Mantle Cell Lymphoma With Leishmaniasis: A Rare Association

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Introduction
Mantle cell lymphoma (MCL) is a B-cell NHL. Previously it was referred as intermediate lymphocytic lymphoma, centrocytic lymphoma, mantle zone lymphoma and lymphocytic lymphoma of intermediate differentiation. Malignant transformation takes place in the outer edge of a lymph node follicle, called the mantle zone. MCL occurs more frequently in older adults – the average age at diagnosis is the mid-60s. It usually begins with lymph node enlargement and can spread to other tissues such as the marrow, liver, gastrointestinal tract and central nervous system. The peculiar characteristic of this lymphoma is its clinical course which combines the worst features of aggressive lymphomas (i.e aggressive course) and the indolent lymphomas (i.e frequent recurrences). It comprises about 7% of adult Non-Hodgkin’s lymphomas (NHL).

Leishmaniasis is a vector-borne protozoan infection spread by the bite of the female sandfly (Phlebotomus and Lutzomyia species). It is caused by protozoal parasites belonging to genus Leishmania. It has a varied spectrum of clinical manifestations which can be divided into cutaneous leishmaniasis, mucosal leishmaniasis and visceral leishmaniasis (Kala Azar). The mortality of untreated Visceral Leishmaniasis is 75-95% and is endemic in 88 countries largely located in the tropics and subtropics. We report one such case.

Case Report
A male patient 65 years of age, resident of Muzaffarabad Azad Kashmir presented to Oncology Department of CMH Rawalpindi having fungating, nodular masses with areas of crusting and induration covering nose and adjoining both cheeks (Fig 1). He had a history of irregular low grade fever with subjective feeling of weight loss and had moderate splenomegaly (5 cms) along with the skin lesion on face. Rest of the clinical examination was unremarkable. A skin biopsy done at Muzaffarabad was suggestive of cutaneous lymphoma. He was advised further evaluation including baseline investigations, repeat biopsy of nodular skin lesions, bone marrow aspiration and trephine biopsy and CT scans of chest and abdomen for staging of suspected lymphoma. His peripheral film showed TLC 159000/cmm with 97% abnormal lymphocytes, bone marrow aspiration showed 92% abnormal lymphoid cell infiltration with surprising finding of large number of LD bodies (Leishmania donovani). Along with lymphoid hyperplasia (Fig 2). Repeat biopsy of skin lesion along with immunohistochemistry revealed that the cells were characteristically CD5+ and pan B-cell antigen positive (CD19, CD20, and CD22) but lacked expression of CD10 and CD23. Cyclin D1 was over expressed. CT Scans were unremarkable however Leishmania antibody titer was found to be high. Thus the final diagnosis was mantle cell lymphoma in leukemic phase with visceral leishmaniasis. Considering the high incidence of silent gastrointestinal involvement in this lymphoma upper GI endoscopy was done which surprisingly showed lesions in gastric mucosa and duodenum which proved to be MCL involving these sites also. Treatment was started with parenteral pentavalent antimonials compound, Glucantime for leishmaniasis and patient was given 6 cycles of standard CHOP chemotherapy for MCL. Rituximab was not given due to financial constraints. The skin lesions regressed rapidly and at the end of treatment few fibrotic scars were left (Fig 3). A subsequent biopsy confirmed the clearance of lymphoma from skin site. Gastrointestinal lesions also disappeared after completion of chemotherapy confirmed on rebiopsy. The bone marrow also showed complete clearance of LD bodies. The patient is on followup for last 8 months and so far is in remission.
Discussion

MCL patients usually present with advanced stage disease. MCL cells are small to medium sized lymphoid cells with notched or irregular nuclei. Diffuse, nodular, confined to mantle zone or a combination of the three could be the histological pattern. Flow cytometry characteristically shows expression of pan B cell markers, surface immunoglobulins, CD5, FMC7 and Cyclin D1 (a protein that stimulates cell growth). Most of the cases of MCL show t(11:14) by conventional cytogenetics or FISH. Prognosis is poor as it has an aggressive course and frequent relapses. It remains incurable with current chemotherapeutic approaches. Median survival time is approximately 3 years. Management options include first line therapy with hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone (Hyper CVAD) with or without rituximab. This regime is intense and very myelotoxic. Other options include CHOP and CVP regimens. Bone marrow transplant following hyper CVAD does not appear superior. Newer agents being tried include Bortezomib which is a proteasome inhibitor.

Leishmaniasis is characterized by a large diversity and complexity in a wide range of clinical presentations and causative species. Visceral leishmaniasis is a systemic disease that is caused by Leishmania donovani complex in the Indian subcontinent. It has a variable incubation period after which majority of infections may remain subclinical. However, common clinical manifestations are fever, weight loss, anorexia with hepatosplenomegaly, lymphadenopathy and pancytopenia. These manifestations may vary because of different host factors and local species in different endemic regions. In any situation the disease remains fatal if untreated.

In an elaborated review studying the aspects of association between leishmaniasis and malignant disorders, Kopterides et al searched electronic databases and evaluated 37 studies involving 44 patients. They described four types of such association: leishmaniasis mimicking a malignant disorder such as lymphoma. Leishmaniasis arising as a difficult to diagnose and treat infection among patients receiving chemotherapy for various malignant disorders, simultaneous diagnosis of leishmaniasis and a neoplastic disorder in the same tissue samples of immunocompromised patients and direct involvement of Leishmaniasis in the pathogenesis of malignant lesions, especially of the skin and mucous membranes. In studying the causative association, Mangoud et al found dysplasia in cells surrounding the leishmanial ulcer. Leishmaniasis adversely affects activation and functioning of macrophages and dendritic cells thus allowing the transformed malignant cells to escape from immune destruction. It is suggested that some remarkable hematological findings which are characteristic for leishmaniasis may resemble some of those with hematological malignancies. In another case report of rare association of Hodgkin's lymphoma in cervical lymph nodes with visceral leishmaniasis, the authors highlighted the mutual immunomodulation resulting...
in presentation of leishmaniasis as an opportunistic infection in a patient of prechemotherapy Hodgkins lymphoma.  
Leishmaniasis usually presents with pancytopenia but in present case there was lymphocytosis due to lymphoma in leukemic phase and the bone marrow also showed lymphoid infiltration. This rare association was a mere incidental coexistence of two disorders or one inciting the other needs to be elucidated but cannot be reliably confirmed.

References