Annals of Hematology & Oncology

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Austin Publishing Group

Case Report

A Case of Splenic Marginal Zone Lymphoma with Mismatched Morphology and Phenotype, Karyotype and Clinical Course

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Received: November 06, 2014; **Accepted:** January 05, 2015; **Published:** January 07, 2015

Abstract

Background: Splenic marginal zone lymphoma is a rare chronic lymphoproliferative neoplasm with a very indolent clinical course and a non-characteristic phenotype and karyotype. Peripheral blood morphology can be the first clue to the diagnosis.

Methods: Here, we report a case of a patient with splenic marginal zone lymphoma, alive 20 years after initial diagnosis, with very atypical and immature lymphocytes in peripheral blood smear since then.

Results: Peripheral blood phenotype and karyotype and pathological analysis of splenectomy sample, as well as the clinical evolution were compatible with splenic marginal zone lymphoma. Conversely, peripheral blood morphology was, from the start, atypical and suggestive of a high-grade lymphoproliferative disorder.

Conclusion: Integrating all clinical and laboratory data is essential to make an appropriate diagnosis and guide the therapeutic options offered to patients.

Keywords: Splenic marginal zone lymphoma; Atypical morphology; Indolent lymphoma

Abbreviations

MZL: Marginal Zone Lymphoma; MALT: Mucosa-Associated Lymphoid Tissue; SMZL: Splenic Marginal Zone Lymphoma

Case Presentation

A 65 year-old woman was sent for hematologic evaluation in 1994 because of the incidental finding of peripheral blood lymphocytosis. She was asymptomatic. On physical examination splenomegaly, without hepatomegaly or any enlarged lymph nodes, was palpable. The peripheral blood smear revealed large-sized cells, with a wide nucleus occupying most of the cell space, with immature and reticulated chromatin, and one or more conspicuous nucleoli. In some cells the nucleus adopted an irregular form. The cytoplasm was basophilic without any granularity (Figure 1). However, phenotypical exam of the lymphocytes was compatible with SMZL and peripheral blood cytogenetic analysis revealed a complex karyotype, including a trisomy of chromosome 3 and an imbalanced traslocation involving chromosome 7q36. Methacrylate-embedded bone marrow showed a nodular and paratrabecular pattern of infiltration by small, mature and monomorphic lymphocytes. The diagnosis of SMZL was made.

Tests at diagnosis are shown on Table 1.

The clinical course has also been characteristic of indolent lymphoma. For 20 years she has been followed up in the outpatient setting. She has been admitted on 6 occasions, 3 of them because of B symptoms, which led to the administration of chemotherapy, and the other 3 because of pneumonia. She also received a therapeutic splenectomy in 2001. The pathological analysis revealed infiltration by a chronic lymphoproliferative disease positive for CD20 and CD79a, compatible with SMZL. Overall, the patient has been treated for her lymphoproliferative disorder 5 times, 4 of them with polychemotherapy (3 of those including rituximab), and has achieved as many clinical complete responses, i.e., normalization of the blood counts and disappearance of splenomegaly and any enlarged lymph nodes. Tests performed before the start of each course of chemotherapy are also shown in Table 1.

In 2013 she was admitted because of delirium and worsening of her functional and cognitive impairment secondary to pneumonia, which resolved favorably with antibiotics. Lymphocytosis (16.6x10e9/L) and mild anemia (hemoglobin 117g/L) were noted, and there were no enlarged lymph nodes. Peripheral blood lymphocytes still showed the same morphology (Figure 2) and phenotype observed at diagnosis. The patient is currently alive and asymptomatic.

Discussion

MZL is a low grade chronic lymphoproliferative disorder arising from post-germinal center marginal zone B cells. It encompasses three entities, depending on the affected organ; MALT lymphoma, SMZL and nodal marginal zone lymphoma.

SMZL is often diagnosed incidentally, either because of cytopenias, splenomegaly or detection of clonal peripheral blood lymphocytosis with a compatible phenotype, which can be seen in more than half of cases (SMZL with villous lymphocytes) [1]. Enlarged lymph nodes are rarely seen. Although diagnosis is traditionally made by histological examination of the spleen, bone marrow histology along

Citation: Sorigue M, Juncà J, Gassiot S, Navarro JT, Mate JL and Millà F. A Case of Splenic Marginal Zone Lymphoma with Mismatched Morphology and Phenotype, Karyotype and Clinical Course. Ann Hematol Oncol. 2015;2(1): 1016.

Table 1: Physical findings, analytical findings and treatment during the course of the disease.

	September 1994	May 25th, 1999	August 8th, 2001	March 5th, 2002	September 9th, 2005	October 29th, 2007	December 10th, 2013
Splenomegaly	4cm below costal border	15cm below costal border	6cm below costal border	Not applicable			
Hepatomegaly	Not palpable	6cm below costal border	Not palpable				
Lymph nodes	None palpable						
CT scan	Splenomegaly.	Splenomegaly, hepatomegaly and enlarged nodes in splenic hilum (1-2cm)	Splenomegaly	No findings			
Hemoglobin (g/L)	120	87	95	136	146	142	117
Lymphocyte count (x10e9/L)	28	13.5	24.3	38.1	139	43	16.6
LDH	Normal						
β2M (mg/L)	2.5	4.4	4.3		3.1	2.6	7.8
IgM (mg/dL)	498	1590				450	2120
HCV, HIV	Negative						
Phenotype	CD19+, CD20+, CD22+, DR+, CD5-, CD10-, CD23-						
Cytogenetic findings	48, XX, +1, del(1)(p32), +3, del(3)(p21), der(7)t(1;7)(p32;q36)[20] (peripheral blood)		48, XX, +1, del(1)(p32), +3, del(3)(p21), der(7)t(1;7)(p32;q36)[2] (spleen)				
Bone Marrow biopsy	Evidence of chronic lymphoproliferative disease	Evidence of chronic lymphoproliferative disease	Not repeated				
Treatment indication		B symptoms	B symptoms	B symptoms	Progressive lymphocytosis	B symptoms	
Treatment	None	CNOPx6	Splenectomy	RCVPx6	RCVPx6	RCVPx6	

HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; CNOP: Cyclophosphamide, Mitoxanthrone, Vincristine, Prednisone; RCVP: Rituximab, Cyclophosphamide, Vincristine, Prednisone; Normal laboratory values: Hemoglobine 120-160g/L; lymphocyte count: 1.5-3.5x10e9/L; β2M (mg/L) <2.4mg/L; IgM<230mg/dL.

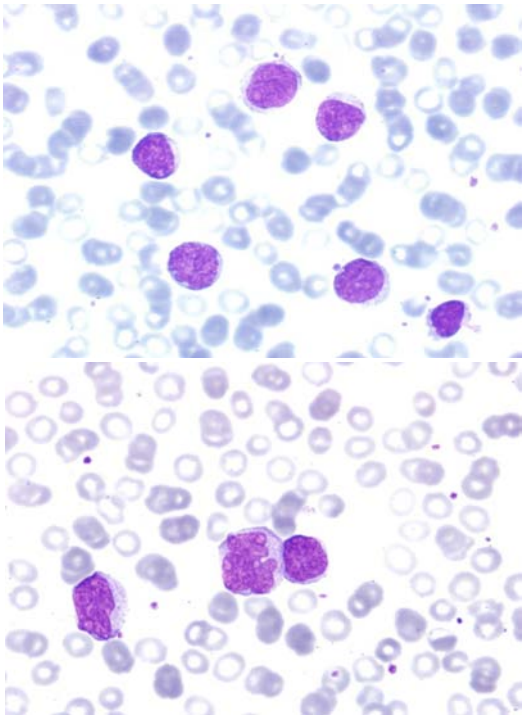

Figure 1: Peripheral blood smear at diagnosis in 1994. Atypical and large lymphocytes showing convoluted nuclei and fine chromatin. (May-Grünwald Giemsa x40 and x100, top and bottom).

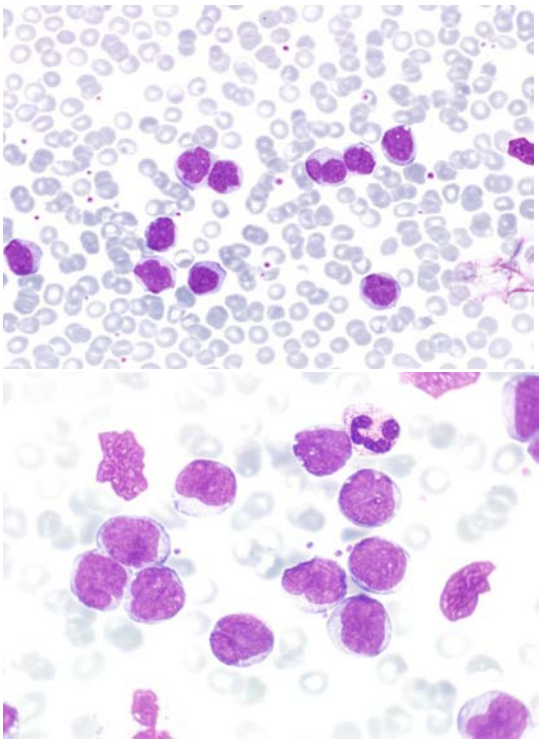

Figure 2: Peripheral blood smear in 2005 where the same lymphocytes could be seen (May-Grünwald Giemsa, x40 and x100, top and bottom).

with a suggestive phenotype are considered enough to establish it [2-4]. However, some groups have made the diagnosis with peripheral blood lymphocyte morphology and phenotype [5-7].

On peripheral blood smear, SMZL typically presents with middle-sized, mature and villous lymphocytes. Unlike the villous cells of hairy-cell leukemia, lymphocytes in SMZL are smaller, their villi are shorter and polar, and their nuclei contain a more condensed chromatin [8].

The phenotypic exam of all subtypes of MZL is characterized by the expression of B-cell antigens and surface immunoglobulin, along with lack of expression of CD5, CD10, CD43 and CD103 although CD5 is occasionally positive [4,9]. It is currently unknown whether CD5 positivity confers a different clinical course [10].

Cytogenetic abnormalities are frequently found in SMZL. The most common are gain of 3q and deletion of 7q [9,11]. The characteristic translocation seen in MALT lymphoma, t (11;18) (q21;q21), is always negative in SMZL [9].

Diagnosis has classically been established by microscopic examination of splenic tissue, where small, mature lymphocytes are seen surrounding or invading the germinal centers in the white pulp and infiltrating the red pulp. Differential diagnosis includes other low-grade lymphoproliferative disorders in the rare cases in which they affect the spleen primarily. These include: follicular lymphoma, which typically presents with preserved or only slightly altered germinal centers in which centrocytes (i.e., small, mature and cleaved lymphocytes) often predominate; mantle cell lymphoma, which presents with mature lymphocytes with a particularly irregular nucleus and almost always cyclin D1 translocation; and small lymphocytic lymphoma, which presents with small lymphocytes with hyper condensed chromatin, a high nucleus-to-cytoplasm ratio and variably effaced germinal centers.

At the time of diagnosis SMZL may not require treatment, particularly if the patient is asymptomatic. When therapy is required, splenectomy or alkylating agents have historically been the agents of choice although rituximab seems to have improved Reponses and time to next treatment [12].

Like other indolent lymphomas, MZL is generally considered not curable, except when treated with allogeneic stem cell transplantation. Nevertheless, the time between relapses is often measured in years and patients' quality of life is usually preserved [5,13,14], even though a small percentage of cases do follow a more aggressive course [1,15,16] or undergo transformation to diffuse large B cell lymphoma [6,7,17].

In the case reported here there was a clear mismatch between, on the one hand, a very indolent clinical course and a phenotype and karyotype suggestive of marginal zone lymphoma and, on the other hand, a very atypical morphology. Both morphological and cytometric exams were repeated several times during the course of the disease.

The patient is still alive 20 years after initial diagnosis, having achieved complete clinical responses with every course of chemotherapy. Although, typically, relapses in indolent lymphomas are increasingly frequent with each successive therapeutic course, this has not been the case in our patient. In light of recent evidence [15,18,19] this might be partly explained because of the addition of rituximab in the last three courses of therapy.

In clinical practice it is not unusual to find a patient where not all clues point to the same diagnosis. This case underscores the need for a comprehensive hematological evaluation, taking into account cytology, cytometry and cytogenetics to reach the proper diagnosis and offer the most appropriate therapeutic options.

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Ann Hematol Oncol - Volume 2 Issue 1 - 2015
ISSN : 2375-7965 | www.austinpublishinggroup.com

Citation: Sorigue M, Juncà J, Gassiot S, Navarro JT, Mate JL and Millà F. A Case of Splenic Marginal Zone Lymphoma with Mismatched Morphology and Phenotype, Karyotype and Clinical Course. Ann Hematol Oncol. 2015;2(1): 1016.