A case-report of extra-pulmonary tuberculosis presenting as multi-loculated mediastinal, pleural and paravertebral fluid collections with chest pain.

Maureen Maleche[1], Betty Sirera[2], Kennedy Masika[1], Kibet Keitany[3], Chrispine Oduor[4], and Lameck Diero[1]

[1]Moi University College of Health Sciences
[2]Moi Teaching and Referral Hospital
[3]MTRH
[4]Moi University School of Medicine

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Abstract

We present a case report of an immunocompetent African young man who presented with persistent chest pain and fever, and was diagnosed with EPTB following chest CT scan, pleural biopsy histopathology examination and Ziehl-Neelsen (ZN) staining, and pleural fluid gene Expert studies.

CASE REPORT

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Key clinical message

Extra pulmonary TB presenting as multiloculated fluid collections in the pleural cavity, mediastinum and paravertebral is rare but should be suspected in patients living in TB endemic regions.

Introduction

Tuberculosis (TB) is a bacterial infection caused by *Mycobacterium tuberculosis*, of the mycobacterium complex. Despite it being preventable and curable, it remains one of the leading infectious cause of death worldwide[1]. Without proper treatment, approximately 45% of HIV-negative people with TB and nearly all HIV-positive people with TB will die[1]. It is estimated that in 2021, 10.6 million people worldwide had TB, an increase of 4.5% from 2020. In 2021, approximately 1.6 million people, including 187,000 people living with HIV (PLHIV) died as a result of tuberculosis[2].

The epidemiologic pattern of TB has become heterogenous in the last two decades due to migration of people from traditionally high prevalence, low-income countries to high-income countries. Despite this, the highest incidence still occurs in low and middle-income countries, such as Kenya[3,4, 1].

The prevalence of TB in Kenya is high. According to National tuberculosis survey of 2016, the overall national prevalence of TB in Kenya was 558 per 100000 adults. Data also suggests that Kenya misses approximately 40% of people with TB[5]. This has been postulated to be due to

similar challenges faced by TB care globally: poor health care providers' knowledge on the protean manifestations of the TB disease, diagnostic delay and inappropriate therapy[5].

Two forms of TB which have been described; pulmonary TB, which constitutes about 70-80% of cases and extra pulmonary TB (EPTB). Pulmonary TB primarily presents with respiratory symptoms and can be diagnosed based on a compatible history, radiological findings and demonstration of the organism on laboratory testing. Extra pulmonary TB can affect any organ in the body including pleura, mediastinum, lymph nodes, intestines, genitourinary system, skin, joints and bones, and meninges[6].

Pleural and mediastinal tuberculosis are the second and third most common forms of EPTB after TB adenitis constituting about 20 % of EPTB[7,8,9]. It can occur in the setting of a primary infection or as part of a reactivation disease process. In younger people (less than 18 years) it is mainly due to primary infection. In persons with pre-existing pulmonary TB it can occur via hematogenous spread from the primary source. Pathogenesis is as a result of direct seeding of the Mycobacterium tuberculosis into the pleura, followed by a delayed hypersensitivity immune reaction. In majority of the cases, it presents as unilateral effusion and occupies less than 80 % of the hemithorax on imaging, and is often self-limiting[10]. In rare cases, loculation of pleural fluid occurs, signifying an intense intra-pleural inflammation[7]. Pleural and mediastinal TB presents with non-specific symptoms; these include non-productive cough, chest pain, dyspnea, weakness and constitutional symptoms such as weight loss, fever and night sweats.

Chest radiographs, which are more readily available in resource limited settings, have a high false-negative rate i.e., a normal chest-radiograph does not rule out TB. However, some typical radiological patterns have been described, including parenchymal signs such as consolidation, hilar lymphadenopathy, pleural effusion, airway stenosis with parenchymal atelectasis, cavities and miliary pattern in the lung parenchyma that raise the index of suspicion for TB[11]. Chest computerized tomography (CT) is considered the most sensitive for detection of occult early disease; it can detect micro nodules, infiltrations, consolidations, lymph node enlargement, formation of traction bronchiectasis and pleural thickening and aid in earlier diagnosis[5,12,13,14].

Definitive diagnosis of pleural and mediastinal TB requires detection of *Mycobacterium tuberculosis* in respiratory specimen, pleural fluid or pleural biopsy or histological demonstration of necrotizing granulomas in the pleura[15].

EPTB has been shown to have worse outcomes compared to pulmonary TB[9]. If left untreated or not treated early it can cause permanent lung damage[16,17].

Case report

A 16-year-old Kenyan male who was referred to Moi Teaching and Referral Hospital, Eldoret, Kenya, in November 2022. He presented with complaints of cough and chest pain for 2 months, associated with episodes of difficulty in breathing and fatigue, without any history of fevers, weight loss, night sweats or identifiable comorbidity. On physical examination he had tachypnoea and tachycardia but had no cyanosis, pallor, jaundice, oedema or lymphadenopathy. Respiratory examination revealed reduced chest movement and excursion on the right side, tracheal deviation to the left, reduced tactile fremitus on the right and a stony dull percussion note and decreased breath sounds in the right mid and lower lung zones. Chest radiograph showed a right middle-lobe loculated effusion and increased broncho-vascular markings bilaterally.

A complete blood count with differentials showed hemoglobin of 10.5g/dl (microcytic hypochromic anemia), white blood cell count of 8.6 ×10 9cells /L (89.8% neutrophils, 8.5% lymphocytes, 1.5% monocytes, 0% eosinophils), and a platelet count of 631 ×10 9/L. C-reactive protein and erythrocyte sedimentation rate were elevated (187mg/L and 55 mm/h, respectively). Liver and renal function tests were within normal ranges. Serological tests for HIV, hepatitis B and C infections were all non-reactive. *Echinococcus* immunoglobulin G (serum EIA) was negative. Gene Xpert assay on the pleural fluid detected *Mycobacterium tuberculosis.* However, sputum Gene xpert assay and culture in the BACTEC media were negative for MTB.

Chest CT scan showed multiple encapsulated fluid collections in posterior mediastinum, paravertebral space, right anterior pericardium and the rest of the right pleural space, with mediastinal shift. Also identified were pulmonary infiltrates, right lower lobe pulmonary partial collapse, right horizontal fissure extension, atelectasis and pleural thickening.

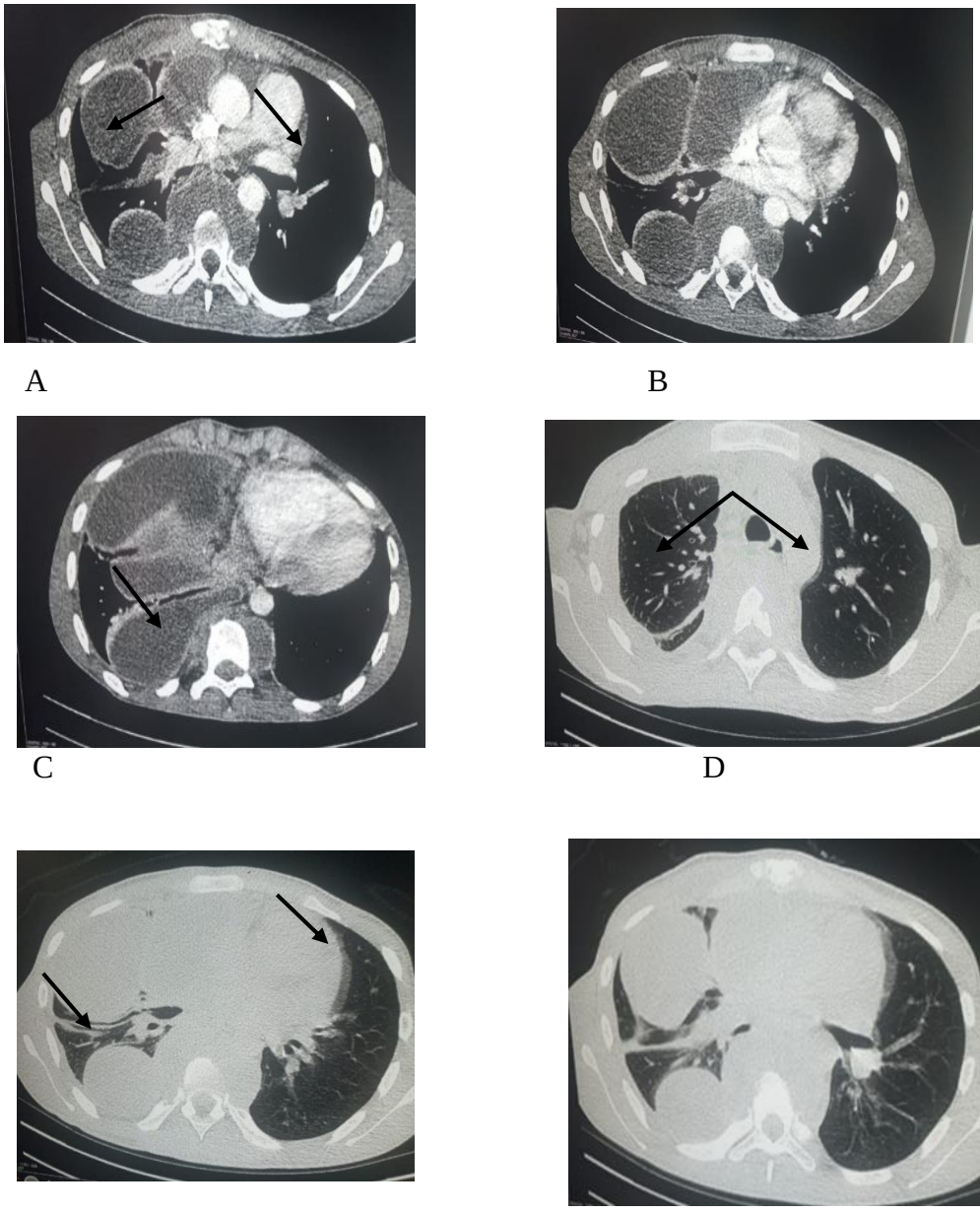

Fig. 1. Extra-pulmonary TB presenting as multi-loculated mediastinal, pleural and paravertebral fluid collections with chest pain.
A, B & C. Chest CT scan showing multiple encapsulated fluid collections in posterior mediastinum, paravertebral space, right anterior pericardium and the rest of the right pleural space, with mediastinal shift.
D, E, F and G. Chest CT scan showing pulmonary infiltrates, right lower lobe partial lung collapse, right horizontal fissural extension, atelectasis and pleural thickening.

The patient underwent evaluation by the interventional radiology (IR) team where multiple right sided pleural, interstitial and paravertebral fluid collections were visualized and the fluid drained via ultrasound (U/S) guidance. A size 12 pigtail catheter was placed in the pleural

cavity for continued fluid drainage. Serial pleural biopsies collected using a size 18F percutaneous biopsy gun were submitted for histological examination.

Histopathological examination of the pleural biopsy tissue revealed multiple necrotizing granulomas attended by langhans multinucleated giant cells (Fig.2). Ziehl Neelsen's (ZN) staining on the tissue showed acid fast bacilli (AFB).

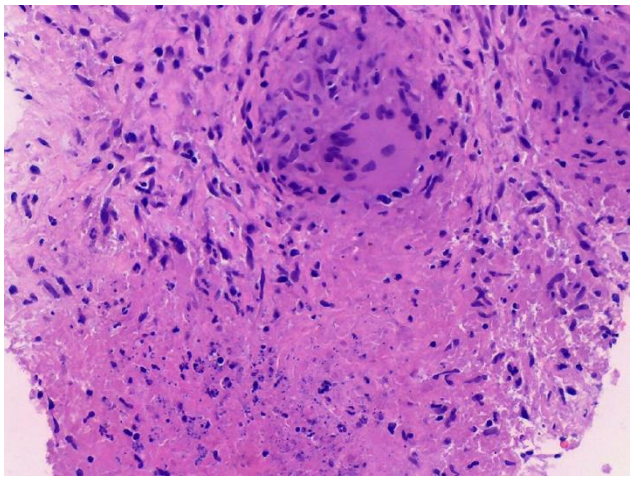

Fig. 2. H &E, x400: Demonstrating areas of necrosis, clustering of epithelioid histiocytes and langhans giant cells.

He was started on anti-tuberculous regimen (Rifampicin, Isoniazid, pyrazinamide and Ethambutol), pain management and oxygen therapy. At day 12, the patient had improved clinically as evidenced by subsiding pain and good oxygen saturation without the need for oxygen supplementation. Interventional radiology team (IR) re-evaluation at week 2 post EPTB diagnosis showed significant residual loculated effusions in the pleural and paravertebral spaces; more fluid was drained via pigtail catheter size 12, intrapleural gentamycin 160mg administered and pigtail catheter retained for subsequent fluid collection drainage.

Discussion

Despite Pleural and mediastinal TB being common manifestation of EPTB, their diagnosis remains challenging. Identification of Mycobacterium tuberculosis (MTB) is required to confirm diagnosis and for successful therapy based on drug sensitivity. However, the diagnosis of pleural and mediastinal TB becomes difficult to ascertain in smear negative cases. Pleural fluid AFB stain and culture require a very high organism load. In addition, the sensitivity any of these tests is low, especially in immunocompetent individuals[10]. It ranges from 5-30 % for AFB stain, 20-40 % for TB culture and 40-60 % for gene Xpert. Furthermore, literature shows that the sensitivity and specificity of gene Xpert for MTB is higher on pleural fluid than AFB

stain and culture. This is attributable to a greater burden of organisms in immunosuppressed patients, including those with HIV infection[18,19,20,21].

Our patient was a HIV negative patient in whom Gene Xpert assay on pleural fluid detected Mycobacterium tuberculosis despite sputum Gene xpert and culture in the Bactec media being negative for MTB.

Pleural and mediastinal TB generally present with non-specific symptoms and a high index of clinical suspicion is needed to avoid significant delay in the diagnosis and initiation of treatment. The most common presenting symptoms from literature are non-productive cough (94%) and pleuritic chest pain (78%). Other non-specific symptoms include fever, night sweats, chills, weakness, dyspnea, and weight[22]. In our patient, cough and pleuritic chest pain were the most predominant symptoms.

Radiological examinations are quite helpful in better evaluating characteristics of pulmonary parenchymal, pleura and mediastinum pathology. The sensitivity and specificity of CT or MRI are high and quite comparable. According to literature, approximately 10-50% of EPTB have concomitant pulmonary involvement[23]. This was consistent with our case whereby pulmonary changes were noted on the Ct scan evaluation.

Histological results from the pleural biopsy in our case showed necrotizing granulomatous lesions and positive ZN consistent with TB. Scientific data shows that diagnostic accuracy increases with tissue biopsy for histological examination. Conventional tests (AFB smears, TB culture and PCR) have low sensitivity and it takes days-to- weeks for *M. tuberculosis* to become evident during culture. As a result, the diagnosis of EPTB mostly depends on histological evidence.

British Thoracic Society recommend biopsy as the gold standard for diagnosis of pleural and mediastinal TB[24]. In one study of tuberculous pleurisy patients, diagnostic success of more than 90 % was achieved when the pleural biopsy, PCR and culture results were combined[25].

Histopathological characteristics of pleural and mediastinal TB includes, caseous necrosis, presence of necrotizing granulomas and presence of AFBs on ZN staining. However, loss of host immune function can result in histopathologic findings demonstrating greater suppurative response and less well-formed granulomas[26]. Additionally, the granulomas can be seen also in nontuberculous mycobacteria disease, fungal infections, brucellosis, or syphilis, so cautious interpretation is required[27].

Multi-loculated pleural and mediastinal fluid collections can be a sign of many different underlying medical conditions[28]. Thus, diagnostic work-up for alternative cause of multiloculated pleural fluid collections is quite important. In our case, we considered pulmonary hydatid disease and malignancy as possible differential diagnosis. Echinococcus IgG (hydatid disease) antibody was negative and CT scan abdomen and chest plus histological examinations were negative for malignancy.

The treatment of EPTB with anti-tuberculous medications is effective and adjuvant surgery is limited to complications such as loculated pleural effusion, frankly purulent/turbid fluid, organism staining or culture, PH<7.2 and lack of clinical improvement despite adequate medical therapy (ATS/ERS/ESTS/BTS guidelines). Kenyan and WHO guidelines recommends same approach for anti-tuberculous therapy in EPTB as same as in pulmonary TB. There is currently no evidence to support the use of steroids in the management of pleural and mediastinal TB [22]. In drug susceptible pleural and mediastinal TB, as in our case, the first-line medications include a two-month intensive phase of rifampicin, isoniazid, pyrazinamide, and ethambutol, followed by a continuation phase of at least 4 months of rifampicin and isoniazid (total duration of at least six months). However, some varied literature on EPTB suggests a longer treatment course of 9 to 12 months for EPTB due to worse outcomes compared to pulmonary TB. In other studies, shorter course of treatment has been found to be just as effective as an extended period, with the added benefits of better compliance and savings on cost [29].

Therapeutic thoracentesis is recommended, for symptomatic management, if the effusion is causing dyspnea. Routine complete drainage of pleural fluid at the time of diagnosis does not appear to affect long-term outcomes[30].

There is insufficient data to support routine use of intrapleural antibiotics and fibrinolytic agents for management of pleural effusion [31,32]. However, consideration can be given to the use of fibrinolytic agents such as tissue plasminogen activator-deoxyribonuclease and intrapleural antibiotics in patients with complicated effusion requiring adjuvant surgery but who are poor or borderline candidates for surgery and concomitant parapneumonic effusion, when conventional medical therapy and therapeutic thoracentesis is not adequate [33,34].

With appropriate therapy, most patients improve symptomatically within two weeks and the pleural fluid is resorbed within months of anti-tuberculous drugs initiation. However, some patients may take longer to improve and for the effusion to clear. Our patient improved

clinically within one week of anti-tuberculous initiation and by week 3 the effusions had cleared. The patient is currently on intensive phase of anti-tuberculous drugs and doing well.

Conclusion

Pleural and mediastinal TB has non-specific clinical and radiological manifestations that may mimic other pulmonary conditions, thus, a high index of suspicion is required to reduce morbidity and mortality. Confirmatory diagnosis is by isolation of AFB on respiratory specimens (pleural fluid and biopsy), and histopathologic demonstration of necrotizing granuloma. The main stay of treatment is first line anti-tuberculous drugs with good outcomes with early diagnosis. Our case most likely had primary EPTB given his age and clinical presentation.

Data Availability

Dataset used to support the findings of this case report is included within the article and figures.

Consent

Written informed consent was obtained from the patient for publication of this case report and utilization any accompanying images.

Disclosure

None

Conflicts of interest

No conflict of interest to declare

Funding source

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Ethical approval

Approval was not required

Authors' contributions

MMA, SB and MK involved in designing and writing up of the case; KK reviewed the histology slides; OC and LO reviewed the manuscript and provided critical specialist input.

All authors approved the final draft.

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