Evolution of Marginal Zone Lymphoma Towards Myeloproliferative Disorder: A Case Report

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Introduction
Lymphoma is a hematologic malignancy characterized by nodal or extranodal malignant infiltration by monoclonal lymphoid cells (B lineage cells in 70% of the cases). Its etiology is not precisely known. Prolonged life expectancy has resulted in increase of the disease incidence. Marginal zone lymphoma is a low-grade small B-cell lymphoma incorporated in the World Health Organization classification.¹,² Low-grade lymphomas usually demonstrate a characteristic natural history with multiple remissions and relapses.

Myeloproliferative syndromes (MPS) are characterized by clonal proliferation of one or more hematopoietic progenitor cell lines such as granulocytes, erythrocytes, megakaryocytes, or mastocytes. These syndromes include chronic myeloid leukemia, polycythemia vera, essential thrombocytthemia, myelofibrosis, chronic eosinophilic leukemia (hypereosinophilic syndrome), chronic neutrophilic leukemia, and systemic mastocytosis.³ They are thought to arise from malignant transformation of hematopoietic stem cells.⁴

Here, we present a case report of a patient followed and treated for marginal zone lymphoma that evolved to a myeloproliferative disorder.

Case Report
On April 2005, a 75 year-old woman presented with petechiae and ecchymosis localized on both legs. She was in a good general state. Physical examination revealed no evidence of extramedullary tumors. There was no positive point in her past history. She had 10 gestations, 10 deliveries with 8 living children. Laboratory data showed normal hemoglobin (Hb=12g/dL), leukocytosis (23000/µL) with 57% lymphocytes (12540/µL), and thrombocytopenia (41000/µL). Bone marrow evaluation showed a rich marrow with rare megakaryocytes. Normoblastic and granular lineage were well represented with 10% lymphoid cells. Flow cytometric immunophenotyping of these lymphoid cells demonstrated a monoclonal B cell population expressing the following markers: CD19+, CD5-, CD25+, and Lambda+ (figure 1). Due to CD103 negative expression we excluded hairy cell leukaemia. The immunophenotypic feature was in favour of a marginal zone lymphoma (stage IV).

Protein electrophoresis revealed a monoclonal IgM macroglobulinemia, which is usually found in 20% of marginal zone lymphoma patients. Renal, hepatic, and coagulation studies were normal. HIV, and hepatitis B and C serology tests were negative. Blood group was A+. Thoracic, abdominal, and pelvic computed tomography (CT) scans were normal. The echocardiogram was normal, with 70% ejection fraction.

Three poor prognostic factors were found (age, hemoglobin level, and stage IV). Considering the patient's age, we decided to start four cycles of
mini-CHOP (Cyclophosphamide, Vincristine, Doxorubicine, and Prednisone). Treatment was started on January 2006. She developed an important hematologic toxicity during the 3rd cycle; severe anemia and leukopenia requiring transfusion and growth factors.

The situation did not change until January 2007; during this period the patient received supportive care (7 units of packed red blood cells). On February 2007, the general state was worsened and physical examination revealed a stage III splenomegaly and hepatomegaly. Laboratory data revealed anemia (Hb=10.8 g/dL), leukocytosis (25000/µL) with 62% neutrophil and 38% immature granulocytes (promyelocyte=1%; myelocyte=12%; metamyelocytes=25%) and platelet count of 198000/µL. Direct Coombs test was negative. Bone marrow evaluation showed a large population of

**Figure 1.** Flow cytometric immunophenotyping: Gating on CD19+ population (A), CD5- and CD10- (B), CD22+ (bright) and CD25+ (C), Kappa- and Lambda+ (D).

**Figure 2.** Blood smear revealing immature granulocytes.
megakaryocytes, as well as, hyperplasia of the granular lineage (80%) with all stages of maturation. Erythroblastic lineage represented 18% and lymphocytes only 2% of nucleated cells.

We decided to provide the patient just with supportive care such as blood transfusion, if needed. On May 2007, complete blood count (CBC) revealed leukocytosis (80000/µL) with 50% neutrophils, 40% immature granulocytes (promyelocytes, myelocytes, and metamyelocytes), and 5% acidophilic normoblasts (figure 2).

The platelet count was 300000/µL. Anemia was still present (Hb=8.8g/dL) requiring periodic blood transfusion. Bone marrow showed an increased cellularity with fibrosis (figure 3).

Indirect Coombs test was negative. Splenomegaly became larger and reached the iliac crest. Flow cytometric evaluation showed a population of polyclonal B cells (figure 4).

Cytogenetic study was negative for t (9;22). BCR-ABL chimeric gene was not found on molecular biology tests. The most probable diagnosis was idiopathic myelofibrosis. We decided to prescribe...
Hydroxuurea and corticosteroids. On October 2007, splenic radiotherapy was performed in a 4-week course, at the same time, we tapered corticosteroids gradually. On March 2008, the patient was in a good general state with stage II splenomegaly and no hepatomegaly. Hemoglobin level was 10.0g/dL. White blood cells (WBC) count was 10000/µL with 83% PMN, 3% lymphocytes, 7% immature granulocytes, and 7% normoblasts. Platelet count was 437000/µL. The patient did not receive transfusion anymore. On January 2009, the patient died of cardiac attack.

Discussion

In the literature, a case of BCR-ABL negative chronic myeloproliferative disorder followed by acute lymphoblastic leukemia was reported, in whom the evolution was the result of complex chromosomal mutation.5 Another case report described an acute lymphoblastic leukemia without a Philadelphia chromosome following a chronic myelogenous leukemia (CML) with a Philadelphia chromosome.6

Lungeanu et al. described the relationship between complexity of chromosomal changes and disease aggressiveness in myeloid and lymphoid disorders.7 They reported on four cases with unusual chromosomal abnormalities identified at the first presentation, among over 100 patients with acute and chronic myeloid and lymphoid leukemia cytogenetically investigated. The complexity and nature of cytogenetic abnormalities were in direct relationship with the disease evolution.

Evolution of malignant lymphoma in agnogenic myeloid metaplasia was reported.8 Two young Arab patients were described in whom malignant lymphoma was developed after less than 1 year of agnogenic myeloid metaplasia diagnosis. These observations demonstrate closed relationship between myeloproliferative and lymphoproliferative syndromes.

Only one report has previously described the evolution of lymphoplasmocytic lymphoma to chronic myelocytic leukemia.9 It was a 62 year-old woman presented in November 1999 with anemia and thrombocytopenia. Bone marrow smear showed infiltration by lymphoid cells, in which immunophenotyping established the diagnosis of lymphoplasmocytic lymphoma. Monoclonal IgM dysgobulinemia also existed in the patient. She had karyotype abnormality t(9;14). On May 2003, evolution was toward CML (positive BCR-ABL). The authors described the hypothesis that chromosome 9 might undergo a second translocation that may explain this evolution.

In our case, karyotype was normal at the time of initial diagnosis, lymphocytosis and monoclonal IgM existed but no splenomegaly was observed. It was probably due to a complex oncogenic event occurring at the level of an early progenitor (lymphoid and myeloid).

Other similar observations may be helpful to better understand the mechanisms of such unusual evolutions.

References