THE NEW ARMENIAN
MEDICAL JOURNAL
Vol. 3 (2009), N 3, 29 - 34
www.ysmu.am

MYELOPROLIFERATIVE PATTERN OF BONE MARROW IN SPLENIC MARGINAL ZONE LYMPHOMA

Kanayan A., Mkhitaryan A.

Department of Clinical Pathology, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

Abstract

Two cases with splenic marginal zone B-cell lymphoma (SMZL) clinically presented as chronic idiopathic myelofibrosis (CIM) during the first, initial laboratory investigation are described: case No.1 male 73-year-old, case No.2 female 55-year-old. The morphology of the bone marrow of these two cases demonstrated peritrabecular coarse to delicate foci of fibrosis. Small areas of haematopoetic islands as well as megakaryocytes and micromegakaryocytes with dysplastic features were surrounded by the connective tissue. The marrow showed a marked positive reaction for CD15 and scattered CD79a lymphoid cells. There were no evidences of lymphoid infiltration of the bone marrow. Second bone marrow trephine biopsy investigation of the case No.1 demonstrated acompletely different picture of nodular lymphocytic infiltration with lymphoid aggregates formation, which were positive for CD20 and negative for CD15. Splenectomy specimens of two cases finally demonstrated SMZL. Such cases are extremely rare and need further investigantion.

Keywords: bone marrow, myelofibrosis, splenic marginal zone lymphoma.

Introduction

The term "marginal zone" (MZ) was initially proposed by T. Snook to describe the pale corona surrounding the mantle zone of splenic follicles [*Snook T., 1964*]. The MZ can also be observed in mucosa-associated lymphoid tissues (MALT), such as tonsils and Peyer's patches, in hyperplastic follicles arising in the gastrointestinal tract (follicular gastritis due to *Helicobacter pylori* infection), and in autoimmune disorders, such as thyroiditis or sialadenitis [*Saacson P., Wright D., 1984*]. The MZ can occasionally be observed in lymph nodes, particularly in those draining MALT, such as the cervical lymph nodes draining the tonsils and the mesenteric lymph nodes [*Van den Ord J., 1986*].

Lymphomas consisting of cells thought to be derived from MZ B-cells were first reported in the spleen in 1980. [*Cousar J. et al., 1980*] and then in salivary glands [*Schmid U. et al., 1982*].

The splenic marginal zone lymphoma (SMZL) is a specific low-grade small B-cell lymphoma that has recently been incorporated in the World Health Organization classification. Characteristic features are splenomegaly, moderate peripheral blood lymphocytosis, usually with villous morphology, intrasinusoidal pattern of involvement of various organs, especially bone marrow, and relative indolent course. Tumor progression with the increase of blastic forms and aggressive behavior are observed in a minority of patients [*Cualing H. et al., 2000*]. SMZL often presents with the bone marrow involvement with a high frequency of intravascular infiltrates, which can be associated with interstitial and nodular pattern of infiltration. The intrasinusoidal infiltration of the bone marrow is not specific for SMZL since similar infiltrates, although subtle, can also be found in patients with other small B-cell lymphoproliferative disorders, including patients, whose bone marrow samples are found to be infiltrated by lymphocytes in extranodal marginal zone lymphoma (EMZL) [*Kent S.A. et al., 2002*]. Transformation into diffuse large B cell lymphoma occurs in about 10 to 15% of the cases [*Camacho F. et al., 2001*]. The outcome in many splenic MZ lymphomas is characterized by a lengthy survival after splenectomy (9 to 13 years or longer), despite the absence of a consensus on the optimal treatment [*Diebold J. et al., 2005*]. Immunophenotypically, the tumor cells have a mature B-cell phenotype and frequently express IgM and IgD but typically lack CD5, CD23,

Address for Correspondence:
Yerevan State Medical University after M. Heratsi
2 Koryun Street, 0025, Yerevan, Armenia
Tel.: + (0037494) 911-503, +(0037410)54-54-95
E-mail: armpath@yahoo.com

CD43, CD10, Bcl-6 and cyclin D1 [*Dogan A., Isaacson P., 2003*]. The lymphoma cells show positive immunohistochemical reaction for CD20, CD45 RA, CD79a and bcl-2 [*Huyen J.-P. et al., 2000; Van Krieken J.H.J.M. et al.*1989]

Myelofibrosis is often observed in a variety of hematologic malignancies, including acute megakaryoblastic leukaemia, chronic myelogenous leukaemia and hairy cell leukaemia. The myeloproliferative pattern of bone marrow in malignant lymphoma is very rare. To our knowledge there is only one reported case of splenic marginal zone lymphoma presented as myelofibrosis [*Matsunaga T. et al. 2004*].

Aim

The main aim of this article is to present rare cases of unusual morphological presentation of splenic marginal zone B-cell lymphoma as idiopathic myelofibrosis.

Methods

Routine histological and Peroxidase-Anti-Peroxidase (PAP) immunohistochemical methods were used to evaluate the morphology of both, spleen and bone marrow trephine biopsies. Specimens from ectomed spleen and bone marrow trephine biopsies were fixed in 10% neutral buffered formalin (pH 7.4) for 2 hours at 37ºC followed with decalcination of the bone marrow trephine biopsies in de-Kastro solution overnight. Dehydration processing of specimens was performed by tissue processing machine Shandon Citadel 2000. Paraffin-embedded tissue blocks were cut on rotatory microtome Leica DSC 1. Tissue sections with thickness of 4 *μm* for histological examination were taken onto untreated glasses. For immunohistochemical examinations sections were taken onto silan-treated glasses. Histological examination included routine hematoxylin and eosin staining method. Primary antibodies (DAKO cytomation) for detection of the antigens CD3, CD5, CD15, CD20, CD23, CD34, CD43, CD79a, Tdt, CyclinD1 were included in PAP immunohistochemical method. Microscopic slides were examined with the light microscope; digital photos were taken with uEye IDS digital camera.

Results

We present two cases, which were examined in the Department of Clinical Pathology of the YSMU. The bone marrow trephine biopsy samples of both cases were sent to the department with an initial clinical diagnosis of splenomegaly of the unknown etiology.

The first patient (No. 1), a 73 years-old male, presented with the symptoms of splenomegaly and the following laboratory findings (Table 1).

The peripheral blood analysis during the first

Table 1.

Hb	60 *g/l*
RBC's	1.76
WBC's	3
Metamyelocytes	1
Band	4
Segmented	28
Eosinophils	5
Lymphocytes	42
Monocytes	7
Platelets	46‰
ESR	63 *mm/h*

presentation of this patient showed lymphocytosis, marked increase of the ESR and anemia.

Bone marrow biopsy was taken for histological examination, which showed moderate hypercellularity with islands of haematopoetic cells separated by loose connective tissue (Figure 2). Atypical megakaryocytes as well as micromegakaryocytes with dysplastic features were also observed (Figure 1)

The immunohistochemical examination of the marrow revealed marked positivity for the granulocytic CD15 antigen (Figure 3) as well as for monocytic marker CD68. Lymphoid antigens CD3 and CD79a revealed only few, scattered lymphocytes with no predilections for follicles formation (Figure 4). Only few CD34 positive cells could be found in marrow.

The equivocal interpretation of this bone marrow was difficult. Our initial opinion was Chronic idiopathic myelofibrosis (CIM). For additional opinion and more precise interpretation the digital images were sent to the haematopathology forum of Basel telepathology platform (https://telemed.ipath.ch./ipath/object/175081). By the experts of the haematopathology and the head of the mentioned forum Dr. Nina Hurwitz the following diagnoses were suspected – myelofibrosis with myeloid metaplasia, or other myeloproliferative

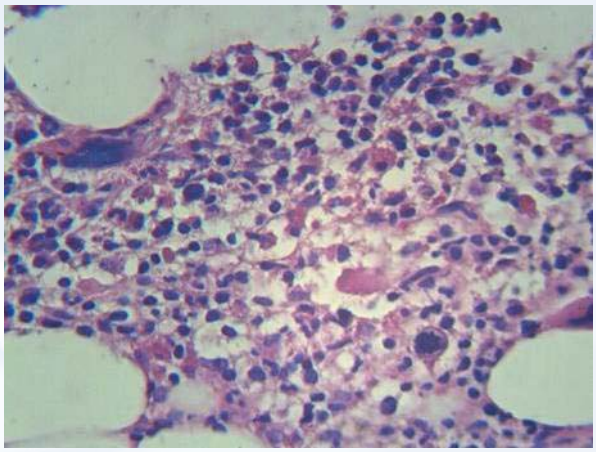

Figure 1. *Megakaryocytes and micromegakaryocytes with dysplastic features. Bone marrow section. H@E. ×150*

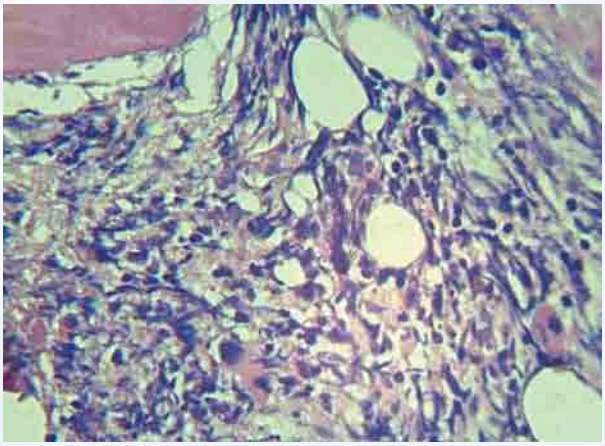

Figure 2. *Tiny islands of heamatopoetic cells surrounded by loose connective tissue. Bone marrow section. H@E. ×150.*

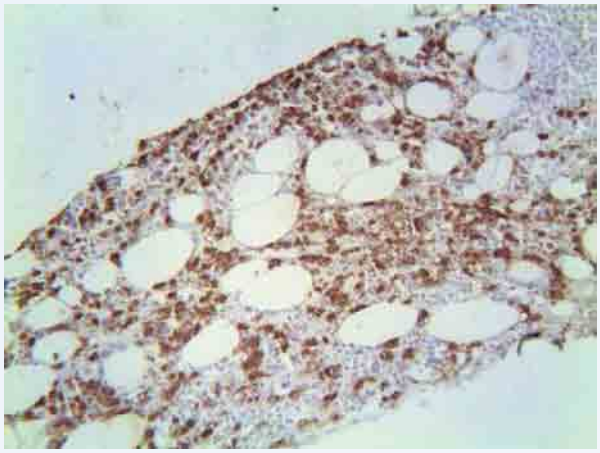

Figure 3. *CD15 positive cells of granulocytic origin. PAP immunohistochemical reaction. × 150*

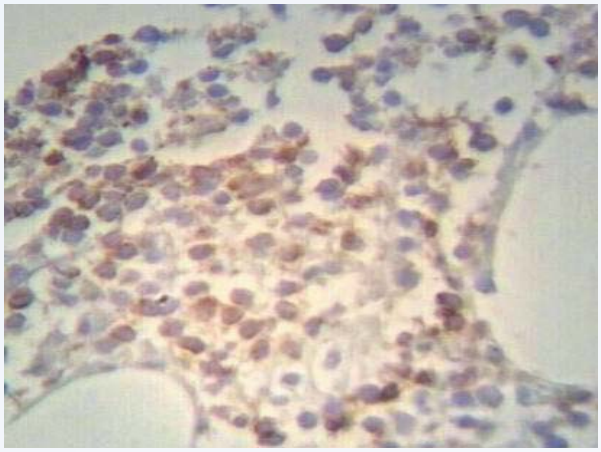

Figure 4. *Scattered CD79a positive lymphocytes. PAP immunohistochemical reaction. × 300.*

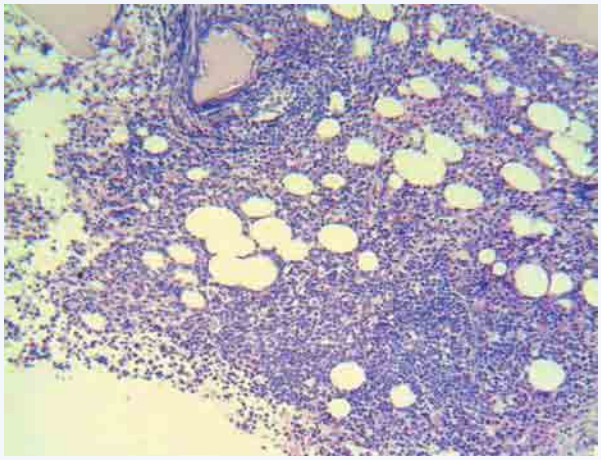

Figure 5. *Nodular lymphocytic infiltration of the marrow. H@E. ×150.*

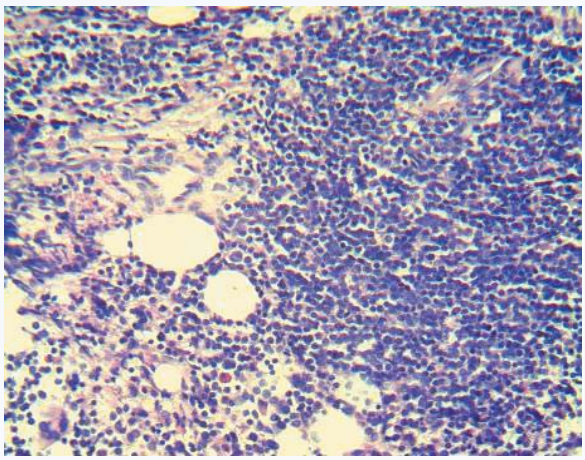

Figure 6. Nodular lymphocytic infiltration with lymphoid aggregates. Bone marrow section. H@E. ×300.

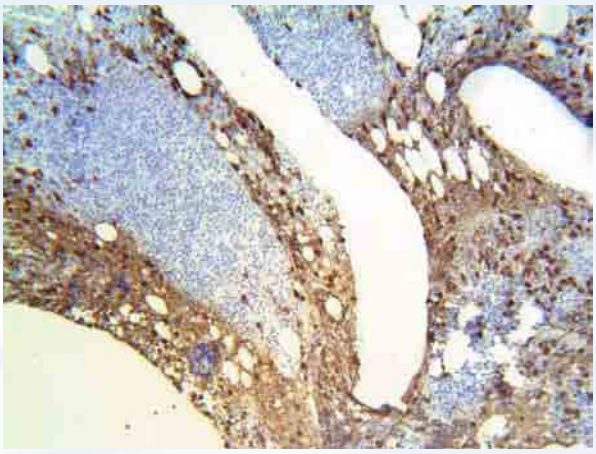

Figure 7. *Scattered CD15 positive cells in bone marrow. Note the negative reaction within lymphoid aggregates. PAP immunohistochemical reaction. ×150.*

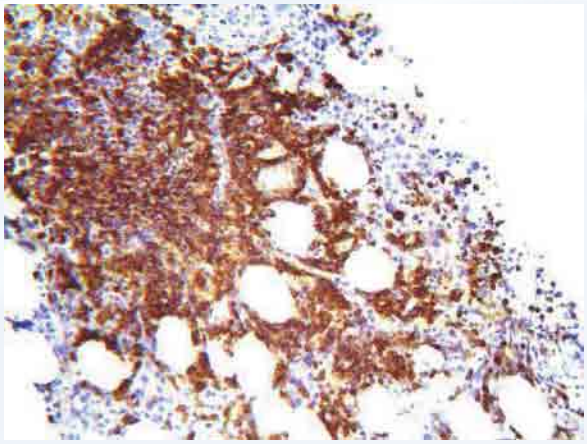

Figure 8. *CD20 positive lymphoid aggregate in marrow. PAP immunohistochemical reaction. ×300.*

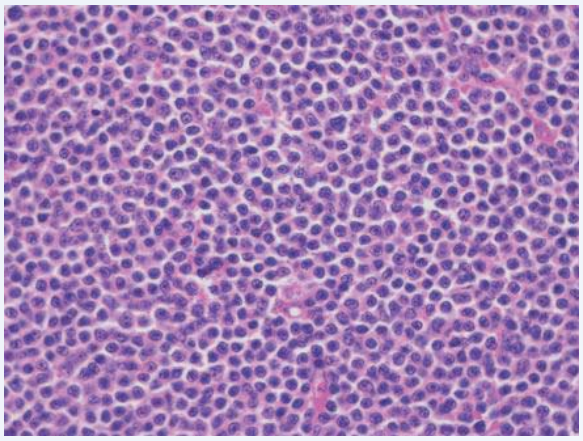

Figure 9. *Diffuse infiltration of the spleen with marginal zone cells. H@E.×300*

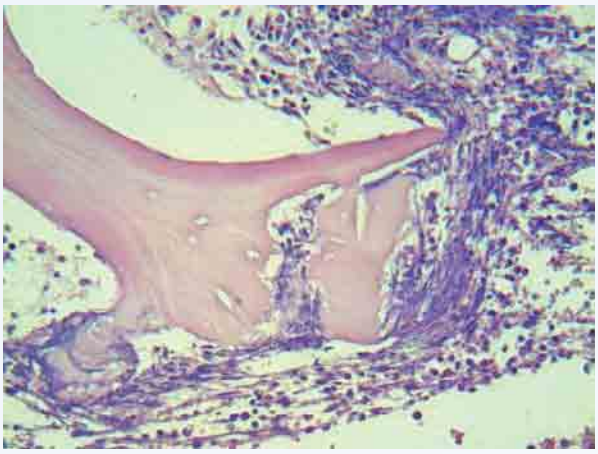

Figure 10. *Increase of loose connective tissue fibers in bone marrow. H@E. × 150*

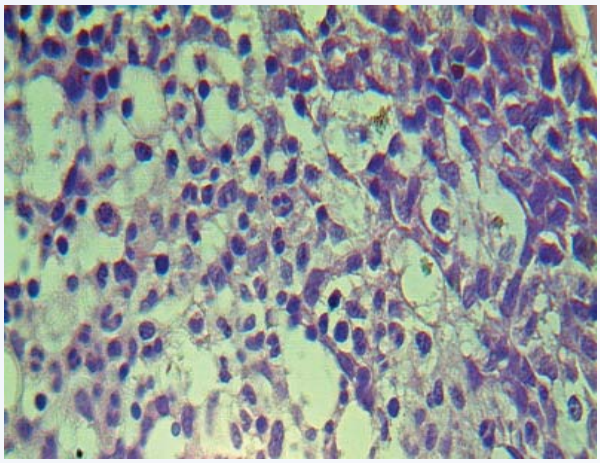

Figure 11. *Activated erythroid (upper right) and granulocytic (center and left) lineages. Note the xantomatous changes. H@E. ×300.×400.*

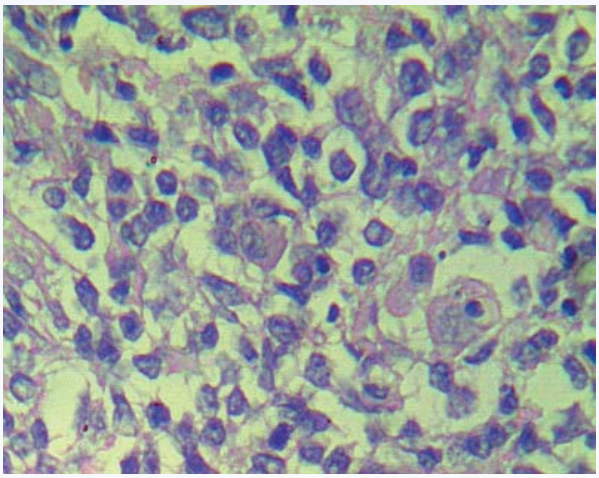

Figure 12. *Small to medium-sized lymphocytes with transformed cells of blasts morphology. H@E. ×400.*

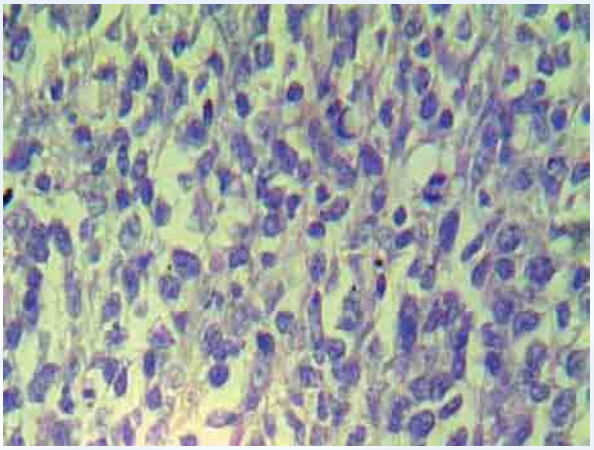

Figure 13. *Small to medium-sized lymphocytes resembling marginal zone cells. H@E. ×300.*

disorder, or high-grade myelodysplastic syndrome with possible leukemic transformation.

Because of the bad response to treatment and increasing peripheral blood lymphocytosis (Table 2), after 1 month clinicians performed the second bone marrow trephine biopsy.

The histological examination of the second bone marrow trephine biopsy specimen on a background of marked hypercellularity revealed many foci of nodular lymphocytic infiltration (Figures 5, 6), which showed positive reaction for the CD79a and CD20 lymphoid markers (Figure 8). CD15 immunostain highlighted few scattered positive cells (Figure 7).

The immunostain for CD34 and CD5 revealed only few positive cells throughout of the marrow. Other immunostains including CD23, Tdt and Cyclin D1 were negative.

After the second bone marrow investigation any types of myeloproliferation were completely ruled out and the diagnosis of SMZL was apparent. Splenectomy was performed and the specimen was sent to the department for further histological examination. The histology of ectomed spleen showed typical picture of SMZL (Figure 9).

The next presented patient (No. 2), a 55 years-old female, was clinically found to have also the symptoms of splenomegaly and the following peripheral blood data (Table 3):

The histological examination of the marrow revealed marked, mainly paratrabecular increase of the loose connective tissue fibers (Figure 10). The activation of the myeloid, granulocytic and erythroid lineages, and xantomatous changes of cells were also apparent (Figure 11). No any suspicious type of lymphoid infiltration pattern was found. Hence, we diagnosed the chronic myeloprolifarative disease, histology consistent with CIM.

Surprisingly, after the histological examination of splenectomy specimen we found the picture of the SMZL. Small round lymphocytes replaced reactive germinal centers of the follicles. The peripheral zones of the lymphoid follicles were presented by the small to medium-sized cells with more dispersed chromatin and abundant pale cytoplasm, which resembled marginal zone cells and were interspersed with transformed blasts (Figures 12, 13).

Conclusion

We conclude that the B-cell splenic marginal zone lymphoma, although rare, but at the certain point of development can be presented as bone marrow myeloproliferative pattern, mimicking chronic idiopathic myelofibrosis. Such cases need further deep examination to highlight the possible molecular and genetic mechanisms of morphogenesis.

Table 2.

Hb	90 *g/l*
RBC's	3.1
WBC's	2.6
Atypical forms	1
Band	2
Segmented	21
Lymphocytes	61
Monocytes	14
ESR	38 *mm/h*

Table 3

Hb	110 *g/l*
RBC's	4.7
Platelets	60‰
WBC's	11
Band	4
Segmented	78
Eosinophils	3
Lymphocytes	5
Monocytes	10
ESR	25 *mm/h*

References

1. *Camacho F.I., Mollejo M., Mateo M.S., Algara P., Navas C., Hernondez J.-M., Santoja C., Sol F., Snchez-Beato M., Piris M.A.* Progression to Large B-Cell Lymphoma in Splenic Marginal Zone Lymphoma. A Description of a Series of 12 Cases. Am J Surg Pathol 2001; 25: 1268-1276.
2. *Cousar J.B., Mc Kee L.C., Greco F.A., Grick A.D., Corrins R.D.* Report of an unusual B-cell lymphoma probably arising from perifollicular cells (marginal zone) of the spleen (abstract). Lab. Invest. 1980; 4: 109.
3. *Cualing H., Steele P., Zellner D.* Blastic transformation of splenic marginal zone B-cell lymphoma. Arch. Pathol. Lab. Med. 2000; 124(5): 748-752.
4. *Diebold J., Le Tourneau A., Comperat E., Molina T., Audouin J.* Primary Splenic and Uodal Marginal Zone Lymphoma, J. Clin. Exp. Hematopathol. 2005; 45 (1,) 1-14
5. *Dogan A., Isaacson P.G.* Splenic marginal zone lymphoma. Semin. Diagn. Pathol. 2003; 20(2): 121-127.
6. *Huyen J.-P. D.V., Molina T., Delmer A., Audouin J., Le Tourneau A., Zittoun R., Bernadou A., Diebold J.* Splenic Marginal Zone Lymphoma With or Without Plasmacytic Differentiation. Am. J. Surg. Pathol. 2000; 24:1581-1592.
7. *Kent S.A., Variakojis D., Peterson L.C.* Comparative study of marginal zone lymphoma involving bone marrow. Am. J. Clin. Pathol. 2002; 117(5): 698-708.
8. *Matsunaga T., Takemoto N., Miyajima N., Okuda T., Nagashima H., Sato T., Terui T., Sasaki H., Ohmi N., Nirayama Y., Tamura Y., Niitsu Y.* Splenic marginal zone lymphoma presenting as myelofibrosis associated with bone marrow involvement of lymphoma cells which secrete a large amount of TGF-β. Ann. Hematol. 2004; 83: 322-325.
9. *Saacson P.G., Wright D.H.* Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. Cancer. 1984; 53: 2515-2524.
10. *Schmid U., Helbron D., Lennert K.* Development of malignant lymphoma in myoepithelial sialadenitis (Sjogren's syndrome). Virchow's Arch. 1982; A395: 11-43.
11. *Snook T.* Studies on the perifollicular region of therat's spleen. Anat. Rec. 1964; 148: 149- 159,.
12. *Van den Ord J., De Wolf-Peeters C., Desmet V.* The marginal zone in the human reactive lymph node. Am. J. Clin. Pathol. 1986; 86: 475-479.
13. *Van Krieken J.H.J.M., von Schilling C., Kluin P.M., Lennert K.* Splenic marginal zone lymphocytes and related cells in the lymph node: a morphological and immunohistochemical study. Hum. Pathol. 1989; 20: 320-325.