

Co-Existent Hodgkin's Lymphoma and Tuberculosis

A Rare Case Report.

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Abstract

Coexistence of Hodgkin's Lymphoma and tuberculosis in the same organ is rare but has been reported in very few cases worldwide. It is well documented that the risk of leukemias and lymphomas is increased in individuals with history of tuberculosis. On the other hand, cell mediated immunodeficiency in leukemia increases the chances of re-activation of tuberculosis. Introduction of immunosuppressive chemotherapy, in a patient of Hodgkin's Lymphoma may worsen the clinical course of tuberculosis if not recognised and treated promptly. In this case report, we present a case of an 18 years old boy, who presented with complaints of fever, weight loss and anasarca. On clinical examination, he had generalised lymphadenopathy, hepatosplenomegaly and ascites. Cervical lymph node biopsy revealed large atypical lymphoid cells with presence of typical Reed Sternberg cells, which were positive for CD15 and CD30. RT-PCR for Mycobacterium tuberculosis in the same lymph node was positive. The patient underwent treatment for both Hodgkin's disease and tuberculosis and improved subsequently.

Introduction

Hodgkin's disease has a bimodal presentation including both the younger age group (20-30 years) and the elderly (above 50 years) with equal male and female distribution. 20-30% of the patients of Hodgkin's disease are asymptomatic [1]. Histopathologically, it is characterised by the presence of Reed Sternberg cells and its variants. Among patients with Hodgkin's disease with mediastinal involvement, nodular sclerosis variant is the most common histological subtype. Hodgkin's lymphoma usually causes B-cell mediated immune deficiency and co-existent infections with various pathogens, such as Epstein-Barr virus, Herpes Simplex, Cytomegalovirus, Pneumocystis Carini and Mycobacterium species are usually found [2]. Lymphomas are often preceded by chronic inflammatory diseases and cripples the immune system of the host. Tuberculosis (TB), on the other hand, is a chronic infectious disease, presentation and re-activation of which is promoted by cell-mediated immunodeficiency in the host [3]. Hodgkin's lymphoma and Tuberculosis occurring in the same organ is a rare, literature shows few cases worldwide and even fewer

reported from India. The various organs involved in co-existent lymphoma and extra-pulmonary tuberculosis include bronchus, small bowel, kidney and lymph nodes [4]. It has been also reported that the risk of Non-Hodgkin's lymphoma is significantly increased (odds ratio 1.8) in individuals with a history of tuberculosis, however reports on the exact risk of Hodgkin's Lymphoma is still awaited [5].

Case Report

An 18 years old male student, presented to the out-patient department of our hospital with chief complaints of loss of appetite for two months, fever for one month, swelling in bilateral feet and abdominal distension for 15 days. Loss of appetite was insidious in onset and gradually progressive. He reported a loss of 8 kg of weight in last 2 months. Fever was low grade, intermittent and was associated with evening rise of temperature. No history of cough with expectorations, burning sensation during micturition, rashes or chills was present. Swelling over bilateral feet and abdomen were also insidious in onset, not associated with shortness of breath/paroxysmal nocturnal dyspnea/orthopnea/chest pain/decreased urine output/ jaundice. There was no history of trauma or redness. The family and relevant personal history were unremarkable.

On general physical examination, the weight, height and BMI of the patient were 46kg, 160cm and 16.9kg/m² respectively. Moderate pallor and pedal edema were present. Lymph nodes were palpable in anterior cervical,

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posterior cervical, axillary and inguinal region. They were 5-6 in number in each region, 3×2cm in size, firm, discrete, mobile, non-matted as well as non-tender. On palpation, hepato-splenomegaly was evident. The liver span was 18 cm, firm in consistency and non-tender. Free fluid in the abdomen was elicited. Rest of the systemic examination were unremarkable.

On complete blood examination, serum hemoglobin was 6.9 gm/dl with a normal total leucocyte count with differentials. ESR level was raised 120 mm in the first hour. Lipid profiles, renal functions tests and liver function tests were within normal limits except raised serum alkaline phosphatase (562 U/L). Viral serologies including HIV, Hepatitis B and Hepatitis C were negative. Serum LDH level was raised.

Ultrasound examination of the abdomen revealed hepatosplenomegaly, portal vein diameter (PVD) of 13 mm and multiple lymph nodes in the para-aortic, peripancreatic and splenic hilar region. Ascitic fluid examination showed total leucocyte count of 480 cells/mm³ with 100% lymphocytes. Ascitic fluid protein was 1.4 gm/dl and SAAG was 1.86. Gram stain and examination for malignant cells yielded negative results. Computed tomography scans of the chest and abdomen revealed bilateral thickening of oblique fissures in lung, calcified lymph nodes in pre and para tracheal, pre and sub carinal regions as well as in the para-aortic regions. (Figure 1)

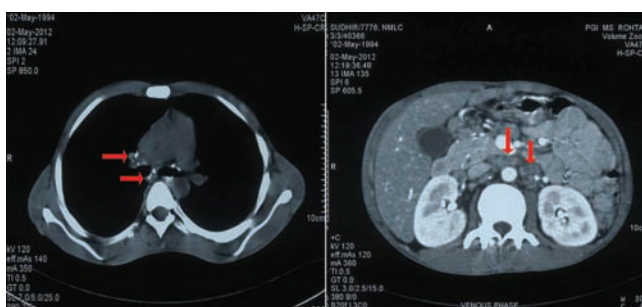


Figure 1

Excision biopsy of cervical lymph node was done and histopathological examination revealed diffuse nodal architectural effacement by large atypical lymphoid cells with enlarged nucleus and prominent nucleoli. Few eosinophils and plasma cells were also seen. Numerous uni, bi and multinucleated RS cells (Reed Sternberg cells) were seen (Figure 2a). Focal areas showed caseous necrosis surrounded by calcification and epithelioid cells forming granuloma (Figure 2b). Immunophenotyping in the lymphoid cells were positive for CD 3 and CD 20, whereas immunophenotyping in the Reed Sternberg cells showed positive results for CD 15 and CD 30. Real time polymerase chain reaction for *Mycobacterium*

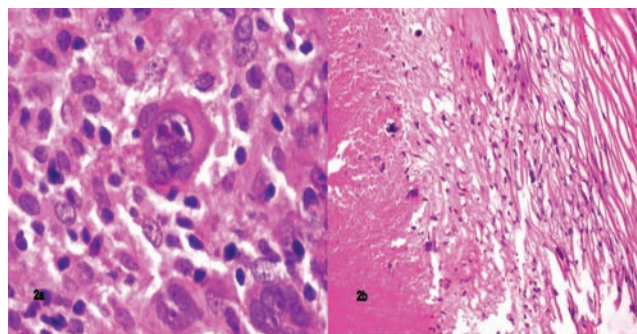


Figure 2

tuberculosis in the same lymph node was positive. IgG Epstein Barr virus serology in the same lymph node was positive in high titres (30.42 U/ml). The final diagnosis was Hodgkin's lymphoma; mixed cellularity, stage IIIB, with tubercular lymphadenitis.

The patient was put on anti-tubercular therapy as well as ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) regimen for Hodgkin's lymphoma in cycles of 28 days. After 4 months of combined anti tubercular treatment and chemotherapy for Hodgkin's lymphoma, the patient showed remarkable clinical outcomes in terms of decrease in incidence of fever, improved appetite, weight gain, regression in hepato-splenomegaly, decrease in size and number of lymphadenopathy and absence of pedal edema and ascites. His blood examination also showed improvement increase in hemoglobin and serum proteins whereas fall in ESR, Serum Alkaline Phosphatase and serum bilirubin values. CECT abdomen on follow up showed decrease in size of organ involvement and no significant lymphadenopathy or any ascites. Side effects noted during chemotherapy were hair loss and leucopenia.

Discussion

Hodgkin's lymphoma is a B-cell neoplasm which cripples immune system of the host and promotes opportunistic infections like tuberculosis. Cell mediated immunity plays a pivotal role in the control of mycobacterial infection [2]. Immunosuppression in Hodgkin's lymphoma often leads to Mycobacterial infection in these patients, hence increasing morbidity and mortality [6,7].

Mycobacterial infection causes direct DNA damage, inhibition of apoptosis, increase in cell mutation as well as promotes angiogenesis: all these factors contribute towards development of a neoplasm. Various mycobacterial cell wall components are responsible for producing various nitric oxide and reactive oxygen species which are implicated in inflammation related carcinogenesis. Of note both nitrate as well as oxidative mechanisms of DNA damage are involved in the process

[8-10]. Tuberculosis infection can precede malignancy in an immunosuppressed individual. Whereas, IL-10 levels in Non-Hodgkin's lymphoma (NHL) patients have been implicated in reactivation of latent TB. Increased serum IL-10 concentration further compromises the cell mediated immune system of the host thus favouring mycobacterial infection [11].

In the present case, there has been a dilemma regarding whether chronic latent mycobacterial infection has led to the development of malignant lymphoma through mechanisms discussed above, or the weakened immune system of the host due to the malignant growth has promoted tuberculosis infection. This question is highly debated and still remains unanswered. It has been reported that the risk of NHL is increased in individuals with a history of TB [12]. On the other hand NHL patients report much higher incidences of TB than in the general population [13]. TB associated with malignant lymphomas usually have an atypical clinical course which are difficult to diagnose and treat. Unusual extra pulmonary locations like lymph nodes, breasts, spleen, liver, jejunum and skin are often involved [2,14,15]. The clinical spectrum of both the diseases include low grade fever, anorexia, loss of weight, cough, night sweats, hepatosplenomegaly or mediastinal lymphadenopathy, resulting in misdiagnosis or delay in diagnosis. No response to anti tubercular therapy, reappearance of lymphadenopathy, worsening clinical condition and persistence of fever have prompted physicians to search for an alternate diagnosis.

Biopsy has remained the sole definite investigation modality to establish the diagnosis. Owing to underlying immunosuppression diagnostic utility of tuberculin skin test is very low in the background of malignancy [1]. Modern imaging modalities such as FDG PET, FDG PET/CT fusion, whole body MRI and Multidetector CT(MDCT) have aided in the staging of lymphoma but do not replace the gold standard histopathological diagnosis.

Histopathological examination may also give inconclusive results in terms of differentiating the two diseases. HL or NHL often shows caseating or necrotising granulomatous lesions which are otherwise considered typical of mycobacterial infection. Chemotherapy for lymphoma may lead to granuloma formation [16]. Lung or parasternal HL infiltrates can present as cavitary lesions like TB. Reed Sternberg cells are also evident in NHL, cancers, sarcomas or during the course of EBV infection. Hence, immunophenotyping with CD 15 and CD 30 antigens are essential in order to confirm the diagnosis of HL. In order to prove mycobacterial infection, not only Ziehl-Neelsen staining but often cultures and Polymerase chain reaction tests are necessary [2,17-19].

Conclusion

Mycobacterial tuberculosis infection is the most common offending agent behind cervical lymphadenopathy in India and majority of lymphadenitis respond to anti tubercular therapy. Few patients may complain of increase in number or size of lymph nodes despite therapy. The most important cause behind unresponsiveness to therapy is infection with drug-resistant mycobacteria. Rarely, simultaneous dual pathology of lymph node can exist and the underlying malignancy like Hodgkin's lymphoma may be missed. The overlap of clinical spectrum of both the diseases is a diagnostic challenge for the physician and may lead to delayed treatment or therapeutic failure. In endemic regions, tuberculosis may be present before, during and after the diagnosis of Hodgkin's lymphoma. Biopsy from the affected tissue is the gold standard diagnostic modality in such cases which clears the diagnostic dilemma [20-21]. These patients respond significantly to combined therapy for Tuberculosis and Hodgkin's lymphoma.

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