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Case Report
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Splenic Marginal Zone Lymphoma with Concurrent Myelofibrosis: A Case Report

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Abstract

Myelofibrosis associated with lymphoid neoplasms is a rare occurrence with the exception of hairy cell leukemia. Its incidence in splenic marginal zone lymphoma, as we report in this article, has only been reported once in the past.

We report the case of a 62 year old male with splenic marginal zone lymphoma and concurrent myelofibrosis. The diagnosis of splenic marginal zone lymphoma was achieved by a combination of clinical, morphological, and immunohistochemical findings. Increased reticulin staining of the bone marrow, cytopenias and macrocytes on peripheral blood smear supported the diagnosis of myelofibrosis. Features of primary myelofibrosis and other myelodysplastic features including associated genetic mutations were absent.

Further investigation of the association between splenic marginal zone lymphoma and concurrent myelofibrosis may assist in future identification of its effect on disease course and overall prognosis, possibly playing a role in risk stratification and personalized therapy.

Background

Increased fibrosis in the bone marrow is common in several myeloid malignancies but its incidence in lymphoid malignancies is less common. Myelofibrosis is frequently encountered in cases of hairy cell leukemia but is much less common in other lymphoid malignancies [1]. To our knowledge, only one case was reported in Japan, in which Splenic marginal zone lymphoma was complicated by myelofibrosis, associated with bone marrow involvement of lymphoma cells [2]. Lymphoid myelofibrosis represents a particular and rare entity in which medullary fibrosis associated with abnormal lymphoproliferation replaces normal hematopoiesis. Here we report a second case of lymphoid myelofibrosis associated with splenic marginal zone lymphoma in a 62 year old male.

Case Presentation

We report a case of a 62-year-old male, with splenic marginal zone lymphoma. He presented with lymphocytosis, normocytic normochromic anemia and thrombocytopenia. Peripheral smear showed smudge cells, teardrop red blood cells and elliptocytes.

Blood chemistry studies showed elevation of lactate dehydrogenase (LDH) and decreased haptoglobin, but no hemoglobinuria.

There was neither hypergammaglobulinemia nor monoclonal gammopathy. There was significant splenomegaly on imaging.

Bone marrow biopsy obtained from the left iliac crest showed a diffuse infiltrate of small mature B cells (Figure 1) which were positive for CD20 and negative for CD5, CD10, BCL1, DBA44, Annexin A1 and CD123. These findings were consistent with a low-grade B-cell lymphoproliferative disorder. The marrow also showed foci of normal trilineage hematopoiesis with a spectrum of maturing myeloid and erythroid precursors and normal appearing megakaryocytes. The bone marrow also showed a diffuse moderate increase in marrow reticulin (MF-2) (Figure 1).

The patient's enlarged spleen was subsequently removed. The resected spleen weighed 2733g, and measured 30 x 17.5 x 8.5 cm. Pathology on the spleen showed a low grade lymphoma involving the red and white pulp (Figure 1) with an immunophenotype similar to that seen in the bone marrow, supporting a diagnosis of splenic marginal zone lymphoma. Extramedullary

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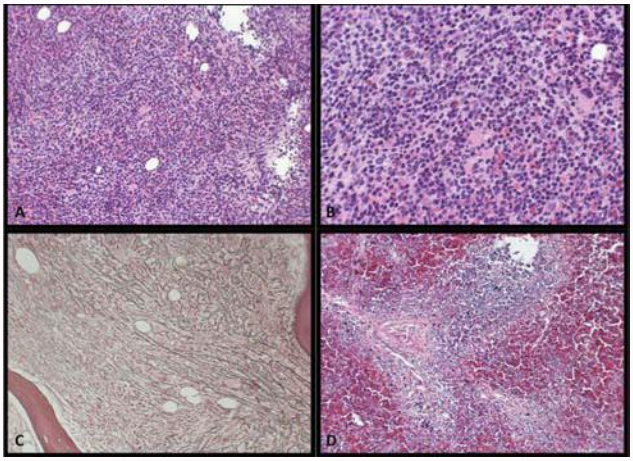

Figure 1: A, B. Bone marrow, H&E, medium and high power, infiltration of the bone marrow by intertrabecular lymphoid aggregates composed of small lymphoid cells. **C.** Bone marrow, reticulin stain, showing diffuse staining with many intersections. **D.** Spleen, H&E, medium power, infiltration of white and red pulp with small lymphocytes.

hematopoiesis was identified. Reticulin fibrosis was not increased in the spleen. Florescence in-situ hybridization analysis was negative for rearrangements of *BCL6* and *MALT1* genes. However, three copies of BCL6 gene signals were observed in 82.5% of the cells studied suggesting the presence of trisomy 3 or gain of 3q in the sample. *BCR-ABL1* fusion was negative. Analysis for the *JAK2* V617F, *JAK2* exon 12 and exon 13, *MPL* and *calreticulin* mutations was negative. Serum TGF-beta were not elevated.

Discussion

In addition to primary and post chronic myeloproliferative disorders, myelofibrosis has been reportedly associated with a large subset of diseases. The association with lymphoproliferative diseases other than hairy cell leukemia however, is rarely described. Rare cases have been reported in multiple myeloma, T-cell lymphoma, and lymphoplasmacytic cell lymphoma [3]. Only a single case has been previously described with splenic marginal zone lymphoma [4].

A literature review from 2009 found an incidence of 6.6% of myelofibrosis associated with lymphoma cases [5]; this was not associated with a specific type of lymphoma, however there was a relatively more frequent association of myelofibrosis with low-grade non-Hodgkin lymphoma. B-symptoms and splenomegaly were frequently present, and the LDH level was frequently elevated at initial presentation. Two patients presented with myelofibrosis prior to the diagnosis of lymphoma. Myelofibrosis was mild to moderate in all cases. *JAK2* V617F was negative in ten cases analyzed, suggesting a distinct etiology from primary myelofibrosis. Response to therapy, relapse rate, disease free and overall survival were not different from lymphoma without myelofibrosis. A direct relation between the tumor cell and myelofibrosis has also been evidenced by concomitant regression of the myelofibrosis with the lymphoma in response to chemotherapy and its reappearance with relapse.

Myelofibrosis has been suggested to arise in cytokines secreted by the tumor cells and PDGF, TGF-beta, VEGF and beta-FGF have been shown to play an important role in the development of secondary stromal proliferation.

TGF-beta levels were reportedly elevated in the plasma of the previously reported patient with splenic marginal zone lymphoma and myelofibrosis, showing positive marrow immunostaining in the lymphoma cell cytoplasm [6].

Interestingly, the spleen in that case also showed diffuse reticulin fibrosis. A karyotype showed t (9;14)(p13;q32) and rearrangement of the immunoglobulin JH gene by Southern blot was demonstrated.

Similarly, our case showed a low grade B-cell neoplasm with B-symptoms, massive splenomegaly and elevated LDH. Anemia, thrombocytopenia and leukoerythroblastic features were present. The degree of myelofibrosis was similar and *JAK2* V617F mutation was negative, as were *JAK2* exon 12 and exon 13, *MPL* and *calreticulin* mutations, which are commonly seen in myelofibrosis associated with myeloproliferative disorders. The negative *BCR-ABL1* fusion was negative, excluding myelofibrosis associated with CML.

TGF-beta serum levels were not elevated; however, other cytokines secreted by tumor cells could be involved in the pathogenesis of myelofibrosis associated with this case.

Treatment response remains to be seen in the patient presented here. The small number of described cases makes it difficult to assess whether myelofibrosis affects treatment response, however, myelofibrosis can lead to significant morbidity, and further investigations should be performed to allow identification of patients at risk.

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