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Case Report

Primary lymphatic tuberculosis in children - Literature overview and case report ☆,☆☆

Cung-Van Cong, MD, PhD[a,1], *Tran-Thi Ly, PhD*[b,*], *Nguyen Minh Duc, MD, MSc*[c,1,*]

[a] *Department of Radiology, National Lung Hospital, Ha Noi, Vietnam*
[b] *Center of Training and Direction of Healthcare Activities, National Lung Hospital, Ha Noi, Vietnam*
[c] *Department of Radiology, Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam*

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ABSTRACT

Tuberculosis bacilli can enter the human body through the digestive system, the skin, and the mucous membranes, although they mainly enter through the respiratory tract. TB bacilli can enter the bloodstream and attack other organs including the lymphatic system. The TB bacillus can cause miliary tuberculosis once they have entered the bloodstream and infiltrated the lymphatic system, which can then manifest as large lymph nodes in the hilum, mediastinum, and lung. Complicated primary TB infection occurs when enlarged lymph nodes compress the airways, causing a partial or complete obstruction that can lead to air retention or atelectasis. More serious complications can occur if the lymph nodes fill with pus and burst, as this can lead to TB spreading through the airways via a humoral mechanism. Making a differential diagnosis of hilar and mediastinal lymphadenopathy is often difficult because diagnostic interventions in this area are problematic. We report on a clinical case of a child with primary TB of the lymphatic system. The patient presented with mediastinal lymphadenopathy and miliary lesions in the lung, which was confirmed by a transthoracic biopsy performed under CT guidance. It is hoped that this report can provide doctors with a more comprehensive approach when diagnosing this disease.

Introduction

Despite having been identified more than 100 years ago, tuberculosis (TB) is still a common infectious disease, and is particularly prevalent in developing countries [1–3]. The disease kills more than 1 million people each year and still places a burden on the healthcare systems of many countries, including Vietnam [3]. TB bacilli can enter the human body through the digestive system, the skin, and the mucous membranes, although they enter through the respiratory tract in 70%-80% of cases [16]. When entering the lungs, TB bacilli often encounter

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* Corresponding authors.
E-mail addresses: ly13021984@gmail.com (T.-T. Ly), bsnguyenminhduc@pnt.edu.vn (N.M. Duc).
[1] These authors contributed equally to this article as first authorship
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fierce resistance from the body's immune system, meaning that they can lie dormant for a long time (known as inactive or latent TB). When the body's immune system is weakened, or the bacteria detect favorable conditions, they can reactivate, causing widespread damage by entering the bloodstream to attack other organs including the lymphatic system [2,4]. Hematogenous infiltrates often manifest as military TB or tuberculous meningoencephalitis [5] and lymphatic infiltration often manifests as large hilar and mediastinal lymph nodes [6–9]. If only large hilar lymph nodes are seen, the mediastinum is usually classified as primary TB. According to the World Health Organization, primary infection is classified into 2 types: uncomplicated, and complicated. In the case of TB, uncomplicated primary TB usually only shows enlarged hilar lymph nodes in the mediastinum alone. Complicated primary TB infection occurs when these enlarged lymph nodes compress the airways, causing partial or complete obstruction, which can lead to air retention or atelectasis. More serious complications can occur if the lymph nodes become pus-filled abscesses and burst, as this can lead to TB spreading through the airways via a humoral mechanism [10–15].

Enlarged lymph nodes in the hilum and mediastinum can have many etiologies. Differential diagnosis of large hilar and mediastinal lymph nodes caused by TB or other pathologies is often difficult because diagnostic interventions in these areas are problematic [8–11]. Endobronchial transbronchial lymph node biopsy is a "blind" technique that is rarely performed due to inherent risks, whereas an endobronchial ultrasound and biopsy (EBUS) procedure requires expensive equipment and highly trained medical operators.

There are many possible causes of lymphadenopathy in this region, particularly malignant (primary and secondary) lymph node lesions [1,2,12]. In our clinical practice, we have seen rare cases of both mediastinal lymphadenopathy, and miliary lung lesions. We report a case of pediatric TB with the above-mentioned symptoms and with a variety of differential diagnoses, which were confirmed by a CT-guided transthoracic mediastinal lymph node biopsy. A histopathological examination of the specimen pieces confirmed that they were consistent with a TB lesion, while a culture of the specimen pieces in a mycobacteria growth indicator tube (MGIT) tested positive for MTB. The patient is currently being treated for TB and is responding well to treatment.

Case report

The patient was a 16-year-old male who presented at the National Lung Hospital with a cough, low-grade fever, and chest pain. His medical history showed normal development with no family history of TB. The patient was given a chest X-ray, which is shown in Fig. 1.

The chest X-ray showed a widened superior mediastinum (96 mm) with enlargement of the right paratracheal line (yellow arrow). The right hila had 2 opacities that were synonymous with large hilar lymph nodes (red arrows). There were many small opacities seen on both lungs, with a central predominance, while left pleural thickening was also observed (white arrow).

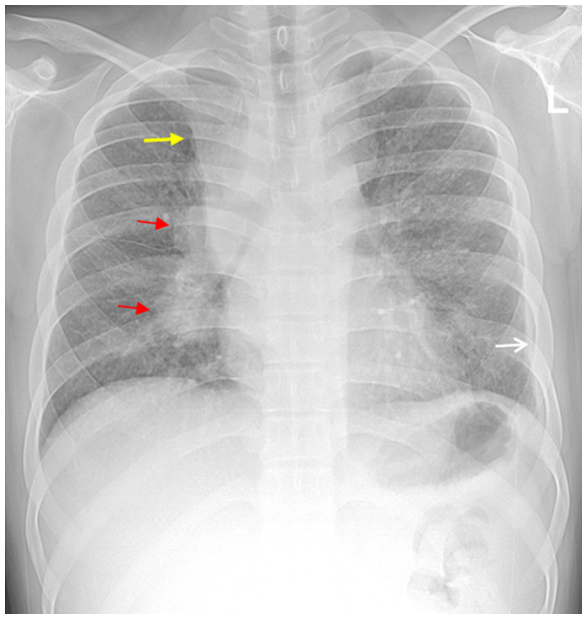

Fig. 1 – Conventional chest radiograph, PA.

The patient was tested for Acid Fast Bacillus (AFB) (-) using a direct fluorescein sputum smear test; Gene Xpert MTB and/or RIF test with direct sputum and bronchoalveolar lavage (-) with MTB. A complete blood count was taken, and blood biochemistry results were within normal limits. Additionally, urinalysis, echocardiography, abdominal ultrasound, and an electrocardiogram showed no abnormalities.

The patient underwent a chest CT scan with a 64-slice scanner both before and immediately after intravenous contrast injection (contrast: Xenetic 350 × 100 mL at 4 mL/sec; capture formula: 130 kV, Xtube 115 mA, slice thickness: 3 mm; WW/WL: 1200/ -800 [lung parenchymal window]; WW/WL: 350 of 50 [mediastinal window]). The images were reconstructed in 0.75 mm slices with the results shown in Figs. 2 and 3.

A–D: Many small nodules are of the same size, same density, and evenly distributed throughout the 2 lung fields.

A–D: There are numerous large anterior, middle, and posterior mediastinal lymph nodes (white arrows). Contrast-enhanced lymph nodes are fairly uniform in size and shape. B, C: The lymph node is compressing the superior vena cava (yellow arrow). Left pleural effusion, little degree (red arrow).

Synthesis of clinical, paraclinical, imaging, and differential diagnoses data were set up by a panel of experts: (1) Miliary TB and lymph node TB ?; (2) Lymphoma with pulmonary lymphatic metastasis? (3) Sarcoidosis? (4) Histiocytosis X? The difficulty for us then was to find a way to diagnose.

The contrast-enhanced CT shows that the patient's right posterior mediastinal lymph node mass is quite large. If the patient is lying face down, a transthoracic biopsy can be performed. After liaising with the patient's family, and with the patient, who was considered to be Gillick competent with good awareness and coordination ability, a transthoracic biopsy was performed under CT guidance. The results are shown in Fig. 4.

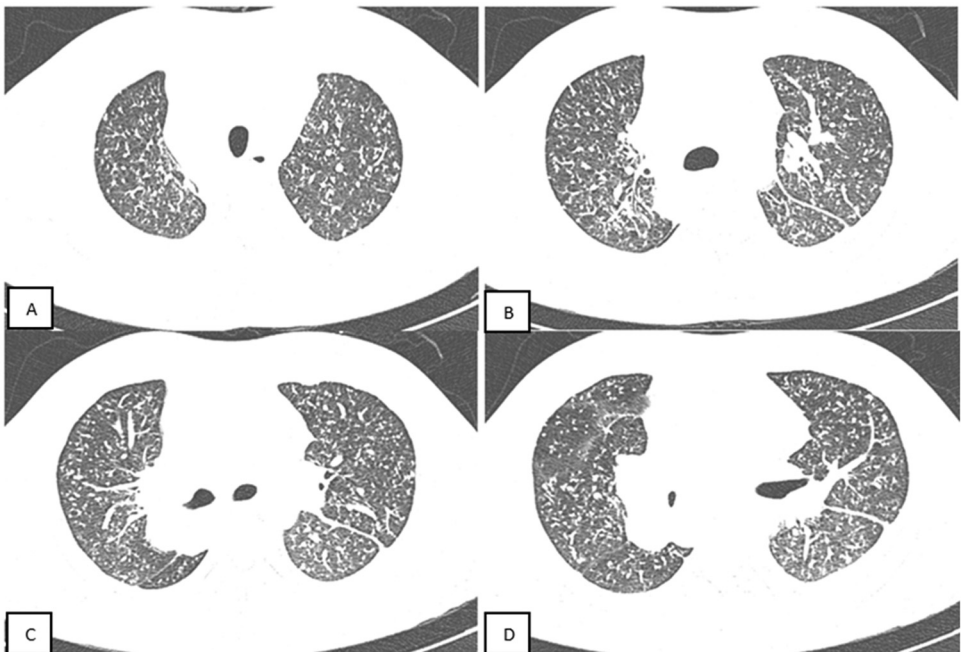

Fig. 2 – CT chest, lung window (top to bottom slices).

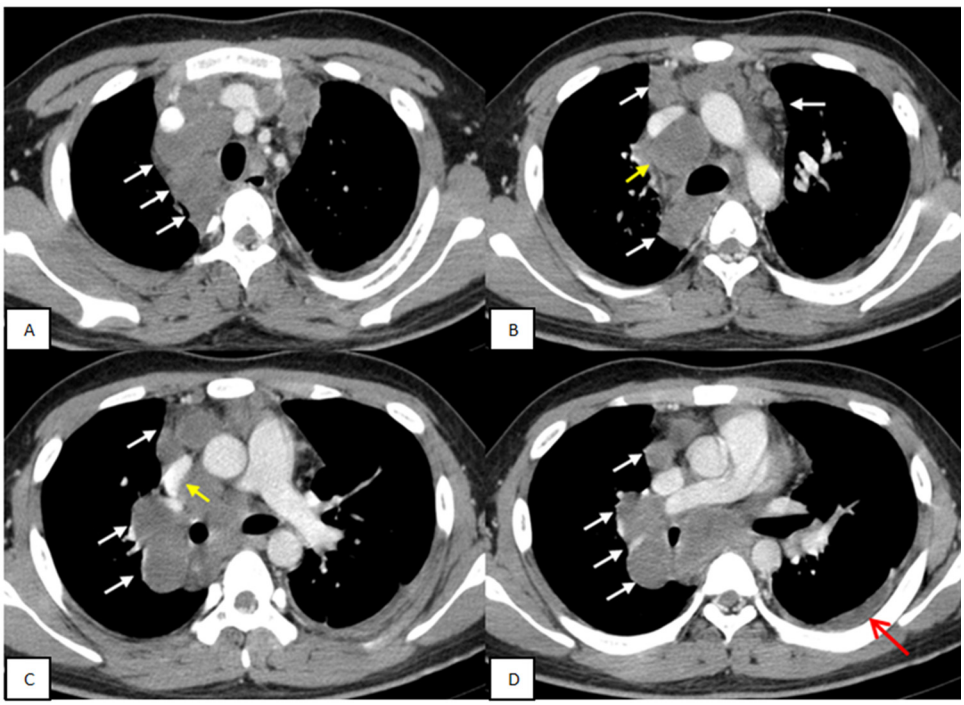

Fig. 3 – CT chest, mediastinal window after intravenous contrast injection (slices from top to bottom).

A: With the patient prone, a biopsy needle was inserted from the back using an 18G coaxial core biopsy needle (yellow arrow) and 4 specimens were removed. B: After the biopsy, a small, low-grade pneumothorax was visible (red arrow).

Specimens were made histopathologically and cultured on liquid medium of mycobacteria growth indicator tube (MGIT). The results of the microscopic pathology: Langhans giant cells (+); Caseous neccrosis (+); Other necrosis (+); Chronic inflammatory cells (+); Acute inflammatory cells (-); Inflammatory granulomatous tissue (-); Fibrous tissue (-). Details of microscopic specimens are shown in Fig. 5.

Specimen No. 5140 - B20. The green arrow shows normal lung tissue, the yellow arrow shows TB cysts with Langhans

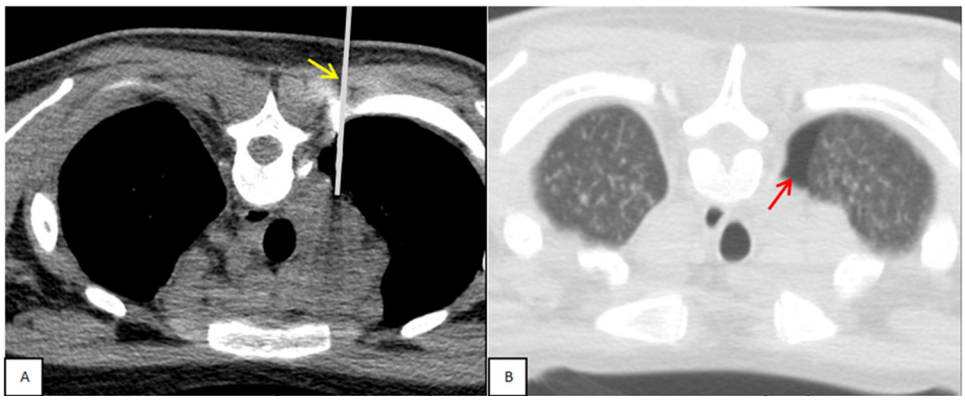

Fig. 4 – Transthoracic mediastinal lymph node biopsy under CT guidance.

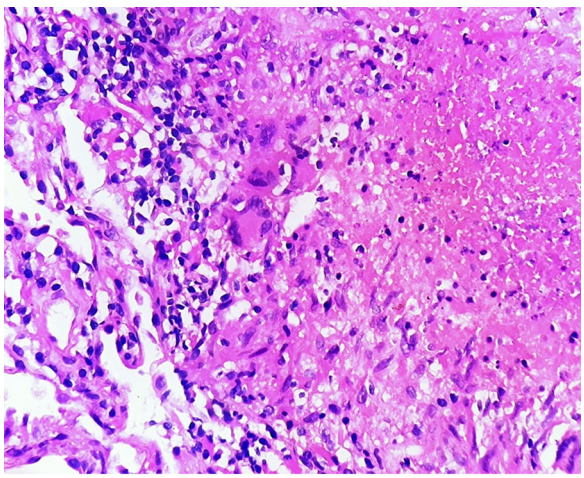

Fig. 5 – Microscopic lesions of a lymph node specimen after a transthoracic biopsy under CT guidance, HE x 400.

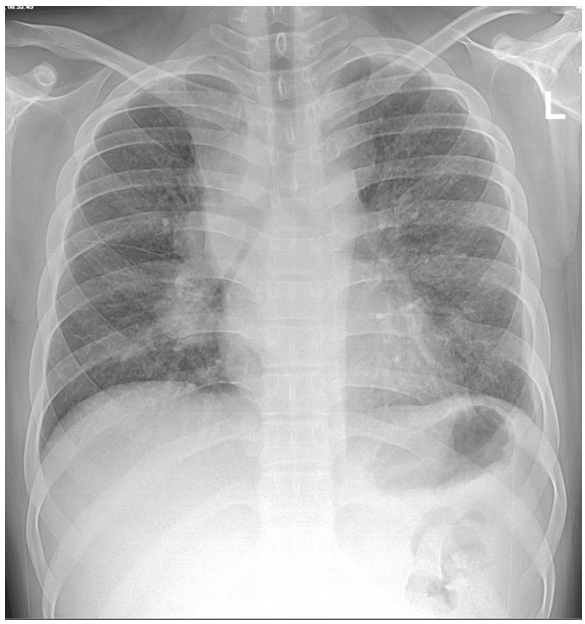

Fig. 6 – Chest X-ray radiograph, PA, after 1 month of TB treatment.

giant cells, and the red arrow shows an area of caseous necrosis.

Results of biopsy specimen culture in MGIT: MTB (+).

Antibiogram: Not resistant to first-line anti–TB drugs.

Because of the miliary lung lesions, the patient underwent magnetic resonance imaging of the brain (MRI), but no abnormalities were detected. The patient then began treatment with the pediatric tuberculosis regimen 2RHZE and/or 10RH as an outpatient, according to the guidelines of the National TB Program. After 1 month, the patient returned to the hospital for a scheduled follow-up examination. The patient was given a routine chest X-ray, with the image details shown in Fig. 6.

Compared with the radiograph in Fig. 1 (before treatment) the image is almost unchanged.

Other laboratory tests were also conducted, and the results were within normal limits. The patient continued to be given the drug for a second month, in the form of outpatient treatment.

The patient was due to have a follow-up visit after a further month. However, because of the Covid-19 situation, the patient was unable to return to our hospital for re-examination on time. We sent an official letter requesting that the provincial TB hospital continue to provide treatment for the patient and advised the patient to strictly follow the treatment regimen. The provincial TB hospital continued to supply the requisite drugs to the patient once a month for a further 6 months. Eventually, after 7 months had passed, the patient was able to return for a follow-up examination at our hospital. The patient had basic vital function tests, which were all within normal limits, and a routine chest X-ray, which is shown in Fig. 7.

The inferior mediastinum is markedly wider (65 mm). Two opacities in the right hilum are still present but are now internally calcified. The calcified nodules are visible on the left but the small nodules that spread to both lungs disappeared. No thickening of the left pleura.

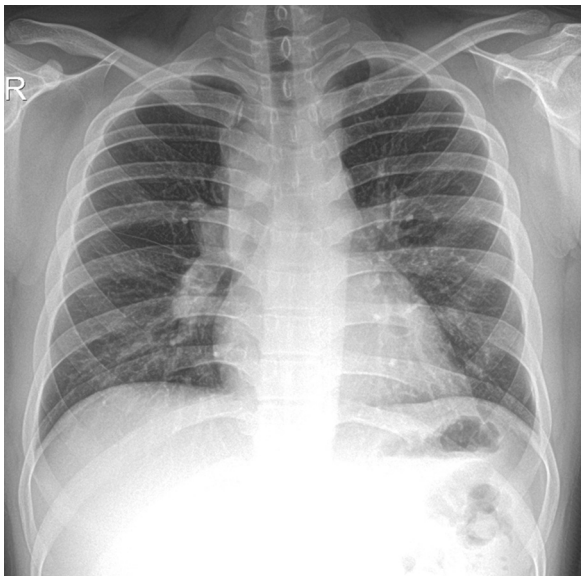

Fig. 7 – PA chest X-ray radiograph after 7 months of TB treatment.

Because of the improvement shown in the chest X-ray image, we decided not to perform a chest CT. Instead, the patient continued their treatment following thesame drug regimen.

Due to the Covid-19 epidemic, the patient continued to receive medicine from the provincial TB hospital for another 5 months (a total of 12 months). During this time, the patient received 2 doses of the Covid-19 vaccine (4 months apart). After finishing the TB treatment, the patient returned to our hospital for a follow-up examination where they were found to be in remission. Vital function tests were also performed, and the results were normal. The patient had a chest CT scan, with detailed results shown in Figs. 8 and 9.

A and B: Wide anterior mediastinum (yellow arrow) and C: abnormal right umbilical convexity (red arrow). Small nodules with the characteristic 3 uniformity (as shown in Fig. 2) are no longer visible seen. D: Normal lungs.

A, B, C: There are still a few large anterior mediastinal lymph nodes, group 4R; 10R (white arrows) although they are much smaller when compared with Fig. 3. A and B: The superior vena cava is no longer compressed (yellow arrow). D: No left pleural effusion is seen.

After 12 months of treatment, a chest CT scan showed that the mediastinal, and hilar lymph nodes were greatly reduced in size but there was still a modest degree of calcification. The 2RHZE and/or 10RH drug treatment program had been completed, so we decided to cease treatment, and make an appointment to see the patient again after 3 months.

After 3 months, the patient returned for a chest CT scan, and the results are shown in Fig. 10.

A: Anterior mediastinal lymph nodes are calcified (white arrows). A, B, C: Group 2R, 4R lymph nodes are calcified (yellow arrow). D: Group 7 lymph nodes are calcified (red arrow).

After assessing the patient's CT scan 3 months after stopping treatment, we determined that the patient was responding well to treatment, and the lesions were progressing according to the trend of sequelae (small lymph nodes and calcification). The patient is still being monitored and evaluated 1 year after stopping treatment.

Based on the synthesis of clinical data, methods, and the diagnostic gold standard (biopsy of mediastinal lymph nodes

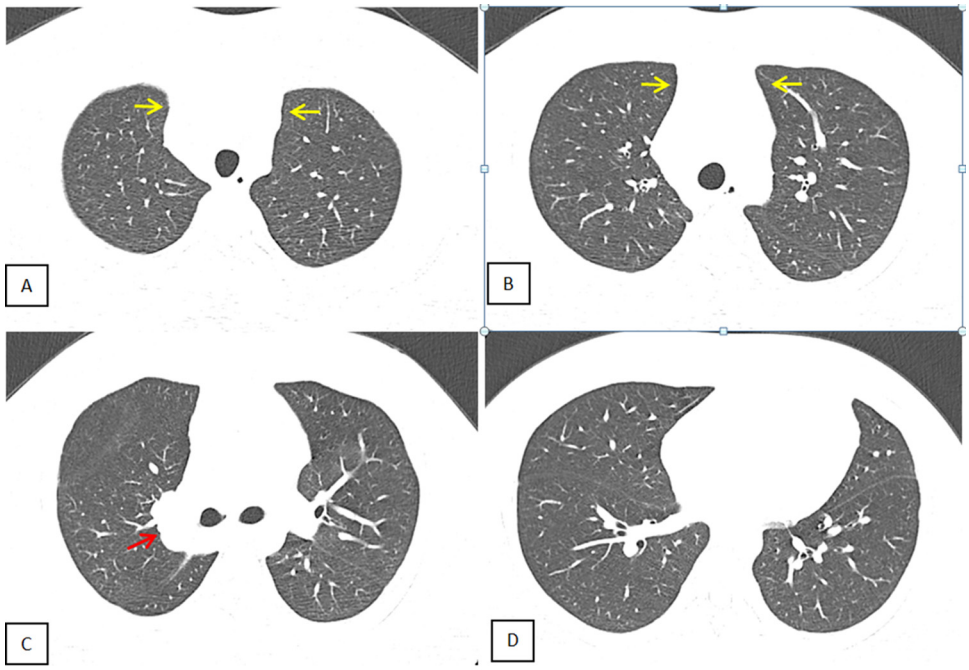

Fig. 8 – CT chest, lung window (top and bottom slices).

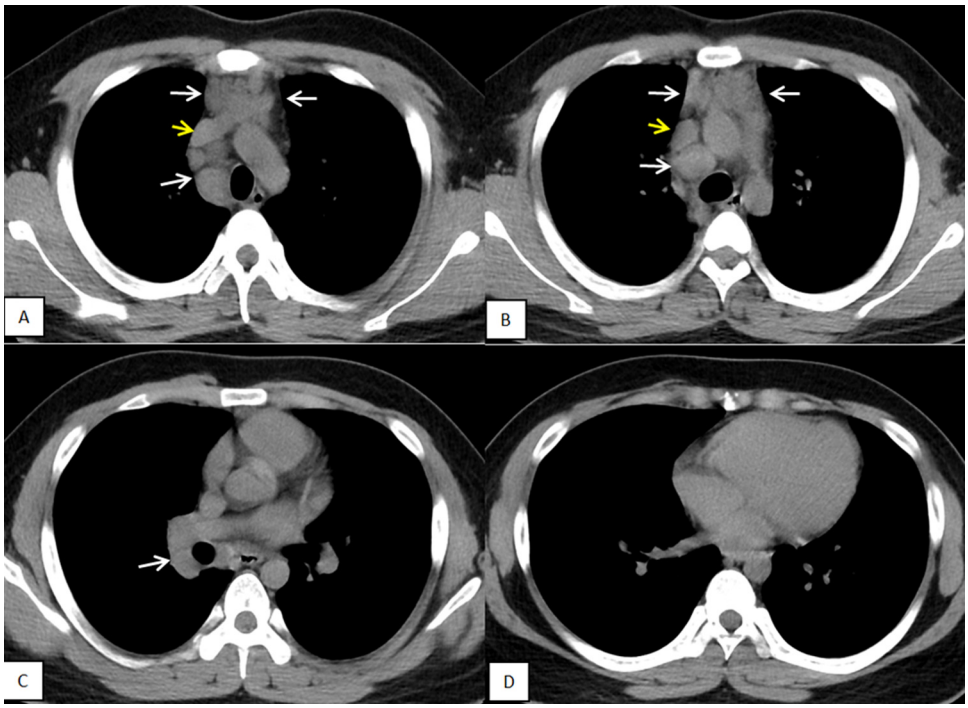

Fig. 9 – Chest CT, anterior mediastinal window with intravenous contrast (slices from top to bottom).

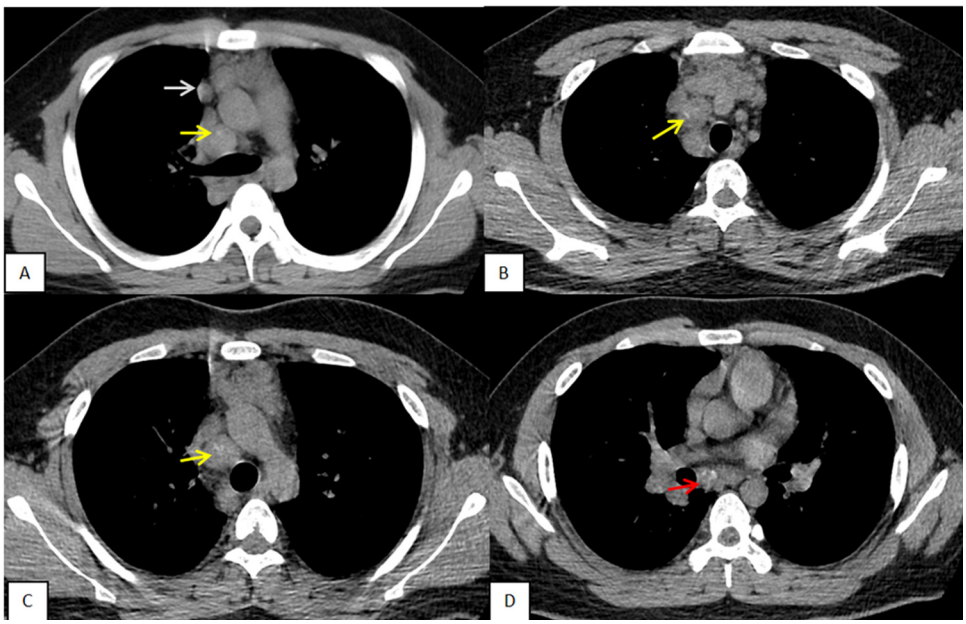

Fig. 10 – Chest CT, anterior mediastinal window with intravenous contrast (slices from top to bottom).

through the chest wall, histopathology of the specimen is suitable for TB lesions; culture of specimens in liquid medium (MGIT) positive for MTB, no drug resistance), and based on the results of TB-specific treatment, we would like to suggest this is a case of primary thoracic lymphatic TB, which we will discuss in more detail in the discussion section.

Discussion

Humans have known about tuberculosis for more than 100 years. However, despite a vaccine being readily available, it is still a common infectious disease in many parts of the

world, particularly in developing countries. According to the WHO, the disease kills approximately 1.2 million people every year, with 10 million new cases diagnosed every year. Of these, nearly 9% of new cases are in children [3]. The disease still places a burden on the healthcare systems of many countries, including Vietnam. TB bacilli can enter the human body through the digestive system, the skin, and the mucous membranes, although they enter through the respiratory tract in 70%-80% of cases [16]. When entering the lungs, TB bacilli often encounter fierce resistance from the body's immune system, meaning that they can lie dormant for a long time (known as inactive or latent TB). When the body's immune system is weakened, or the bacteria detect favorable conditions, they can reactivate, causing widespread damage by entering the bloodstream to attack other organs including the lymphatic system [1,2,17,18]. When entering the bloodstream, TB is often manifested as military TB, brain TB, and meningoencephalitis. Lymphatic infiltration usually leads to enlarged lymph nodes in the hilum, mediastinum, and sometimes in the lung. If only large hilar lymph nodes are seen, the mediastinum is usually classified as primary TB [19–21].

According to the World Health Organization, primary infection is classified into 2 types: uncomplicated, and complicated. In the case of TB, uncomplicated primary TB usually only shows enlarged lymph nodes in the hilar lung and the mediastinum [22]. Complicated primary TB infection occurs when these enlarged lymph nodes compress the airways, causing partial or complete obstruction, which can lead to air retention or atelectasis. More serious complications can occur if the lymph nodes become pus-filled abscesses and burst, as this can lead to TB spreading through the airways via a humoral mechanism [10–15,21].

Studies have shown that up to 50% of children who live with TB patients are infected with mainly latent TB [3,18]. Between 5% and 10% of people diagnosed with latent TB will never be cured [21]. Many countries, including Vietnam, are attempting to eradicate TB by treating all latent TB cases [23–26].

Latent and primary MTB infections are classified as primary TB [1,2,4,12]. Latent TB is diagnosed when a patient only has immunologic changes to TB, confirmed by a positive TST and IGRA test (either or both), without clinical abnormalities on either a clinical examination or s chest X-ray [12,13,16,21].

Primary TB infection is a type of primary TB that is commonly seen in children and in individuals who have been previously diagnosed with latent TB. Diagnostic criteria for primary infection include criteria for latent TB plus clinical signs, organ damage, and evidence provided by imaging and histopathology [4,6,10,15,18,20,21].

Miliary TB is a severe form of TB that is particularly common in children under 5 years old. It is also often associated with both brain and meningeal TB. The disease spreads through the bloodstream, taking an acute course, and can be life-threatening if not treated promptly [5].

Returning to our case report, it was clear that TB had damaged the mediastinal lymph nodes. Microscopic examination of the specimen was consistent with TB lesions and the culture was positive for MTB. The problem is that if only the mediastinal lymph nodes were involved, then this was a case of primary (primary) TB. On the other hand, to the best of our knowledge, lymphadenopathy in primary tuberculosis is very rare in the anterior mediastinum group, especially in the internal breast group. In malignancies, especially primary lymphomas (eg, Hodgkin's and non–Hodgkin's), large mediastinal lymph nodes are very common, including for this group. Therefore, we established a differential diagnosis of malignant lymphoma.

Features of enhanced tuberculous lymph nodes on CT scans have also been noted in specialized radiological reports and literature. Since TB lymph nodes tend to exhibit caseous necrosis on contrast-enhanced CT scans, they often show strong peripheral enhancement, with the core region not being fully penetrated due to the necrosis [1,2,10,20]. On the other hand, TB nodes are always in a wet inflammatory state, so they tend to stick together. These features were not observed in our case report. At that time, most of the clinical staff suspected malignant lymphadenopathy, particularly since the patient was only 16. The orientation to find a way to exclude tuberculosis demonstrating malignancy prompted us to conduct a transthoracic mediastinal lymph node biopsy in this case. The child has since made a full recovery and the biopsy was successful. After the biopsy, we noted a small left pneumothorax, which resolved itself after 5 days.

The appearance of small nodules with 3 uniform features on the initial chest CT made us doubt whether a diagnosis of miliary TB was correct, as the image was not convincing. To the best of our knowledge, the nodules in miliary TB are usually smaller in size, denser, and more evenly distributed throughout the 2 lung fields.

At the time, the patient was complaining of chest pain and did not have a fever, so a diagnosis of miliary TB was not convincing. Additionally, physical metastases to the lung from mediastinal lymphadenopathy are also rarely reported in the literature. Finally, the decision that this was a case of thoracic lymphatic TB was the consensus of most of the doctors (ie, damage to all groups of lymph nodes, including the small nodes in the interstitial space), and TB-specific treatment cleared up the small nodules in the lungs, which is rare in cases of hematogenously spread TB. In our opinion, although this may not be a convincing explanation it is a logical one when observing the appearance as well as the change in the lesions during the treatment process. Anatomically, we know that there are 2 parallel lines of lymphatic circulation and pulmonary veins in the interstitial space, so it is very difficult to accurately pinpoint the lesion location on CT and pathology.

As with any TB lesions anywhere, calcification will also be noted as tuberculous lymph node calcification is very common with or without treatment. In our case report, 3 months after finishing treatment, the core area of the nodes appeared calcified. This agreement with the literature further strengthens our confidence in the diagnosis and treatment of this case. Our patient is still very young, he will hopefully live a full life, and we are happy with the results that we have worked so hard to get.

A CT-guided transthoracic mediastinal lymph node biopsy is a technique that is often considered contraindicative. However, through the fact that the cases we have done at the imaging department of the National Lung Hospital, this technique

is not "too scary," "too difficult," "too dangerous" as we often think.

Group 7 lymph nodes, anterior and posterior mediastinal groups we still do often. However, we must ensure the patient is in the correct position, and use CT to guide the insertion of the biopsy needle.

Treatment regimens for lymph node TB often have to be longer than those for pulmonary TB alone due to the characteristics of TB drug infiltration into the lymphatic system unlike the vascular system [24–26]. Our patient followed WHO guidelines for their treatment and has had good results. They are now living a normal life, although we are closely monitoring their recovery.

Conclusion

We reported a case of pediatric tuberculosis with atypical clinical signs and imaging findings, where many differential diagnoses were made before a diagnosis was confirmed by a trans mediastinal lymph node biopsy under CT guidance. The biopsy piece was both pathologically and cultured on a liquid medium (MGIT) and tested positive for MTB. The patient was treated for TB and has an excellent prognosis. We hope that our case report can be used as a reference for clinicians who encounter similar cases in the future.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

Cung-Van C and Nguyen MD contributed equally to this article as co-first authors. All authors read and approved final version of this manuscript.

Ethics approval

Not applicable.

Patient consent

Written informed consent was obtained from the patient for the publication of patient information in this article.

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