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CASE REPORT

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# A case of multidrug-resistant miliary tuberculosis mimicking lymphoma: a matter of life or death

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## Abstract

**Background** Tuberculosis (TB) is a systemic infectious disease that is caused by Mycobacterium tuberculosis and which can affect many tissues and organs. Despite the development of curative and preventive therapies in recent years, TB continues to be a serious health problem, in the developing countries in particular.

**Case presentation** In this case report, an extraordinary case of miliary tuberculosis with unexplained fever, joint pain, weight loss, pancytopenia, lymphadenopathy and splenomegaly, who was clinically suspected of lymphoma and successfully treated with a multidisciplinary approach without any complications, was presented. This case has been reported not because it is a rare case, but to raise awareness. It is a case, where early diagnosis and initiation of treatment early, as well as an individualized and multidisciplinary treatment approach emerged as the most important factors resulting in an improvement prognosis.

**Conclusion** Extrapulmonary TB, if with lymph node involvement in particular, can easily mimic lymphoma. Imaging methods and clinical findings may be insufficient to distinguish these two conditions at the time of diagnosis. In such a case, it will be beneficial for the patient to proceed with an experienced team in the management of the patient.

**Keywords** Lymphadenopathy, Miliary tuberculosis, Unexplained fever, Hemophagocytic lymphohistiocytosis

## Background

Led by *Mycobacterium tuberculosis,* tuberculosis (TB) is a systemic infectious disease affecting many tissues and organs. Although novel curative and preventive therapies have been leveraged in recent years, TB continues to be a serious health challenge, especially in the developing countries (Zumla et al. 2015; Zumla et al. 2013; Busatto et al. 2022). Resistance to commonly used anti-TB drugs is one of the significant causes of the increase in the third world countries (Liebenberg et al. 2022). Mainly affecting the pulmonary system, TB can also lead to the extrapulmonary involvement in 15–20% of patients with hematological spread (Sharma et al. 2021).

Patients infected with TB may clinically present with cough, fatigue, fever, nocturnal sweating, chest pain, shortness of breath and hemoptysis, as well as pulmonary involvement (Pirina 2014). However, TB-related findings can sometimes reveal an atypical course. In such cases, patients may pathologically present with diffuse large B cell lymphoma without pulmonary involvement, that is,

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with a lymphoma-like clinical picture. Hematological abnormalities, such as anemia, leukopenia, thrombocytopenia or even pancytopenia, in which all three types of bloods cells are affected, may be observed in patients with miliary TB and bone marrow involvement. In addition, TB-associated hemophagocytic lymphohistiocytosis (HLH) has also been reported in such patients despite its rarity (Lombard and Mansvelt 1993; Glasser et al. 1970; Knobel et al. 1983; Poornachandra and Ayele 2022). The absence of visible miliary nodules on chest radiography, which may cause the physician to be confused with the disease, may lead to misdiagnosis, late diagnosis or even fatal outcomes (Maartens et al. 1990; Bobrowitz 1982; Choe, et al. 2021).

In the present case report, an extraordinary case of miliary TB with unexplained fever, joint pain, weight loss, pancytopenia, lymphadenopathy and splenomegaly, and clinically suspected of lymphoma and successfully treated with a multidisciplinary approach without any complications, was presented based on the abovementioned data.

## Case presentation

A 62-year-old male patient was admitted to the outpatient clinic with widespread palpable purpura, ankle swelling, redness, migrating joint pain and ongoing intermittent fever (40 °C) for one month. As well as accompanying the condition, such symptoms as weight loss, night sweating and fatigue were also detected in the case. The laboratory test readings were found to be as follows: white blood cell (WBC): 1.12 K/μL, neutrophil (Neu): 0.88 K/μL, lymphocyte (Lymph): 0.136 K/μL, hemoglobin (Hgb): 8.78 g/dL, platelet (Plt): 92.8 K/μL, creatinine (Cre): 0.78 mg/dL, aspartate transaminase (AST): 124 U/L, alanine transaminase (ALT): 135 U/L, lactate dehydrogenase (LDH): 799 U/L, total bilirubin (TBIL): 1.72 mg/dL, direct bilirubin (DBIL): 1.19 mg/dL, erythrocyte sedimentation rate (ESR): 46 mm/hr, ferritin: 34,859 μg/L, beta-2 microglobulin (B2M): 5.631 mg/L, triglycerides (TG): 240 mg/dL, C-reactive protein (CRP): 13.3 mg/dl, and procalcitonin (PCT): 0.35 ng/Ml. The findings are presented in Table 1.

**Table 1** Laboratory findings detected in the case on admission

| | |
|---|---|
| WBC (K/μL) | 1.12 (4.5–11) |
| Neu (K/μL) | 0.88 (2–6.9) |
| Lymph (K/μL) | 0.136 (1.3–3.8) |
| Hgb (g/dL) | 8.78 (12.5–16.5) |
| Plt (K/μL) | 92.8 (145–400) |
| Cre (mg/dL) | 0.78 (0.7–1.1) |
| AST (U/L) | 124 (13–30) |
| ALT (U/L) | 135 (9–57) |
| LDH (U/L) | 799 (125–243) |
| TBIL (mg/dL) | 1.72 (0.2–1.2) |
| DBIL (mg/dL) | 1.19 (< 0.5) |
| Ferritin (μg/L) | 34 859 (15–260) |
| B2M (mg/L) | 5.631 (0.6–2.3) |
| ESR (mm/hr) | 46 (0–20) |
| TG (mg/dL) | 240 (40–150) |
| CRP (mg/dL) | 13.3 (< 5) |
| PCT (ng/mL) | 0.35 (< 0.5) |

*ALT* Alanine transaminase, *AST* Aspartate transaminase, *B2M* Beta-2 microglobulin, *Cre* Creatinine, *CRP* C-reactive protein, *DBIL* Direct bilirubin, *ESR* Erythrocyte sedimentation rate, *Hgb* Hemoglobin, *LDH* Lactate dehydrogenase, *Lymph* Lymphocyte, *Neu* Neutrophil, *PCT* Procalcitonin, *Plt* Platelet, *TBIL* Total bilirubin, *TG* Triglycerides, *WBC* White blood cell

A comprehensive serological screening was performed to check for a possible infection given the persistent high fever in the case. The results of multiple blood culture, Epstein–Barr virus (EBV), cytomegalovirus (CMV), parvovirus, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), *Brucella* and *Salmonella typhi* tests were all determined to be negative. Therefore, the case started to receive broad-spectrum antibiotics; yet, the fever in the case was persistent and rose up to 40 °C. Hence, the case was evaluated in terms of malignancy due to pancytopenia, high ferritin and the presence of B symptoms. A full-body computed tomography (CT) scan was performed to check for the lymphoproliferative diseases, revealing hypodense foci, the largest of which was 12 mm in size in the liver. Additionally, splenomegaly (17 cm) and large number of lymph nodes, the largest $14 \times 12$ mm, were observed in paraaortic and aortocaval areas. Consequently, based on the clinical and laboratory data, it was considered that the case might have HLH secondary to lymphoma. An increased number of atypical lymphocytes was witnessed in the peripheral smear. Accordingly, a bone marrow biopsy was performed, and while revealing the infiltration of neoplastic B lymphoid cells, the biopsy demonstrated no findings of hemophagocytosis. In the bone marrow aspiration and imprint, however, the infiltration of diffuse lymphoid cells was detected; the cells showed no tendency to clump together; the cytoplasm of the cells was narrow; and the core chromatin structure was composed of compact cells. No blastic cell or the infiltration of foreign cells was observed. Even so, the inhibition of megakaryocyte/myeloid/erythroid lineages was present. The case with a pre-diagnosis of B cell lymphoma was considered to administer chemotherapy. Repeated chest radiography and thorax CT revealed a mass lesion, not observed in the initial imaging, in the upper lobe of the left lung of the case with a persistent fever (Fig. 1).

It was planned to perform positron emission tomography-CT (PET/CT) and an excisional biopsy to clarify the diagnosis from the most suitable lymph node before

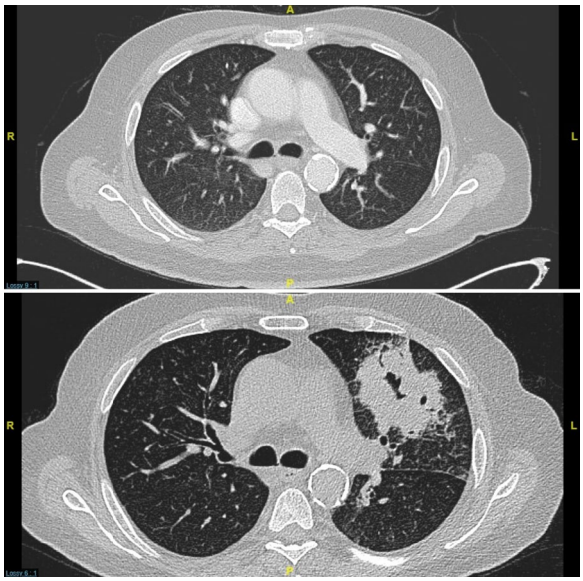

**Fig. 1** Chest tomography

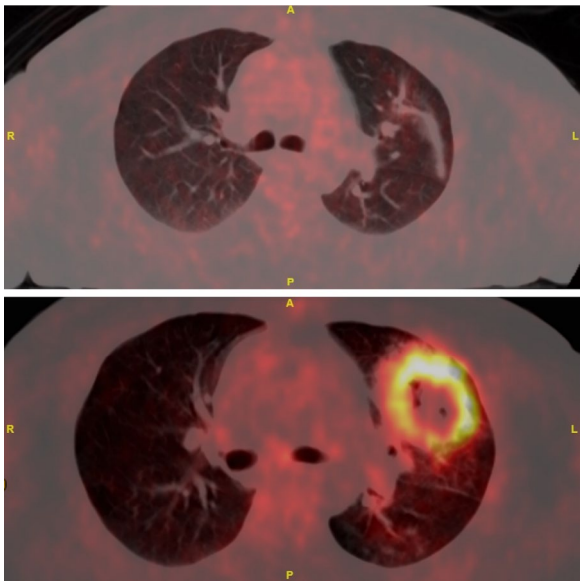

**Fig. 2** PET-CT

the treatment. PET-CT revealed a lesion with hypermetabolic walls and a metabolic central ((maximum standardized-uptake value ($SUV_{max}$) ($SUV_{max}=12.2$)), seeming to be a mass associated with the pleura in the left upper lobe anterior segment of the left lung in size of 6.5 cm. Numerous hypermetabolic lymph nodes ($SUV_{max}=8.5$) were observed along the celiac axis. The metabolic activity of the spleen was determined to have increased homogeneously in the case. It was decided to assess the case in terms of opportunistic fungal infections, nocardia, actinomyces, pseudomonas and TB due to the newly developed lesion in the lung of the case. So, empirical antifungal therapy was added to the antibiotic therapy. Bronchoalveolar lavage (BAL), TB and galactomannan tests were performed, and the results of BAL indicated an increase in TB. Accordingly, broad-spectrum antibiotics were administered to the case for a sufficient period of time and then discontinued. Later on, the case commenced to receive a quadruple anti-TB therapy [isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA)]. However, the resistance to RIF, INH, EMB and streptomycin developed in case; therefore, the treatment regime was revised according to multidrug-resistant (MDR)-TB. Thus, the case received the intravenous treatment for TB for a certain period followed by the administration of amikacin, moxifloxacin, cycloserine, thioamide and para-aminosalicylic acid (PAS). The case was closely followed up during the first six months of anti-TB treatment, and no chemotherapy was started. During the follow-up period, weight loss was seen to stop, and fever returned to the normal limits. Also, cytopenia was detected to improve in the case, as observed in the hemogram. It was decided to re-assess the case in terms of lymphoma, and bone marrow biopsy was repeated. Consequently, normocellular bone marrow containing numerous non-necrotizing granuloma structures and increased B lymphoid cells was observed. The initial bone marrow pathology of the case was re-assessed, and the areas containing focal coagulation necrosis were noticed. Following the repeated PET-CT scan, it was detected that the hypermetabolic mass lesion observed in the upper lobe of the left lung in the previous imaging disappeared; the metabolic activities of the liver and spleen were homogeneous; the ratio of the liver/spleen metabolic activity was normalized; also, the numerous hypermetabolic lymph nodes observed in the paraaortic and aortocaval areas in previous imaging also disappeared (Fig. 2). Therefore, the diagnosis of lymphoma was ruled out, and the findings were attributed to MDR miliary TB infection instead, and the case was successfully treated using anti-TB treatment for a year. Eventually, all of the complaints were seen to regress, and the case was started to be followed-up with no medication.

## Discussion

As an ongoing major health challenge worldwide, TB is one of the leading causes of morbidity and mortality, especially in developing countries. Under the report released by the World Health Organization (WHO) in 2018, TB was emphasized to lead to 1.5 million deaths, making it the most fatal infectious disease among all infections (Harding 2020). The diagnosis, treatment and

prevention of TB have become more complicated than ever due to the resistance developing in patients commonly using anti-TB drugs. Resistance to at least two major anti-TB drugs, INH and RIF, is described as multidrug-resistant TB (MDR-TB). In one of the most recent reports by WHO, more than half a million new TB cases were stated to have drug-resistant TB (Harding 2020). On the other hand, the treatment of MDR-TB also requires a long-term and expensive chemotherapy with the use of second-line chemotherapy drugs with high toxicity. The associated treatment process should be managed with a multidisciplinary approach by specialist experienced doctors in experienced centers (Liebenberg et al. 2022; Nahid, et al. 2019; Organization 2019; Seaworth and Griffith 2017).

Presenting with fever of unknown cause, joint pain, skin rash, weight loss and pancytopenia, our case with a clinical picture initially suggesting lymphoma was diagnosed with MDR-TB following a rigorous process. The case was found to be resistant to INH, RIF, EMB and streptomycin, and so the treatment was appropriately revised by an experienced team of medical experts.

Based on the literature, it was reported that as well as varying degrees of cytopenias in the peripheral blood due to hypersplenism in cases with splenic involvement chronic infections, the infiltration of the bone marrow structure with granulomatous nodules, hemophagocytosis, and immune reactions can be witnessed in cases with TB (Glasser et al. 1970). However, in another study where Maartens et al. evaluated 109 miliary TB cases retrospectively, lymphopenia, leukopenia, thrombocytopenia and pancytopenia were reported in 87, 23, 15 and 5% of the patients, respectively. Additionally, advanced age, lymphopenia, thrombocytopenia, increased levels of transaminase and delayed treatment were found as the independent predictors of mortality in the study by Maartens et al. (Maartens et al. 1990). In the study carried out by Caso et al., it was stated that while anemia was observed in most of the miliary TB patients, lymphopenia or thrombocytopenia was detected in only one quarter of the patients (Caso et al. 1997). As different from the findings reported by Caso et al., in our case, pancytopenia was detected at the time of diagnosis, and the hematological parameters returned to normal levels thanks to anti-TB treatment.

On the other hand, hemophagocytosis is an extremely rare hematological finding limited to the case reports of miliary TB. Accordingly, in a study by Wang et al., hemophagocytosis was reported to be seen in only seven of 833 patients diagnosed with TB (Wang et al. 2005). Related to the cases of cytopenia, hemophagocytosis is a condition characterized by the proliferation of the mature histiocytes and the uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes and their hematopoietic precursors in bone marrow. Hemophagocytosis is often led by infectious and autoimmune diseases, malignancies or drugs (Chen et al. 2022). It is so difficult to prognose hemophagocytosis, and the mortality is high in the cases where the treatment is launched on time.

Both hemophagocytic syndrome and TB are associated with various common symptoms such as fever, splenomegaly, anemia, lymphopenia, thrombocytopenia and high ferritin values, making it difficult to distinguish between the two ailments. Besides, the coexistence of hemophagocytic syndrome and TB may be simultaneously present; along with bone marrow biopsy, patients may display responses to anti-TB therapy in each condition. Given the abovementioned data, our case was considered to have lymphoproliferative disease-related HLH since such symptoms as fever, cytopenia, high ferritin, splenomegaly and lymphadenopathy were determined; however, the results of bone marrow biopsy did not support hemophagocytosis. In our study, the case responded successfully to anti-TB treatment, resulting in an improvement in his well-being, and the improvement led to questioning the pre-diagnosis of lymphoma. Therefore, the tests were repeated, and lymphoma was ruled out.

The differential diagnosis between TB and lymphoma is not always easy to distinguish as both share many common clinical and radiological features. Symptoms such as fever, nocturnal sweating, constitutional symptoms, weight loss, involvement of lungs or lymphadenopathy can be observed in both conditions. Additionally, TB present in lymph nodes may not exhibit any of the typical clinical findings. Due to such effects, TB in lymph nodes is diagnosed difficultly, particularly in those presenting with no pulmonary symptoms and not having a medical history of TB. In a study conducted in Australia and reporting parallel findings, it was emphasized that lymph nodes are the second most involved region after the lungs, and lymph node involvement is observed in 25% of all TB cases and in 51% of the TB cases with extrapulmonary involvement (Lowbridge et al. 2013). In light of the literature, there are also studies in which patients with both lymphoma and TB were reported (Inadome et al. 2001; Audebert, et al. 1983). Tissue biopsy is the most specific and sensitive diagnostic method used to distinguish between both conditions. However, it should be noted that necrotizing granulomas specific to TB may sometimes be observed in lymphomas, as well (Bergter et al. 1996; Bellido et al. 1995). Furthermore, both conditions may lead to hypermetabolic lesions that can be encountered in the analysis through 18F-fluorodeoxyglucose positron emission-CT (18F-FDG PET/CT) (Audebert et al. 1983; Ouedraogo et al. 2000); therefore, it may

be difficult to perform a diagnosis despite the findings obtained by imaging and biopsy. Similarly, in the present case, a clear differentiation between lymphoma and TB could not be achieved in the pre-diagnosis based on the findings of 18F-FDG PET/CT. The presence of acid-fast bacilli, analyzed via bone marrow biopsy, mycobacteria culture tests and specific molecular diagnostic tests, provided a guidance in the management of the case. Consequently, the case recovered after being treated effectively for MDR-TB and a long-term clinical follow-up period.

## Conclusions

Extrapulmonary TB, especially if accompanied by lymph node involvement, can easily mimic lymphoma. Imaging methods and clinical findings may be insufficient to differentiate between both conditions at the time of diagnosis, and HLH may also be observed in both conditions although seen rarely. The present case was reported not because of its rarity, but to raise awareness. Our case is a condition where as well as an individualized and multidisciplinary treatment approach, early diagnosis and initiation of treatment early have emerged as the most important factors resulting in an improvement prognosis. Any treatment modality decided before a correct diagnosis can lead to fatal consequences.

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**Author contributions**
VG reviewed the literature and authored the case history. IE authored the hematological case history. FO, VO and RA contributed to the final report. HA, AD, BE, EK and ED supervised the project. All corresponding authors have read and approved the final version of this manuscript.

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## Declarations

**Ethics approval and consent to participate**
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**Consent for publication**
Written consent was obtained from the case.

**Competing interests**
The authors declare that they have no competing interests.

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**References**

Audebert F et al (2006) Lymph node tuberculosis as primary manifestation of Hodgkin's disease. Medizinische Klinik (Munich, Germany: 1983) 101(6):500–504
Bellido M et al (1995) Extrapulmonary tuberculosis and non-Hodgkin's lymphoma: coexistence in an abdominal lymph node. Haematologica 80(5):482–483
Bergter W et al (1996) Granulomatous hepatitis preceding Hodgkin's disease (case-report and review on differential diagnosis). Pathol Oncol Res 2(3):177–180
Bobrowitz I (1982) Active tuberculosis undiagnosed until autopsy. Am J Med 72(4):650–658
Busatto C et al (2022) Epidemiology and control strategies for tuberculosis in countries with the largest prison populations. Rev Soc Bras Med Trop 55:e00602022
Caso JA et al (1997) High serum ferritin concentration in an AIDS patient with miliary tuberculosis. Clin Infect Dis 25(5):1263–1264
Chen WT et al (2022) Tuberculosis-associated hemophagocytic lymphohistiocytosis misdiagnosed as systemic lupus erythematosus: a case report. World J Clin Cases 10(10):3178–3187
Choe J et al (2021) Clinical and radiologic characteristics of radiologically missed miliary tuberculosis. Medicine 100(8):e23833
Glasser RM, Walker RI, Herion JC (1970) The significance of hematologic abnormalities in patients with tuberculosis. Arch Intern Med 125(4):691–695
Harding E (2020) WHO global progress report on tuberculosis elimination. Lancet Respir Med 8(1):19
Inadome Y et al (2001) Malignant lymphoma of bronchus-associated lymphoid tissue (BALT) coexistent with pulmonary tuberculosis. Pathol Int 51(10):807–811
Knobel B et al (1983) Pancytopenia—a rare complication of miliary tuberculosis. Isr J Med Sci 19(6):555–558
Liebenberg D, Gordhan BG, Kana BD (2022) Drug resistant tuberculosis: Implications for transmission, diagnosis, and disease management. Front Cell Infect Microbiol 12:943545
Lombard E, Mansvelt E (1993) Haematological changes associated with miliary tuberculosis of the bone marrow. Tuber Lung Dis 74(2):131–135
Lowbridge C, Christensen A, McAnulty JM (2013) Tuberculosis in NSW, 2009–2011. N S W Public Health Bull 24(1):3–9
Maartens G, Willcox PA, Benatar SR (1990) Miliary tuberculosis: rapid diagnosis, hematologic abnormalities, and outcome in 109 treated adults. Am J Med 89(3):291–296
Nahid P et al (2019) Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med 200(10):e93–e142
Ouedraogo M et al (2000) Active tuberculosis in a patient with Hodgkin's disease. A case report. Rev Pneumol Clin 56(1):33–35
Pirina P et al (2014) Emerging clinical-radiological-pattern of pulmonary tuberculosis in immunocompetent patients. Eur Med J 1–6
Wotiye AB, Ayele BA (2022) Hemophagocytic lymphohistiocytosis: an unusual presentation of disseminated tuberculosis: a case report and literature review. J Clin Tuberc Other Mycobact Dis 27:100313
Seaworth BJ, Griffith DE (2017) Therapy of multidrug-resistant and extensively drug-resistant tuberculosis. Tuberc Nontuberc Mycobact Infect 129–158
Sharma SK, Mohan A, Kohli M (2021) Extrapulmonary tuberculosis. Expert Rev Respir Med (just-accepted)
Wang J-Y et al (2005) Mycobacterium tuberculosis inducing disseminated intravascular coagulation. Thromb Haemost 93(04):729–734
World Health Organization (2019) WHO consolidated guidelines on drug-resistant tuberculosis treatment. World Health Organization
Zumla A, Raviglione M, Hafner R (2013) Fordham von Reyn C. Tuberc N Engl J Med 368(8):745–755
Zumla A et al (2015) The WHO 2014 global tuberculosis report—further to go. Lancet Glob Health 3(1):e10–e12

## Publisher's Note