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PRIMARY MYELOFIBROSIS WITH CONCURRENT PRECURSOR T-CELL LYMPHOBLASTIC LYMPHOMA OF THE SPLEEN IN 26-YEAR OLD PATIENT

Matjaz Sever¹, Jeffrey L. Jorgensen², Inga Gurevich², Mariana Pinheiro¹, and Srdan Verstovsek¹

¹Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX

²Department of Hematopathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

Abstract

Primary myelofibrosis (PMF) is rare myeloproliferative disease usually diagnosed in older patients. Reports of a concurrent acute lymphoblastic leukemia or lymphoma in PMF are rare. We present a case of a 26-year old patient with PMF and precursor T-cell acute lymphoblastic lymphoma of the spleen and lymph nodes. The patient was treated with splenectomy and allogeneic stem cell transplantation (allo-SCT) and remains in remission from both PMF and lymphoblastic lymphoma 6 months after the full strength allo-SCT. To our knowledge this is second report of concurrent PMF and precursor T-cell acute lymphoblastic lymphoma, and first report of a successful treatment for both underlying conditions.

Keywords

primary myelofibrosis; precursor T-cell lymphoblastic lymphoma; allogeneic stem cell transplantation

Introduction

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterized by abnormal bone marrow megakaryocyte proliferation with reticulin and collagen fibrosis, leukoerythroblastosis, anemia, increased level of serum lactate dehydrogenase and splenomegaly (1). It is a rare condition with a median age of ~65 years at diagnosis (2) and an average life expectancy of ~5–7 years, approaching 15 years in younger patients with good prognostic factors. Transformation to acute myeloid leukemia is a cause of death in 8%

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Address correspondence to: Srdan Verstovsek, M.D., Ph.D., UT MD Anderson Cancer Center, Department of Leukemia, Unit 428, 1515 Holcombe Blvd. Houston, TX 77030, Telephone: 713-745-3429, Fax: 713-794-4297, sverstov@mdanderson.org.

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to 23% of patients within 10 years after establishing the initial diagnosis of PMF (3). However, there are reports of patients that developed transformation to acute lymphoid leukemia (4–6) or developed concurrent lymphoma, such as diffuse large cell non-Hodgkin lymphoma (NHL) (7–10), or chronic lymphocytic leukemia (11). To our knowledge there is only one report describing precursor T-cell lymphoblastic lymphoma (LL) in a PMF patient, who was treated with chemotherapy but later developed acute myeloid leukemia and died (12). Herein, we present a report of the successful treatment of a patient with PMF and precursor T-cell LL with allogeneic stem cell transplantation (allo-SCT).

Case report

A 26 year-old man with an unremarkable past medical history presented with a two month history of early satiety, left-sided abdominal pain, lightheadedness, tiredness and weight loss. On physical exam he had an enlarged spleen at 17 cm below the left costal margin. His blood cell count revealed white blood cell count of $28.3 \times 10^9/L$ with 10% monocytes, 23% eosinophils, 6% metamyelocytes, 1% promyelocytes, and 1% blasts; hemoglobin 8.7 g/L with anisocytosis, poikilocytosis, polychromasia and ovalocytosis; and a platelet count of $20 \times 10^9/L$. His lactate dehydrogenase level was elevated at 746 IU/L. A bone marrow biopsy (Figure 1) showed 100% cellularity with left-shifted granulopoiesis, atypical megakaryopoiesis, eosinophilia and extensive interstitial reticulin fibrosis of grade 3 (scale 0–4). The findings supported a diagnosis of a chronic myeloproliferative neoplasm with extensive fibrosis, consistent with PMF. Cytogenetic evaluation showed a diploid male karyotype. No BCR-ABL transcript or JAK2^{V617F} mutation were detected by polymerase chain reaction testing. As a part of the initial work-up, the patient's brother was found to be HLA-identical and thus a possible donor for SCT. This was then recommended as an initial therapeutic approach.

Prior to SCT a splenectomy was performed with resection of enlarged perihilar lymph nodes. Histological examination of the spleen showed marked fibrosis, with focally preserved white pulp architecture and very extensive extramedullary hematopoiesis, consistent with PMF (Figure 2). One perihilar lymph node showed alteration of the architecture by an ill-defined, paracortical and perisinusoidal infiltrate of neoplastic cells, which were small in size with rounded to slightly irregular nuclear contours, slightly open nuclear chromatin, one to three indistinct nucleoli and scant cytoplasm (Figure 3). Specimens from the left and right liver lobe were normal. Flow cytometry of the spleen and lymph node revealed a population of immature T cells, positive for CD1a, CD2, cytoplasmic CD3, CD4, CD5, CD7, CD8 partial, CD45 moderate to bright, and TdT. They were negative for surface CD3 and myeloperoxidase. The immature T cells accounted for 60% of total lymph node cells and 2–3% of total cells in the spleen. Immunohistochemical stains on a lymph node confirmed these findings, highlighting a neoplastic infiltrate positive for CD3 and TdT, with a high Ki-67 proliferation index of 80–90% (Figure 4). The overall findings supported the diagnosis of precursor T-cell acute LL, with extensive involvement of the lymph node and minimal involvement of the spleen. In light of these findings, additional immunohistochemical stainings of formalin-fixed tissue sections from the bone marrow biopsy were done: CD3 and CD20 highlighted interstitial T- and B-lymphocytes, respectively, CD1a was positive in very rare, scattered small lymphoid cells, and TdT was

negative. Review of flow cytometry results from the initial work up did not demonstrate presence of abnormal T-cell population. Therefore, the findings were not supportive for involvement of the bone marrow by a lymphoproliferative disease. T-cell receptor rearrangement PCR was not done, however. The patient had no signs of peripheral lymph node enlargement and a chest x-ray was normal. PET scan or cerebrospinal fluid examinations were not done. The case was presented at the clinico-pathological conference of the Bone Marrow Transplant Department. In light of a negative bone marrow for precursor T-cell LL, the decision was made to proceed with treatment directed towards generalized myeloproliferative disorder.

Within one month from splenectomy the patient underwent a reduced intensity peripheral blood allo-SCT from his brother (a reduced intensity busulfan and fludarabine conditioning regimen was used). The post transplant course was uneventful without any graft versus host disease (GVHD) while tacrolimus was administered. Five months after the transplant he developed secondary graft failure with pancytopenia and tacrolimus was tapered off. He required hospitalizations because of febrile neutropenia and became red blood cell and platelet transfusion dependent. Seven months after the first transplant the patient received a second allo-SCT from his brother, with standard of care busulfan and cyclophosphamide conditioning regimen (full strength). GVHD prophylaxis was initiated with methotrexate and continued with tacrolimus. One month after the procedure he experienced local skin GVHD which resolved after local corticosteroid application. At last follow up 6 months after the second transplant and 17 months since the initial diagnosis, the patient's peripheral blood cell count was normal. Bone marrow biopsy showed 20% cellularity with trilineage hematopoiesis, a decreased M:E ratio (1:2) and no evidence of PMF or aberrant T-cell population.

Discussion

PMF is very rare hematologic neoplasm in young patients. The patient described here presented with a short history of constitutional symptoms and symptoms related to enlarged spleen which are typical for PMF. Laboratory results and histologic examination of a bone marrow biopsy all confirmed PMF, without any signs of other concurrent hematological disease. Because of the patient's age, allo-SCT was considered to be the best treatment option for long-term disease control and possible cure, especially since an HLA-matched sibling donor was readily available. The reduced intensity conditioning regimen can result in prolonged survival with its low transplantation related mortality (13).

As the patient had marked splenomegaly with related symptoms, a splenectomy was performed prior to SCT. The finding of a precursor T-cell LL in the spleen and hilar lymph node was an unexpected finding. This is a very rare condition on its own. Recent multicenter analysis of 1314 T-cell lymphoma patients identified only 12 patients with precursor T-cell LL (14). Our search of the literature revealed only one similar case to ours (12), with concomitant PMF and precursor T-cell LL. Treatment for precursor T-cell LL usually involves intensive induction therapy, like hyperCVAD (15), with optional allo-SCT in first remission (16). While consideration might have been given to treat our patient first with at least one cycle of intensive chemotherapy directed toward T-cell LL, since there was no

evidence for remaining precursor T-cell LL after splenectomy, he proceeded directly with allo-SCT. The patient currently remains in remission from both PMF and LL, 6 months after full strength allo-SCT.

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Figure 1. Bone marrow core biopsy showing A) hypercellular marrow with megakaryocytic hyperplasia (H&E x500) including some atypical forms, and B) fibrosis score 3 (out of 4; reticulin stain x200).

Figure 2.
Spleen showing foci of extramedullary hematopoiesis in the red pulp (H&E x500). No significant blast infiltrate was identified.

Figure 3.
Lymph node with foci containing sheets of monotonous cells with partially open chromatin (H&E x500).

Figure 4. Lymph node showing T-lineage cells (A: CD3 immunostain x400), demonstrating a lymphoblastic phenotype (B: TdT immunostain x400). Both pictures show the same area as in Figure 3.