Hodgkin Lymphoma Masquerading as Tuberculosis in a Young Chronic Smoker

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Abstract Hodgkin lymphomas are malignant hematolymphoid neoplasms involving lymph nodes and extranodal sites. Bone marrow infiltration at diagnosis is uncommon, occurring in approximately 10 % cases. Such infiltration, when present, is usually focal and often associated with extensive disease, systemic symptoms, cytopenias and unfavorable histology. In the unusual event of the absence of significant peripheral lymphadenopathy, these lymphoma-related B-symptoms may easily masquerade as an infectious illness. A 30-year-old male was initially administered inappropriate anti-tubercular chemotherapy in a primary care setting for a presumptive impression of pulmonary tuberculosis. On re-evaluation due to unresponsiveness to the drugs, bulky mediastinal lymphadenopathy was detected. However, his axillary lymph node aspirate revealed epithelioid cell granulomas further confounding the picture. The correct diagnosis of Hodgkin lymphoma was finally established when a bone marrow biopsy (for fever and pancytopenia) revealed the typical neoplastic Reed Sternberg cells that were confirmed immunohistochemically. The case highlights the necessity of an early bone marrow examination in patients with unexplained fever and peripheral blood cytopenias.

Physicians in tropical third-world countries with resource constraints and high disease burdens need to strike a fine balance between maintaining a high index of suspicion for tuberculosis yet being wary of the risk of missing lymphoma in such patients.

Keywords Anti-tubercular therapy · Bone marrow examination · Hematological malignancy · Histopathological diagnosis · Hodgkin lymphoma · Immunohistochemistry · Reed-Sternberg cell · Tuberculosis

Introduction

Lymphomas may occasionally masquerade as a infectious illness [1]. This is especially likely in patients without significant peripheral lymphadenopathy and in those in whom systemic symptoms like fever and weight loss predominate [1]. We report a 30-year-old male who was clinically misdiagnosed and treated as tuberculosis and was only subsequently found to harbor Hodgkin lymphoma (HL).

Case Report

A 30-year-old male, a chronic smoker since 14 years, was referred from a primary health care centre with persistent complaints of intermittent low-grade fever, fatigability, dyspnoea, anorexia, significant weight loss and cough of one-year duration. He had previously presumptively received anti-tubercular therapy (ATT) for 6 months without improvement. There was no history of jaundice, blood loss, hemoptysis, change in bowel/bladder habits or

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Fig. 1 **a** Bone marrow aspirate shows neutrophilic and dysplastic erythroid precursors. **b** Dyserythropoiesis in the form of nuclear budding. Granulocytic cells show nuclear hypolobation and cytoplasmic hypo- and hypergranularity. **c**, **d** Increased histiocytes, many show hemophagocytosis (May-Grunwald Giemsa, x400)

any personal or family history of tuberculosis. On examination, the thinly built pale man had mild pitting pedal edema and splenomegaly 4 cm below left costal margin without hepatomegaly or significant lymphadenopathy.

Investigations revealed hemoglobin 3.8 g/dl, total leukocyte count $2.6 \times 10^9/l$, and platelet count $65 \times 10^9/l$. Serum LDH was 799 IU/ml. Hepatic and renal function tests, coagulation profile, blood culture and Mantoux test were normal. Contrast-enhanced computed tomography (CECT) chest and abdomen revealed bilateral bulky hilar lymphadenopathy and a few very small (<0.5 cm) abdominal and axillary lymph nodes. Fine needle aspiration (FNA) from the axillary lymph nodes showed a few epithelioid cell granulomas without necrosis or acid-fast bacilli. Pathological sampling of the retro-sternal hilar lymph node mass was not considered feasible. Fibro-optic bronchoscopy was normal.

Bone marrow examination was done for pancytopenia. The aspirate smears showed a polymorphous infiltrate of lymphocytes, neutrophil precursors, dysplastic erythroid cells (Fig. 1a, b) and fibroblasts admixed with epithelioid histiocytes, many of which showed hemophagocytosis (Fig. 1c, d). Imprint smears showed rare large mononuclear and binuclear cells with prominent nucleoli (Fig. 2a, b). The trephine biopsy was hypercellular with diffuse reticulin fibrosis (Fig. 2c, d). In addition to the polymorphous infiltrate, many typical Reed-Sternberg (RS) cells and mononuclear Hodgkin cells were present (Fig. 3a, b). An occasional lymphoid aggregate (Fig. 3c) and ill-defined

granulomas (Fig. 3d) were also present. Ziehl-Neelsen stain for acid-fast bacilli was negative. On immunohistochemistry, the large cells were positive for CD30 (Fig. 4a, b) and CD15 (Fig. 4c, 4d) and negative for CD45 (Fig. 4e), CD3 and CD20. The background showed reactive CD3-positive T-cells (Fig. 4f) and a few CD20-positive B-cells (Fig. 4g). The findings were diagnostic of bone marrow involvement by Hodgkin lymphoma (HL). Based on the conclusive results (HL, stage IV) the patient was referred to clinical haematology for appropriate chemotherapy.

Discussion

HL diagnosed initially or primarily on bone marrow trephine biopsy is well reported in literature [2]. Bone marrow in such cases is usually examined to investigate pancytopenia or unexplained systemic symptoms like fever [3]. Histological indicators of HL in the bone marrow include Reed-Sternberg cells or their variants in a polymorphous cellular background, myelonecrosis, focal fibrosis, granulomas and myxoid change [4]. Typical RS cells, as in our case, are rare in bone marrow aspirates [2–4].

Tuberculosis can mimic many other disorders and may in turn be mimicked by many other diseases too [5]. It remains a major public health challenge in India [6], with an annual risk of infection between 2 and 5 % in young individuals [7]. Physicians in tropical countries harbour a high index of suspicion for tuberculosis, and an empiric

Fig. 2 Trephine biopsy touch imprint smears showing **a** bare nuclei of binuclear Reed-Sternberg and **b** mononuclear Hodgkin cells (May-Grunwald Giemsa, x400). **c** Trephine biopsy showing 100 % cellularity with a polymorphous infiltrate of lymphocytes, neutrophilic precursors and fibroblasts admixed with histiocytes (Hematoxylin and eosin, x200). **d** Reticulin stain showing grade 2/3 fibrosis (EUMNET grading, Gordon and Sweet's reticulin stain, x200)

Fig. 3 **a, b** Reed Sternberg cells showing characteristic owl-eye type eosinophilic nucleoli. **c** Lymphoid aggregate **d** collection of epithelioid histiocytes (Hematoxylin and eosin, x400)

diagnosis in the appropriate clinical setting carries a high likelihood of being correct. Early institution of ATT as a therapeutic trial in itself is helpful in suspected secondary tuberculosis at sites where confirmatory microbiologic or histopathologic sampling is difficult [8, 9], or such confirmation is not forthcoming despite sampling [10]. In such

situations, however, there is a real risk of confusing lymphomas with tuberculosis as the clinical presentations of both diseases (lymphadenopathy, fever, weakness, night sweats, weight loss) are similar [1, 11].

Further diagnostic work-up, especially histopathological evaluation, is therefore crucial in all cases of presumed

Fig. 4 **a, b** Reed Sternberg cells showing CD30 immunopositivity in Golgi region. **c, d** Membranous CD15 positivity. **e** CD45 immunostain reveals negative RS-cells. **f** Background reactive population of

CD3 positive T-cells and **g** CD20 positive B-cells (immunoperoxidase staining, hematoxylin counterstain, x400)

tuberculosis that are unresponsive to empiric ATT. A high index of suspicion for alternative diagnoses, based on complete clinical information is essential even on the part of the reporting pathologist. The axillary lymph node FNA in our case revealed granulomas, a potentially misleading clue. Such non-caseating sarcoid-like granulomas are well-known to occur in Hodgkin and non-Hodgkin lymphomas [1, 11, 12]. The granulomas may be so extensive as to obscure the malignant process enhancing the false impression of tuberculosis [13].

X-ray and/or CT imaging are the first choice in visualization of mediastinal lesions. However, they too cannot usually reliably differentiate between tuberculosis and lymphoma. Even the more recent modalities, such as 3-dimensional single proton-emission computed tomography (SPECT) and positron-emission tomography (PET) are insufficient for the differential diagnosis, chiefly because hypermetabolic lesions are not specific for malignancy [14]. Bone marrow biopsies are invasive procedures. However, when combined with ancillary techniques like immunohistochemistry, they may be the most specific and sensitive diagnostic tools to resolve such difficult cases.

In conclusion, our case alerts physicians to maintain a high index of suspicion for unusual entities like HL even when tuberculosis seems clinically obvious but antimicrobial therapy has failed. Bone marrow examination supplemented by immunohistochemistry can enable a confident diagnosis in such cases. Histological evaluation therefore still plays a vital role in this era of high-resolution imaging.

Conflict of interest None.

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