Secondary Renal Amyloidosis Following Long Standing Tuberculosis Lymphadenitis - A Case Report

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Abstract
Tuberculous lymphadenitis is most frequent presentation of extra pulmonary tuberculosis. Tuberculosis (TB) is responsible for up to 43% of peripheral lymphadenopathy in the developing world. The objective of this case report is to highlight the relationship between secondary amyloidosis and tuberculosis, though it was well established, it’s rarely reported due to extra pulmonary tuberculosis. Besides, to increase awareness on the common clinical features of secondary renal amyloidosis, this finding is important especially in high TB burden countries including sub Saharan Africa where tuberculosis is common.

Abbreviations: AA Amyloidosis; Tuberculous Lymphadenitis; Nephrotic syndrome; Renal amyloidosis.


Introduction

Tuberculosis is not only major public health problem but also the leading cause of death from a single infectious agent throughout the world. Especially, in developing countries like Ethiopia. In 2020, an estimated of 10 million people fell ill with TB and there were 1.3 million TB deaths among HIV-negative, globally [1]. The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extra pulmonary TB). Tuberculous Lymphadenitis is a chronic specific granulomatous inflammation of the lymph nodes with caseation necrosis, caused by infection with Mycobacterium TB or Mycobacterium bovis [2]. Tuberculous lymphadenitis is most common presentation of extra pulmonary TB and is responsible for up to 43% of peripheral lymphadenopathy in the developing world [2,3]. Patients present as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as scrofula). Lymph nodes are usually discrete in early disease but develop into a matted non tender mass over time; a fistulous tract draining caseous material. The diagnosis can be made by radiologic examination, staining for acid-fast bacilli and Fine-Needle Aspiration Cytology (FNAC)/ histological examination of dissected involved lymph nodes [2].

Case presentation

A 38 years old female patient from Ethiopia, Tigray presented with generalized body swelling of two months duration which started from her lower extremity and progressively involved her abdomen and face. This patient was known to have on and off type cervical lymph node swelling for 8 years and she never sought medical advice, she was receiving traditional medicine in a form of cauterization. Recently, she visited a local health center because of increasing in lymph node size. Furthermore, it started to involve inguinal and axillary areas. Associated with this, she has low grade intermittent fever and loss of appetite. The health professional at the health center found multiple cer

Laboratory investigation revealed the following: hemoglobin, 10.2gm/dl (normocytic, normochromic); white cell count, 12,700/µl (differential count: 66% neutrophils, 30% lymphocyte, 2% monocyte, and 2% eosinophil’s); platelet count, 392,000/µl; erythrocyte sedimentation rate was 85mm/hr; sodium, 134mg/dl; potassium, 3.6meq/l; creatinine, 0.8mg/dl; serum calcium 7.77mg/dl; serum albumin, 1.2mg/dl. Urine analysis proteinuria (3+) with 1-2 red-blood-cells/high-power-field; 24-hour urine protein was 3.65g/day. Viral screening for hepatitis B & C and HIV was negative. Serum total cholesterol 351mg/dl and serum triglycerides 325mg/dl.

Cervical lymph node biopsy revealed caseating granuloma with giant cells, a finding consistent with tuberculosis of lymph node Figure 1 (a-f).

Abdominal ultrasound showed bilateral normal sized kidneys with normal echo pattern and cortico medullary differentiation. Echocardiogram and chest x-ray was normal. The patient was admitted with the diagnosis of Tuberculous lymphadenitis with superimposed bacterial infection and nephrotic syndrome. Since we couldn’t find common possible cause of nephrotic syndrome with the available investigative modalities, we have decided to request a renal biopsy. As we don’t have kidney biopsy setup, we sent the patient to be biopsied to a different hospital and came up with result in A4 sized paper.

**Figure 1 (a-f):** Pathological examination of lymph node biopsy demonstrates TB lymphadenitis in the light microscopy. 
(a&b) Areas of central caseous necrosis with giant cells seen (hematoxylin & eosin, ×4 and ×10 respectively). 
(c&d) Epithelioid cells and Langhans giant cells are seen (hematoxylin & eosin, ×40). 
(e) Coalescent epithelioid histiocytic granuloma (hematoxylin & eosin, ×4). 
(f) Granuloma with gaint cells (hematoxylin & eosin, ×10).
Kidney biopsy: Diffuse irregular mesangial matrix expansion consequence to deposition of a material that exhibits tectorial properties of amyloid with pale eosinophilic appearance with H&E stain (Figure 2a), negativity with PAS & silver methylamine stains. Orange-red appearance noted in Congo red stain under light microscopy (Figure 2b). Arteries and arterioles exhibit variably thickened walls showing deposition of amyloid. Immunofluorescence microscopy is positive for serum amyloid A component. Electron microscopy for further characterization of type of amyloid deposit could not be done due to unavailability.

Secondary amyloidosis, representing approximately 45% of all cases of systemic amyloidosis has been associated with various chronic inflammatory conditions such as rheumatoid arthritis, sarcoidosis, Crohn’s disease, ulcerative colitis and tuberculosis [7]. Amyloid precursor is Serum Amyloid A (SAA), a soluble Apo lipoprotein mainly encoded by the SAA1 gene. Although its pathophysiology is unknown, it is believed that an elevation of pro inflammatory cytokines, particularly Tumor Necrosis Factor Alpha (TNF-α), Interleukin-1 Beta (IL-1β) and IL-6, stimulates hepatocytes to secrete large amounts of SAA. A chronically high plasma concentration of SAA results in the aggregation of amyloid into cross-β-sheet fibrillar deposits, which latterly deposit in various tissues [4,5].

Diagnosis of amyloidosis is generally confirmed by tissue biopsy. Congo red-stained amyloid has an orange-red appearance under light microscopy and produces apple-green birefringence under polarized light. Further immunofluorescence or immunochromic staining are needed for serum amyloid A protein or for kappa and lambda light chains presence [8,9].

Kidneys are main target organ in amyloidosis, which are affected in almost all patients with AA amyloidosis and is serious because of its ill effects on renal functions [9,10]. Patient with secondary amyloidosis present with variable degree of proteinuria about 95%, commonly nephrotic syndrome with a high risk for progression to end-stage renal disease [10]. There have been reported cases which show stabilization or improvement in renal function, reduction in proteinuria and partial resolution of amyloid deposits following treatment of tuberculosis [9,11]. Similarly, in our patient, at least clinical remission was seen. Since the clinical onset of amyloidosis is preceded by a variable preclinical stage, the true interval between the preceding disease and the onset of amyloidosis is not known exactly [9]. Thus, we need to suspect renal amyloidosis in any patient with pulmonary or extra pulmonary tuberculosis (past or present infection), presenting with pedal edema and proteinuria, so that early diagnosis is made with timely institution of appropriate treatment. As most patients with renal amyloidosis progress to end-stage renal disease, ultimately they need either dialysis or renal transplantation.

In tuberculosis, body swelling may be caused by other differential diagnosis including malnutrition, anemia and heart failure, which may result in missing amyloidosis in these patients. In our patient, there was pedal edema, proteinuria in nephrotic range (> 3.6 g/24 hours) but on ultrasound, kidney size was normal. She had mild anemia, which was most likely anemia of chronic disease as peripheral smear was normochromic normocytic. Other causes of pedal edema like heart failure were ruled out by normal JVP and echocardiography. Hence, increasing awareness of the clinical features of amyloidosis in tuberculosis including extra pulmonary is important for its early diagnosis and timely treatment. Furthermore, due to local unavailability of facilities to diagnose secondary amyloidosis, our patient was referred to Addis Ababa, capital city of Ethiopia, where the diagnosis of AA amyloidosis was finally reached. This pattern of unavailability of certain diagnostic facilities is common in most developing countries necessitating an overseas referral a process which takes time and ultimately lengthens the diagnosis process. Therefore, a high index of suspicion is necessary in early diagnosis and treatment.
Conclusion

We have illustrated a case of renal AA amyloidosis in a patient with tuberculous lymphadenitis. In this case, a renal biopsy helped us elucidating the etiology of the nephrotic syndrome, and therefore, we continued anti-tuberculous medicine as the core treatment along with diuretics and anti-proteinuric drugs. Secondary amyloidosis should always be considered and investigated; in patients who presented with the nephrotic syndrome and a previous or current history of tuberculosis regardless of its type (pulmonary or extra pulmonary). Indeed, clinicians need high index of suspicion to reach the diagnosis of AA amyloidosis especially high tuberculosis burden countries including sub-Saharan Africa where tuberculosis is common, as early diagnosis and appropriate management is important in improving patient outcome.

Declaration

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing Interests

The authors declare that they have no competing interests.

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Availability of Data and Material

The editor can contact the main author for data requests.

Author’s contribution

This work was carried out in collaboration between all authors. All authors contributed to data analysis, drafting and revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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