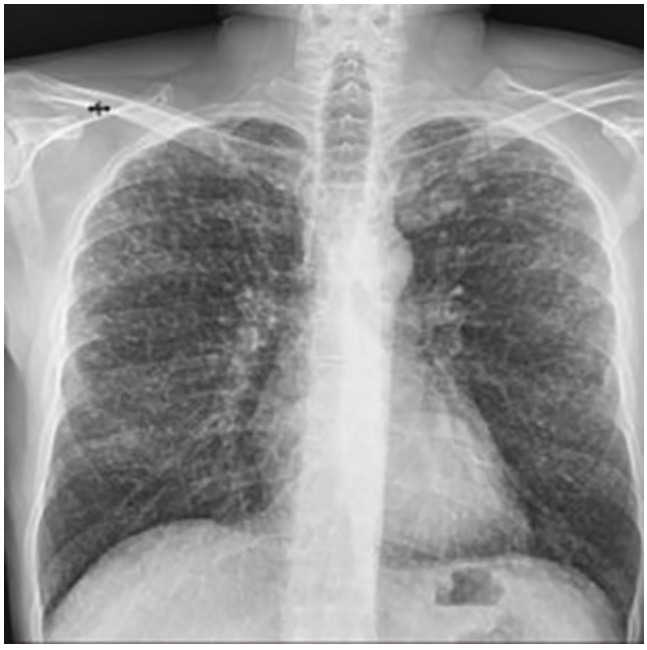

Figure 4. Chest X-ray showing diffuse tiny nodules scattered throughout both lungs in a miliary pattern.

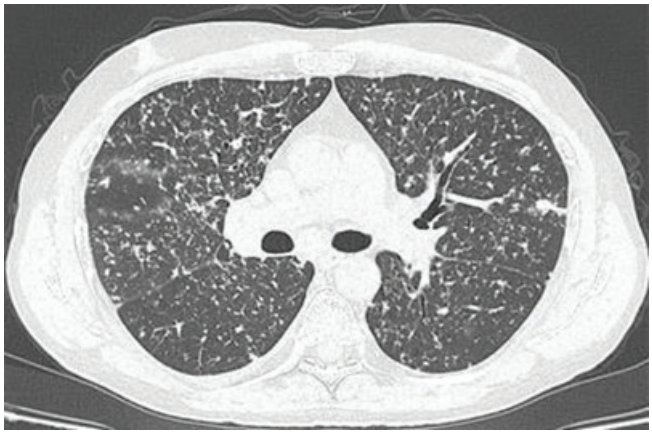

Figure 5. Thoracic CT axial lung window with diffuse pulmonary micronodules in both lungs, small areas of ground glass in the upper right lobe, and bilateral minimal pleurisy.

therapeutic dose was reached, and then rifampicin and pyrazinamide with weekly dose increases. After 2 months, the patient reached the therapeutic dose and was stable both clinically and hemodynamically.
He was discharged after a further 3 weeks of treatment with the full regimen, with an indication to continue the anti-TB treatment and to see the rheumatologist to discuss modification of treatment for ankylosing spondylitis.

Conclusion

In conclusion, this is a case of a 42-year-old man with ankylosing spondylosis and a history of smoking, who was undergoing treatment with adalimumab and presented with a persistent fever, night sweats, fatigue, significant weight loss, and a dry cough, and was eventually diagnosed with miliary TB. Management required discontinuation of adalimumab and anti-TB treatment with the four first-line drugs. Further rheumatological treatment remains to be personalized following a rheumatology review.

Case 3

A 46-year-old male smoker with a history of 15 pack-years of smoking and no occupational exposure presented to the hospital with symptoms of dry cough, fever (39°C), chills, night sweats, and weight loss. Symptoms started 1 week prior to hospital presentation. The patient has an existing condition of ankylosing spondylitis and was receiving treatment with adalimumab since 2009. In 2010, the patient was treated and declared cured of pulmonary TB.
Upon examination, chest X-rays revealed diffusely distributed micronodular opacities bilaterally, highly suggestive of miliary TB (see Figure 6). Sputum analysis confirmed the presence of AFB and *M. tuberculosis* DNA (GeneXpert positive without rifampicin resistance). Consequently, adalimumab treatment was discontinued, and the patient was started on standard first-line anti-TB treatment with the four drugs.
However, after a week of treatment, a significant increase in transaminase levels (10 times above normal) was observed, prompting the temporary discontinuation of anti-TB treatment until the transaminase levels normalized. After monitoring for a month, anti-TB drugs were gradually reintroduced, with careful monitoring of transaminase and bilirubin values.
Given the occurrence of two episodes of TB during biological treatment, the patient was deemed an inappropriate candidate for adalimumab and was referred to a rheumatology department to adjust their therapeutic regimen.

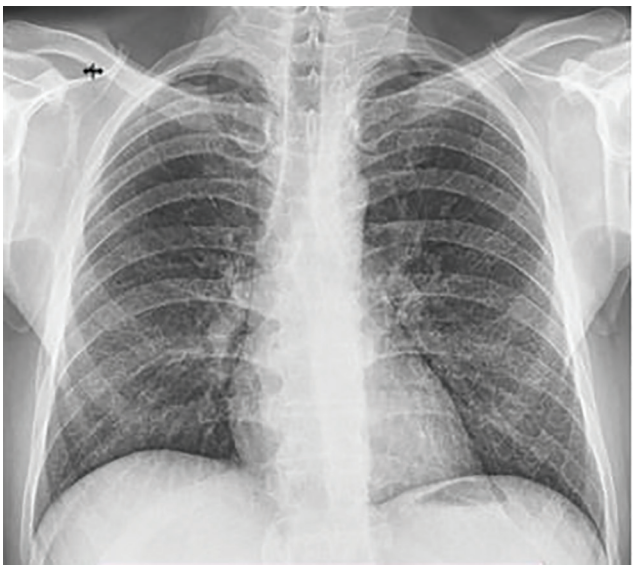

Figure 6. Chest X-ray showing diffuse micronodules in both lungs.

Conclusion

Cases 2 and 3 illustrate the increased risk of TB in patients receiving tumor necrosis factor alpha (TNF-α) inhibitors. The risk of TB associated with different biologics varies considerably, with adalimumab and infliximab having the highest relative risks (9). When TB develops during anti-TNF-α treatment, it is more likely to be disseminated and extrapulmonary, as seen in the aforementioned cases (10). Therefore, early diagnosis and appropriate treatment of TB in patients eligible for biologic therapy are crucial. However, it should be noted that anti-TB treatment can lead to drug-induced liver injury in some cases (11). Anti-TB drugs are not typically linked to the development of CDI. In Case 3, the CDI was considered in the context of the patient's recent levofloxacin treatment (12).

Case 4

A 72-year-old woman with a history of occupational exposure (as a worker in a printing plant), ethanol consumption, and multiple renal and cardiovascular comorbidities presented with dyspnea on low exertion, fatigue, loss of appetite, and significant weight loss (20 kg in 1 year). Her medical history included stage 5 chronic kidney disease, type II diabetes mellitus, hypertension, permanent atrial fibrillation on oral anticoagulants, and autoimmune thyroiditis on hormone replacement therapy.
Upon presentation, she was found to have moderate microcytic hypochromic anemia and disseminated pulmonary micronodules on the chest CT scan (Figure 7).

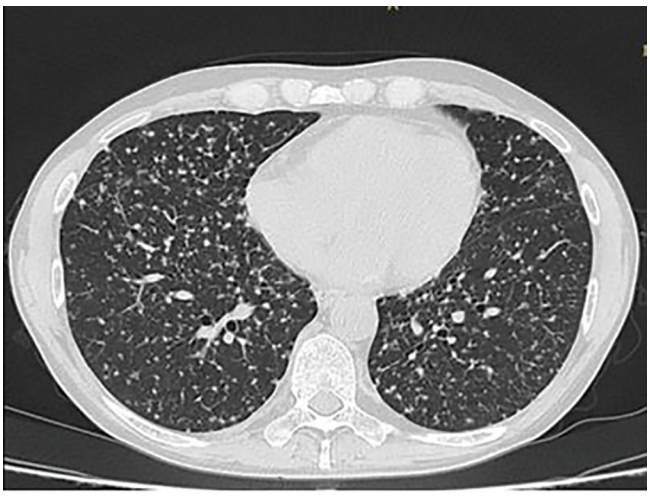

Figure 7. Thoracic CT axial lung window with bilaterally disseminated pulmonary micronodules.

Sputum was negative for TB. A bronchoscopy was performed and the bronchoalveolar lavage obtained did not detect cancer cells but did detect bacillary DNA (GeneXpert positive without rifampicin resistance). As a result, anti-TB treatment was initiated, adapted to the creatinine clearance, with daily administration of isoniazid and ethambutol, and administration of rifampicin and isoniazid 3 days out of 7.

After 1 week of treatment, the patient's condition worsened, she became jaundiced and nauseous, and the transaminase levels increased. The anti-TB treatment was stopped.

However, 2 days after the treatment was stopped, the patient presented with hematemesis and melena. An emergency upper endoscopy was performed, and a pseudotumoral formation was found in the esophagus as a source of hemorrhage. Biopsy of the formation was postponed due to the high risk of bleeding. Although the melena and hematemesis did not recur, the patient's condition continued to deteriorate despite attempts to administer anti-TB treatment. Sadly, the patient passed away a few days later.

Conclusions

In conclusion, this is a case of a 72-year-old woman with a complex medical history and multiple comorbidities presented with respiratory symptoms, weight loss, and anemia eventually diagnosed with TB. The patient had multiple risk factors that may have increased her chances of developing TB, including advanced age, end-stage chronic kidney disease, and diabetes mellitus (13). Additionally, there was a suspicion of esophageal cancer that could not be confirmed. The patient also experienced drug-induced liver injury as a result of TB medication, which may have been exacerbated by her age and alcohol consumption (14).

Case 5

A 67-year-old man with a 30 pack-year smoking history and a previous diagnosis of pseudotumor formation in the left upper lobe was admitted with a productive cough, sweating, loss of appetite, fatigue, and weight loss. The patient had COPD GOLD II risk group B. The pseudotumoral formation was incidentally detected 2 years prior to the examination on a chest CT exam (Figure 8). At that time, a biopsy was performed, which showed histopathological results consistent with necrotizing lymphangitis.

During the admission, a left supraclavicular ganglion–cutaneous fistula was identified, and a chest CT showed dimensional progression of the formation in the left upper lobe (Figure 9). Sputum and bronchial samples were negative for TB, but *M. tuberculosis* DNA was detected from the purulent secretion at the cutaneous fistula site (GeneXpert positive without rifampicin resistance), with subsequent culture positivity after 2 months, leading to a diagnosis of lymph node TB. The patient was treated with a standard 6-month anti-TB regimen.

At the 3-month follow-up, the patient was symptom-free, and the cutaneous fistula showed improvement and was in the process of healing. The pseudotumor formation in the left upper lobe was also found to be significantly regressing. (Figure 10).

Conclusion

This case likely involves the reactivation of secondary pulmonary TB, accompanied by lymph node involvement. Diagnosis was challenging due to negative results on both sputum and bronchial aspirate tests, including negative results on direct smear and GeneXpert testing. The GeneXpert test

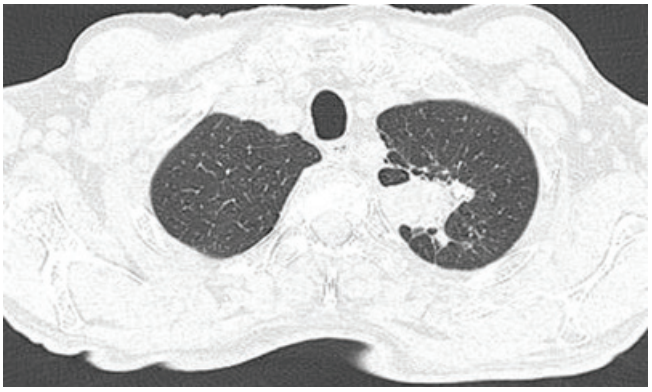

Figure 8. Thoracic CT transversal section showing a solitary pulmonary mass in the upper left lobe.

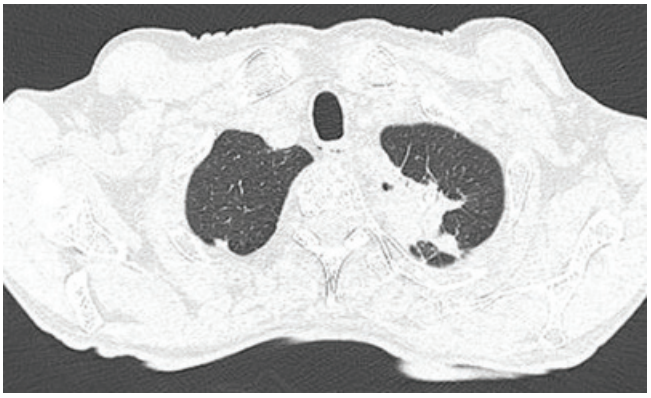

Figure 9. Thoracic CT transversal section showing the dimensional progression after 2 years of the solitary pulmonary mass in the upper left lobe compared with Figure 8.

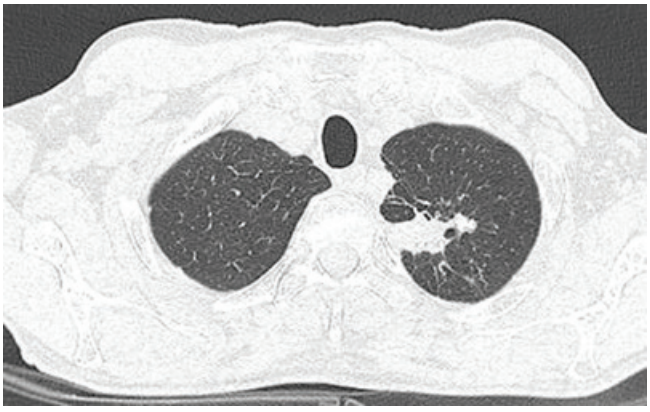

Figure 10. Thoracic CT transversal section showing the dimensional regression at the 3-month follow-up of the solitary pulmonary mass in the upper left lobe compared with Figure 9.

was particularly valuable in identifying *M. tuberculosis* at an early stage despite negative direct smear results. Treatment with the standard anti-TB regimen was successful in resolving the patient's symptoms and reducing the size of the pseudotumor.

Case 6

A 49-year-old female, who is a nonsmoker and has professional exposure to the medical field, had a history of breast cancer treated with chemotherapy and radiotherapy. She was admitted to another hospital for a thyroid biopsy puncture and removal of an enlarged supraclavicular lymph node. The analysis of the thyroid tissue revealed multifocal papillary microcarcinoma of the thyroid, while the histopathological examination of the lymph node revealed TB lymphadenitis. Therefore, an incidental diagnosis of lymph node TB was made.

At the time of presentation, the patient had normal chest X-ray results and did not report any symptoms.

Given the patient's medical history, she was started on a 2-month intensive phase of anti-TB treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide, followed by a 4-month continuation phase with izoniazid and rifampicin. This treatment was to be conducted simultaneously with the patient's oncological treatment for thyroid cancer.

Conclusion

In this case, the discovery of TB was incidental. As we mentioned before, cancer is one of the risk factors that predisposes TB (13).

Discussion

TB is a complex disease with various forms, which makes diagnosis challenging (2). Advancements in medicine have revealed new risk factors that predispose patients to the disease. For instance, extrapulmonary TB cases have been increasingly reported in young patients with systemic inflammatory diseases undergoing corticosteroid and biological treatment. Each biological agent carries a different risk. Screening for latent TB is vital before starting treatment with biological agents, although it does not eliminate the risk of relapse. Collaborative efforts among clinicians are necessary in these cases.

Although HIV-positive patients have the highest risk of developing extrapulmonary TB (15), there are other conditions that cause immunosuppression and predispose to TB. Furthermore, risk factors such as SLE, old age, neoplasm, diabetes, or chronic kidney disease are often associated with a poor prognosis.

Extrapulmonary TB usually has a low bacterial load, and genetic tests for *M. tuberculosis* DNA detection are useful for rapid and accurate diagnosis. These tests also help determine bacterial resistance to both first- and second-line medication, allowing for timely administration of anti-TB medication (3).

Despite the high efficacy of anti-TB treatment, caution and strict supervision are necessary due to the potential adverse effects, such as drug-induced hepatitis and CDI, even in young patients. However, anti-TB drugs are not typically linked to the development of CDI.

The recommended treatment duration ranges from 6 months to 12 months and can be personalized based on factors such as the location of the infection and the patient's clinical and biological progression. This personalization can involve prolonging either the intensive phase or the continuation phase.

In endemic countries, particularly in immunocompromised patients or HIV-infected individuals, TB should be included in the differential diagnosis.

Our key learning points are as the following:

- Collaboration among clinicians is necessary to manage extrapulmonary TB cases, especially in patients with risk factors.
- Genetic tests for *M. tuberculosis* DNA detection should be used extensively as it can help diagnose the disease accurately and identify bacterial resistance, which is essential for timely administration of anti-TB medication.
- Anti-TB medication is highly efficacious, but it should be administered under surveillance and with caution due to potential adverse effects, even in young patients.

Overall, our study presents a comprehensive overview of the challenges of diagnosing TB and managing patients with risk factors for the disease. It is consistent with other publications on the topic and provides valuable insights into the best practices for diagnosing and treating TB.

Authors contributions

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3. Coordinating author: Claudia-Lucia Toma.
4. Others: Ionela Belaconi, Stefan Dumitrache-Rujinski.

Disclaimer

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Informed consent statement

Informed consent was obtained from all the subjects involved in the study.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest

The authors declare no conflict of interest.

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