Malignant Lymphomas

Splenic marginal zone lymphomas with peripheral CD5 expression

We report 4 cases of splenic marginal zone lymphoma (SMZL) with peripheral CD5 positive, B-cell lymphocytosis. This unusual immunophenotypic discordance raises dilemmas in the diagnostic approach of these patients. In addition, this association may be related to a more aggressive clinical course, as 3 out of 4 of our patients died from progressive disease.

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Splenic marginal zone lymphoma (SMZL) is a B-cell neoplasm with an indolent clinical course, characteristic histologic pattern of involvement and a non-specific immunophenotypic profile. The lymphomatous cells express surface immunoglobulin of IgM and IgD class, are CD19, CD22, CD20, CD79a positive and CD5, CD10, CD23, CD43, cyclin D1 negative.[1,2] This immunophenotype differentiates SMZL from follicular and mantle cell lymphomas (MCL), as well as from B-chronic lymphocytic leukemia (B-CLL). However, the lack of specific immunophenotypic markers for SMZL creates problems for the differential diagnosis of SMZL from immunocytoma/lymphoplasmacytic lymphoma. Moreover, CD5 expression has been reported in histologically typical marginal zone B-cell lymphomas.[3,4] This aberrant CD5 expression has been thought to be a marker for early dissemination and aggressive disease in some patients.[3]

We studied four patients with splenomegaly and lymphocytosis. Peripheral blood smears showed monocytoid B-cells, centrocyte-like cells and varying percentages of villous lymphocytes (Figure 1A). Flow cytometry of the peripheral blood revealed an IgMDκ, $CD19^+$, bright $CD20^+$, $CD79b^+$, $CD79a^+$ and $FMC7^+$ B-cell population, co-expressing the CD5 molecule in all 4 cases. None of the cases expressed CD23, CD43, CD10, CD103 or cyclin D1. Bone marrow biopsies revealed a lymphomatous infiltration by small lymphocytes, which ranged from 40-70%. In all cases the pattern of distribution was mainly intrasinusoidal combined, to a lesser extent, with interstitial infiltration, a pattern which has been considered suggestive of possible SMZL.[1]

Immunohistochemically the cells were identified as $CD20^+$, $CD5^+$, $CD10^-$, cyclin D1-, and $CD23^-$. Subsequently, all patients underwent diagnostic and therapeutic splenectomy which established the diagnosis of SMZL according to the criteria of the WHO classification.[5] The reactive germinal centers were replaced by small round lymphocytes with effacement of the normal follicle mantle. This zone was fused with small to medium size lymphocytes, resembling marginal zone cells (Figures 1B, C). The immunophenotype on frozen and paraffin-embedded sections was CD5 negative using BL1a (Immunotech) and 4C7 (Ventana) monoclonal antibodies, respectively. In each case, small reactive T lymphocytes were strongly positive for CD5, CD43 and CD45RO and served as an internal positive control. No cyclin D1 expression was detected. One year later, three patients (cases #1, 3 and 4) developed, massive lymphadenopathy. Lymph node and bone marrow biopsies from these patients were characterized by clusters of $CD20^+$, $CD5^+$ large lymphocytes. The patients had no clinical remission following treatment with CHOP and died from infection. The demographic, clinical, and serological characteristics as well as the outcome of the patients are illustrated in Table 1. We describe 4 cases of histologically typical SMZL with aberrant CD5 positive expression on peripheral and bone marrow B-lymphocytes but CD5 negativity on splenic specimens. The lack of cyclin D1 expression in all cases was strong evidence against a diagnosis of MCL. Moreover the absence of CD23 and the strong expression of CD22, FMC7, CD79b and CD79a (ZL 7.4) excluded B-CLL. In none of these cases was an intravascular pattern of infiltration observed.[6] The discordance between CD5 negative splenic and CD5 positive peripheral as well as bone marrow lymphomatous cells has already been reported in isolated

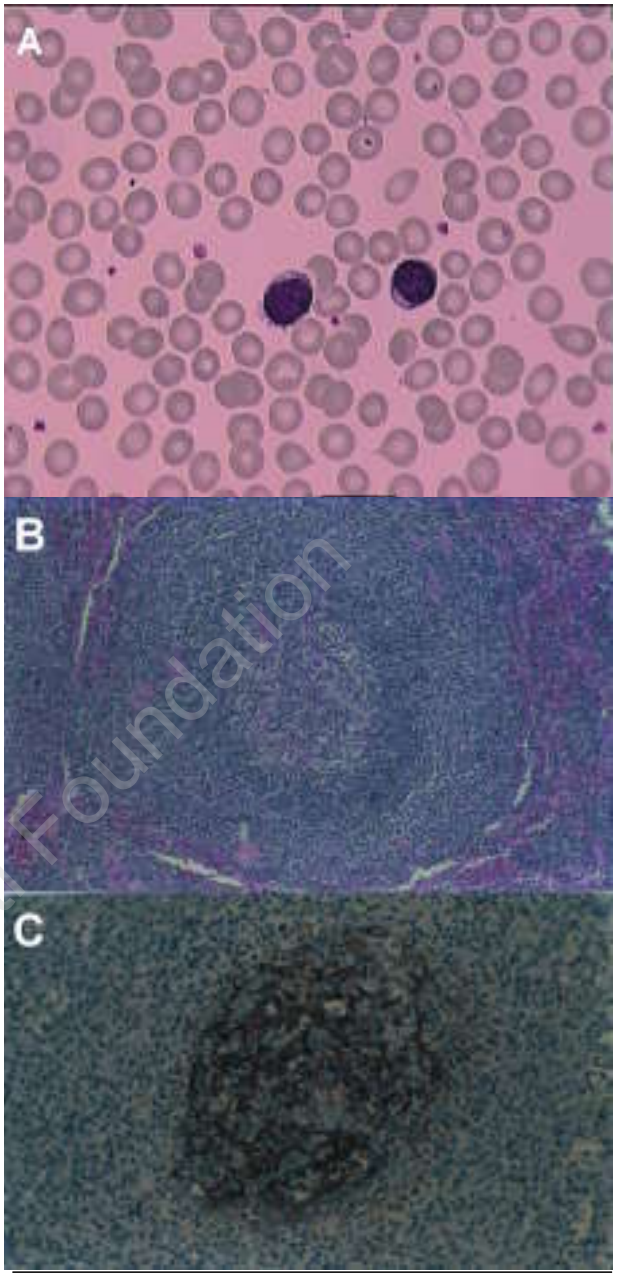

Figure 1A. Lymphocytes with polar villous projections in the peripheral blood of case #4 (May-Grünwald Giemsa stain ×100). B. Splenic biopsy of the same patient: splenic marginal zone lymphoma showing infiltration of white and red pulp. (Hematoxylin-eosin stain ×400). C. Lymphomatous cells surrounding residual germinal centers (anti-CD21 staining × 630).

Table 1. The demographic, clinical, and serological characteristics and outcome of the patients.

	Patient #1	*Patient #2*	*Patient #3*	*Patient #4*
Age (years)	72	44	68	75
Sex	Male	Female	Female	Female
Hb (g/dL)	14.4	13.7	12.1	10,9
B lymphocytes/($\times 10^9$)L	16.6	13.5	40.5	20.1
Platelets ($\times 10^9$)	143.000	114.000	95.000	110.000
Monoclonal band	-	-	IgMκ	-
Hepatomegaly (cm)	4	-	4	5
Splenomegaly (cm)	17	12	20	22
Spleen weight (g)	2.250	1.770	2.725	2.900
Splenic hilum lymphadenopathy	+	-	+	+
Peripheral lymphadenopathy	-	-	-	-
Bone marrow infiltration	+	+	+	+
Therapy	CHOP	CHOP	None	CHOP
Autoimmune manifestations	-	-	- AHA	Hashimoto's thyroiditis
Outcome	PG-death	SD	PG-death	PG-death
Follow-up (years)	1	5	1	2

AHA: autoimmune hemolytic anemia; SD: stable disease; PG: progressive disease; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisolone.

cases of SMZL.[7,8] Differences in the sensitivity of CD5 detection the techniques used (flow cytometry versus immunohistochemistry) or the intensity of the CD5 expression in different tissues have been implicated. However this phenomenon could also be attributed to microenvironmental homing factors on circulating B cells, according to the differentiation hypothesis of CD5+ B-cell ontogeny.[9] In our patients the CD5+ tumor cells could perhaps have corresponded to CD5 negative tumor cells that began to express CD5 after migrating from the spleen to the bone marrow microenvironment, either through antigen-driven processes or as a result of inappropriate B-cell responses to the local cytokine network.

Three out of our four CD5+ SMZL patients died from progressive disease, while 17 other patients with classic CD5 negative SMZL followed up in our department had an indolent disease. This suggests that neoplastic cells become capable of tumor progression after acquisition of the CD5 marker.[10] However, the co-existence of more than one different B-cell clone could not be excluded since molecular studies of the involved tissues were not performed.

In summary, SMZL may be associated with CD5-positive peripheral blood lymphocytosis. Clinicians and pathologists must be aware of this unusual association in order to reach a correct diagnosis. Furthermore, this disease, unlike CD5-negative SMZL, seems to have an aggressive clinical course. On the other hand, the heterogeneity of SMZL has been clearly illustrated by several reports in this journal.[11-14]

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