

Non-Hodgkin Lymphoma Mimicking Lymphadenitis Tuberculosis: Don't Miss It in Tuberculosis Endemic Area

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Introduction: In TB-endemic areas, lymphadenopathy may be misdiagnosed as TB and disguise lymphoma. Specialized professionals or multidisciplinary teams (MDT) must collaborate to solve the diagnostic challenge.

Case Presentation: We present a case of a 27-year-old woman who was initially diagnosed with TB cervical lymphadenitis by open biopsy. After 4 months of anti-tuberculous drugs, the neck wound after surgery worsened, and frequently, air bubbles and food emerged. TB medication was discontinued, and the following chest and head-neck CT scan revealed a soft tissue mass 5.7 x 9.5 cm infiltrating cutis in the pre-sternal region with the destruction of the sternum and multiple lymph nodes in the thorax, axilla, and cervical area, as well as anaplastic large cell lymphoma, a rare type of non-Hodgkin lymphoma with positive Ki67, CD45, and CD3, and negative CD20 and CK from re-biopsy. An MDT meeting concluded non-Hodgkin's lymphoma, Ann Arbor stage IVB. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) treatment was given. After six cycles of chemotherapy, symptoms improved, and the wound healed.

Conclusion: It highlights, misdiagnosis of lymphoma as tuberculosis delays treatment and affects prognosis. Thus, repeated investigations after anti-TB treatment failed, and the MDT meeting helped clinicians diagnose and treat patients.

Introduction

Cancer and tuberculosis (TB) are among the most widespread diseases affecting world health. Tuberculosis is a notable imitator and diagnostic challenge, frequently misidentified as cancer. And in the reverse, owing to its atypical manifestations and absence of definitive diagnostic testing, cancer patients have been erroneously diagnosed with tuberculosis [1]. Extrapulmonary TB is TB outside of the lungs, which can affect many organs and tissues, particularly lymph nodes. Tuberculosis lymphadenitis represents the predominant variant within the extrapulmonary tuberculosis category, constituting approximately 35% of cases. Tuberculosis lymphadenitis can manifest in the mediastinum and hilus within the thorax, axilla, inguinal area, abdomen (mesenteric), and predominantly in the cervical region outside the thorax.

The potential for co-occurrence or misdiagnosis with other diseases, particularly malignancy, is one of the most critical issues. Lymphoma is one of the differential diagnoses that must be considered [2].

In tuberculosis-endemic areas, the diagnosis of lymphoma is further complicated by symptom overlap with extrapulmonary tuberculosis, often resulting in lymphoma being misdiagnosed as tuberculosis [3, 4]. The challenges associated with diagnosing lymphomas have been previously recorded. Tuberculosis and lymphoma may present with identical non-specific systemic symptoms, including a high body temperature, loss of appetite, sweating during the night, lymphadenopathy, and granulomatous inflammation with necrosis, as evidenced by cytological and histological findings. Nonspecific symptoms frequently hinder patients from pursuing medical assistance or eliciting suitable referrals from primary care, complicating the early diagnosis of the disease [5, 6].

Lymphoma, given its rising prevalence, should be regarded as a crucial differential diagnosis when tuberculosis cannot be confirmed and anti-tuberculosis therapy has proven ineffective, particularly in developing countries with endemic tuberculosis, where the diagnosis and management of the disease require careful supervision. Here, we present a case of a young woman patient with non-Hodgkin Lymphoma that was misdiagnosed as lymphadenitis TB in South Kalimantan, Indonesia, as an endemic TB area, aiming to emphasize this diagnostic challenge and explore the different possibilities for additional investigations and interdisciplinary collaboration that are necessary to minimize delays in diagnosis and treatment.

Case Report

A 27-year-old female with a history of 5 months of enlargement of the left cervical lymph node, which progressed to a neck wound following open biopsy. She additionally reported general weakness, fever, night sweats, anorexia, and weight loss. She possesses no notable medical history and has no known tuberculosis contacts. The biopsy result showed granulomatosis inflammation with necrosis. The Real Time Polymerase Chain Method (PCR) sputum and tissue biopsy results were negative for *Mycobacterium tuberculosis*. From the initial Chest X-ray, enlargement of mediastinal and Chest CT-scan with contrast showed an abscess colli bilateral, right paratracheal, and superior mediastinal with sternum destruction suggestive of osteomyelitis (Figure 1A and 1B-C).

Figure 1. (A). Early Chest X-ray showed enlargement of the mediastinal; (B) Chest CT-scan with contrast before ATT showed an abscess colli bilateral, right paratracheal, and mediastinal superior with sternum destruction suggestive of osteomyelitis; (C) Re-chest and head-neck CT scan after 4 months ATT revealed a soft tissue mass 5.7 x 9.5 cm infiltrating cutis in the pre-sternal region with the destruction of the sternum and multiple lymph nodes in the thorax, axilla, and cervical area; (D) Improvement of chest and head-neck CT scan after six treatment cycles CHOP chemotherapy, soft tissue mass pre sternal disappeared and the reduce number and size lymph node enlargement in mediastinal and colli.

She was diagnosed with Lymphadenitis TB with secondary infection in the district hospital and received antibiotics and anti-tuberculosis therapy (ATT) empirically (isoniazid, rifampicin, pyrazinamide, ethambutol) followed by dual isoniazid and rifampicin. Per the patient's request, she continued ATT in primary health care because of distance and socio-economic disadvantage. After 4 months of treatment, the patient showed no improvement; the wound became worse, and air bubbles and food frequently emerged from the wound. Following clinical deterioration, the patient was referred to our province's Ulin Regional Hospital, South Kalimantan, for further examination.

At our hospital, the examination showed body weight was 39 kg, and her body mass index (BMI) was 15 (underweight). An open wound was approximately 6 cm long, ranging from colli sinistra, with purulence and air bubbles positive (Figure 2A).

Figure 2. (A). An open wound was approximately 6 cm long, ranging from colli sinistra, with purulence and air bubbles positive; **(B)** After six treatment cycles, the patient's wound healed. **(C)** A re-biopsy found distribution of cells with large nuclei, irregular shapes, coarse chromatin, and protruding nuclei. The cytoplasm is relatively extensive, sometimes pale basophilic in colour. Some cells show a pattern of "hallmark cells" in the form of a horseshoe-shaped nucleus or kidney with a protruding nucleolus. The background shows necrotic debris and a small number of reactive small lymphocytes, concluding as anaplastic large cell lymphoma with positive Ki67, CD45, and CD3, and negative CD20 and CK.

Lymph node enlargement was also found on the right side of the cervical area, with a diameter of 2 cm, and in the bilateral axilla, 3 cm, firm, not warm, and non-tender. Initial blood tests demonstrated a decrease in haemoglobin to 9.2 g/dL, an elevated white blood count (WBC) of $19 \times 10^9/\text{L}$ (normal range (NR) $4-10.5 \times 10^9/\text{L}$) with neutrophilia (84.5%, NR 50-81%), hypoalbuminemia, 2.4 g/dL (NR 3.2-4.6 g/dL) and imbalance of electrolytes [natrium 131 Meq/L (NR 136-145 Meq/L) and kalium 2.5 Meq/L (NR 3.5-5.1 Meq/L)], LDH 351 U/L (NR < 480 U/L) with normal liver and renal function test. Further investigation revealed a soft tissue mass 5.7 x 9.5 cm infiltrating the cutis in the pre-sternal region with the destruction of the sternum and multiple lymph nodes in the thorax, axilla, and cervical area, as observed in the chest and head-neck CT scan (Figures 1D-E). A re-biopsy of the lymph node found anaplastic large cell lymphoma (ALCL) (Figure 2C) as a rare type of Non-Hodgkin Lymphoma with positive Ki67, CD45, and CD3 and negative CD20 and CK. Due to resource constraints at our facility, we cannot conduct the CD30 and ALK examination. The patient also refused a bone marrow biopsy, and a PET-CT scan was not performed for staging follow-up because of limited resources. Finally, the chest multidisciplinary team (MDT) meeting was conducted, and confirmed a diagnosis of classical non-Hodgkin's lymphoma classified as Ann Arbor stage IVB. Consequently, TB medication was discontinued, and a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy was administered. We cannot give systemic ALCL guidelines (e.g., NCCN) recommend CHOEP (adding etoposide) for fit patients <60 years, or brentuximab vedotin + CHP, because of the limitations of the hospital. After six treatment cycles, the patient's clinical condition improved with the wound healed, and from chest and head-neck CT scan imaging evaluation showed soft tissue mass pre-sternal disappeared and reduced the number and size of lymph node enlargement in mediastinal and collar (Figures 1G-I, and 2B).

Discussion

Notwithstanding enhanced comprehension of disease and technological advancements, lymphomas persist in posing diagnostic difficulties. The standard manifestation of lymphomas encompasses palpable lymph nodes, predominantly in the cervical region, accompanied by symptoms such as fever, nocturnal diaphoresis, and an unanticipated weight loss exceeding 10% within the past six months. Lymphomas can exhibit many appearances, particularly in early-stage disease, causing diagnostic delays that frequently result in misdiagnosis. One of the most prevalent differential diagnoses is tuberculosis [6, 7]. Numerous studies from affluent nations have highlighted the difficulty and delays in lymphoma diagnosis. Delays predominantly transpire throughout the diagnostic interval (from the initial healthcare visit to diagnosis) and, to a lesser degree, within the patient interval (from symptom onset to seeking assistance). A postponed diagnosis is associated with advanced illness stages that result in worse outcomes. Multiple obstacles to diagnosis have been recognized, including insufficient symptom particularity, the absence of an established referral system for lymphadenopathy, and challenges in acquiring adequate tissue for diagnosis [4, 8]. In this case, the patient's history and initial pathology-radiology assessment indicate that the primary differential diagnosis is tuberculosis, particularly in endemic regions such as Indonesia. Tuberculosis may manifest as cervical and mediastinal lymphadenopathy and abscess formation in the mediastinum, which is characteristically necrotic, as evidenced by CT imaging, and histology reveals granulomatous inflammation with necrosis. Considering the epidemiological data and the patient's age, the diagnosis favored tuberculosis, and empirical treatment was initiated. Even though given anti-TB therapy, the patient's condition deteriorated, and finally, the diagnosis of ALCL, a subtype of NHL with positive Ki67, CD45, and CD3 and negative CD20 and CK, was

confirmed with a re-biopsy.

Anaplastic large cell lymphoma (ALCL) constitutes a subgroup within peripheral T-cell lymphoma (PTCL); reports indicate that PTCL may represent 15% to 20% of all lymphoma in Asia [9]. In certain areas of Asia, such as India, the incidence of ALCL is roughly estimated at 4.3% among NHL cases [10]. The misdiagnosis of ALCL as TB lymphadenitis is a significant clinical challenge, particularly in regions where TB is endemic. Yang et al reported that misdiagnosis rates are notably high in some studies; the rate of misdiagnosing lymphoma as tuberculosis can approach 25%, with a significant proportion of patients receiving inappropriate treatment for TB before being accurately diagnosed [11]. Another retrospective cohort research conducted by Bugeyo et al. (2017) revealed that all lymphoma patients exhibited several constitutional symptoms. Chest pain, fever, low hemoglobin, dyspnea, night sweats, and anorexia were the primary variables linked to the potential misinterpretation of tuberculosis in lymphoma patients [8], like in our patient. Table 1 summarizes symptom overlap between lymphadenitis, TB, and NHL.

Symptoms	Lymphadenitis TB	Non-Hodgkin Lymphoma
Lymphadenopathies	Present, often painless and progressively enlarging [15].	Present, typically painless and gradually increasing in duration [15].
Fever	Low-grade fever is common; it can develop into a chronic fever pattern [16].	Often associated with B-symptoms, which included persistent fever [15,17].
Night sweats	Common [15,16].	Common [15,17].
Weight Loss	Unintentionally weight loss, but it is not always prominent [16].	Significant weight loss is usually a B-symptom, potentially severe [7, 17].
Loss of appetite	Maybe present as a result of systemic illness, but not universally noted [16].	Common and associated with the overall decline in health status [7,17].
Cough	May occur if there is respiratory involvement [16].	More common if lymphomatous lesions are mediastinal or involve the lung [15,17].

Table 1. Symptom Overlap between Lymphadenitis TB and NHL.

Masamba et al. (2016) also reported that the predominant malignancies misdiagnosed as tuberculosis were lymphoma, followed by lung cancer. The treatment delay in this series was 5.4 months [12]. Almost similar to this case is 5 months.

Enhancing understanding of the critical distinctions between tuberculosis and lymphoma may facilitate improved diagnostic precision in the early stages of the disease. Continuous evaluation and intensive monitoring should be implemented. Assume that after one month of treatment, there is no observed improvement, and the patient remains AFB smear-negative. In this scenario, biopsies must be conducted with histological assessment for tuberculosis, lymphoma, and other possible conditions [6, 12-14]. The WHO's tuberculosis treatment guidelines for national programs also advocate for empirical TB treatment, emphasizing the necessity of follow-up examinations and evaluations of treatment response after one month to exclude other diseases that may resemble TB. Adhering to the recommendations for early assessment of treatment response facilitates prompt investigation and detection of other conditions, particularly lymphoma that resembles tuberculosis, hence intensifying the survival rate [8].

In conclusion, this case underscores that non-Hodgkin lymphoma is a cancer commonly observed in adolescents and needs to be regarded as a differential diagnosis in individuals presenting with lymphadenopathy, especially in TB-endemic regions where patients exhibit a lack of response to anti-tuberculosis treatment. Lymphoma should be investigated. Timely diagnosis, intervention, and MDT meetings can enhance survival rates in these patients. But this case had limitations, because it lacked CD30 and ALK status, as it is essential for distinguishing ALCL from other lymphomas and its prognosis.



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Statement of Transparency and Principles

- Author declares no conflict of interest
- The study was approved by the Research Ethics Committee of the author's affiliated Institute No. 153/ IX-Reg Riset/RSUDU/25.
- The study's data is available upon a reasonable request.
- All authors have contributed to the implementation of this research

Consent for publication

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Declaration on generative AI and AI-assisted technologies in the writing process

Nothing to disclose.

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