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Case Report

A Case Report of Unusual Malignant Lymphoma Possibly Derived from Spleen

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Abstract

We have encountered a case with unusual type of lymphoma possibly originating in spleen. The case was a 58 years old Japanese male. Clinically he exhibited marked hepato-splenomegaly, no systemic enlargement of lymph nodes (LNs) except for splenic hilar nodes, liver dysfunctions and appearance of a few atypical lymphoid cells in peripheral blood (PB). Splenectomy, lymphadenectomy of the splenic hilar nodes and the wedged-biopsy of liver were performed for histological diagnosis as well as microscopic examinations of bone marrow (BM) and PB. The enlarged spleen (1,200g) displayed diffuse proliferation of immunoblastic cells with prominent plasmacytic differentiation, especially in cords of red pulps and marginal zone of white pulps. These cells revealed immunoreactivity for DBB42, CD19 but minimal reactivity for CD20. Monotypic light chain of immunoglobulins (λ) and bitypic heavy chains (γ and μ) were also detected in their cytoplasms. These cells infiltrated exclusively in sinuses of splenic hilar LNs, in sinusoid of liver and scatteredly in BM. Many T-cells incuding some transformed cells also infiltrated into the hepatic sinusoid, BM and splenic white pulp. Atypical lymphocytes appeared in PB did not show villous projections as far as we examined. The patient keeps disease-free condition after splenectomy without any chemotherapy except for transient thrombocytopenia. The morphological and immuno-cytochemical features of the major proliferating cells indicated that they were corresponding to the terminal stage in B-cell differentiation. These cellular characteristics and the less aggressive chinical behavior suggested us a variant of lymphoplasmacytic lymphoma (polymorphic subtype) possibly derived from spleen as a possible diagnosis. There were, however, some discrepancies between this case and the previous reported cases especially on the distribution pattern of the lymphoma cells in spleen, liver, LNs and BM and on the accompanying T-cell proliferation. Large cell lymphoma arisiag from marginal zone and microvillous lymphoma should be considered for the differential diagnosis.

Key words: DBB42, CD19, immunoblasts, marginal zone, indolent lymphoma and immunohistochemistry.

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Introduction

Several peculiar lymphoid neoplasms such as hairy cell leukemia (HCL)[1,2], splenic lymphoma with villous lymphocytes (SLVL)[1,3], prolymphocytic lymphoma (PLL)[1,4] and so called "marginal zone lymphoma"[5] are known to involve primarily in spleen and to manifest massive splenomegary. We encountered an unigue case which had conspicuous splenomegary but not systemic involvement of lymph nodes (LNs). Characteristics of the tumor cells, their infiltration pattern into liver, LNs and bone marrow (BM), and the clinical behavior did not correspond to the previous reports on the above mentioned splenic lymphomas.

In the present article, the histological and immunohistochemical findings of this case are reported with some discussions on the orgin of the disease, phenotype and characteristics of the proliferating cells and the suitable histological diagnosis and application of the updated kiel classifcation for this case.

Case report

A 58 years old, male Japanese patient consulted Yamagata Prefectural Kahoku Hospital on April 12, 1993 with complaints of abdominal discomfort and general fatigue for a month. The physical, laboratory and radiological examinations indicated marked hepatosplenomegaly, enlargement of some splenic hilar LNs (not palpable of superficial LNs), pancytopenia with a

Table 1. Laboratory data

DATE (1993)	4/12	5/27	6/21	6/30	7/13	8/12	10/01	11/15
WBC (/mm^3)	3,120	2,400	2,700	9,300	6,900	14,400	11,200	11,600
Monocytes (%)	6.0	14.0	-	-	-	-	-	-
Lymphcytes (%)	38	23	36	-	43	66	-	24.7
Lymphcytes (/mm^3)	1185	552	972	-	2967	9504	-	2865
Atypical Lym (%)	20	3.0	9.0	-	0	1.0	1.0	-
RBC (x10^4/mm^3)	409	400	372	320	380	455	469	412
Hb (g/dl)	10.9	10.7	10.0	8.7	10.9	12.8	13.4	12.2
Platelets (x10^4/mm^3)	9.8	8.7	5.4	68.0	69.2	15.8	0.9	46.8
GOT (IU/l)	53	36	58	39	49	57	93	29
GPT (IU/l)	39	22	110	58	42	45	83	63
LDH (IU/l)	614	537	331	318	360	408	446	235
Al-P (IU/l)	763	428	718	592	429	506	-	136
γ-GTP (IU/l)	196	133	390	243	180	264	-	189
TP (g/dl)	5.6	5.7	4.7	-	-	-	-	-
IgG (mg/dl)	-	956	-	-	790	-	PA-IgG	-
IgA (mg/dl)	-	67	-	-	75	-	(947)	-
IgM (mg/dl)	-	98	-	-	52	-	-	-

few percent of atypical lymphoid cells in peripheral blood, increasing level of serum enzymes such as GOT, GPT, LDH and ALP, and increasing numbers of lymphoid cells in BM (Table 1). Since certain lymphocytic leukemia or malignant lymphoma were suspected, he was admitted to the 3rd Department of Internal Medicine, Yamagata University Hospital for further examination and treatment. On June 30, 1993, splenectomy, lymphadenectomy of enlarged splenic hilar nodes and wedge-resetion of liver were performed. After the operation, the above sympoms and laboratory abnormalities were improved without any medications and he discharged the hospital on August, 12 and was followed up. In October, sudden thrombocytopenia with autoimmune IgG appeared. Steroid medication was effective for this symptom and good condition without any progression signs of the disease have been continued at present.

Laboratory data are summarized in Table 1. As mentioned above, pancytopenia, appearance of a few percents of atypical lymphocytes and increasing levels of blood enzymes including GOT (glutamate oxaloacetate transaminase), GPT (glutamate pyruvate transaminase), γ-GTP (γ-glutamyltranspeptidase), LDH (lactic dehydrogenase) and ALP (alkaline phosphatase) were recognized. There were no abnormal increase of each class of immunoglobulins nor detection of M-protein. The abnormal data for LDH, ALP, GOT and GPT have been improved after splenectomy except for a transient elevation in October, 1993.

Pathological findings

Spleen

The spleen was greatly enlarged (weight 1,200g). It displayed a wedge-shaped, focal infarction but no other nodular lesion. Histological sections of the organ demonstrated marked expansion of both of red and white pulp caused by diffuse proliferation of the cells (Fig. 1A), which revealed immunoblastic morphology including abundant basophilic cytoplasm and a oval or slightly indented nucleus having coarse chromatin disribution and a few prominent nucleoli (Fig. 1B). They were especially distributed in red pulps and marginal zone of white pulps (Fig. 1A) and were accompanying plasmacytic differentiation. In addition, numerous small lymphoid cells and macrophages intermingled with these cells. No blood lakes or psuedo-sinus formation were found.

As indicated in Fig. 1C and 1D, most of the proliferating cells revealed prominent immunoreactivity for B4 (CD19), DBB42 (pan-B-cell) and LCA (leukocyte common antigen; CD45). In addition, monotypic light chain (λ) and bitypic heavy chains (μ and γ) of immunoglulins were detected in the cytoplasm of these cells (Fig. 1E, 1F and 1G). Some of them also expressed LN-1 (CDw75), LN-2 (CD74), LN-3 (HLA-DR) and MB-3. In contrast, these cells revealed none or very faint reactivity for L-26 (CD20cy) and B1 (CD20). They did not express detectable T-cell associated antigens such as CD2, CD3, CD45RO (UCHL1), and CD25. Whereas intermingled small lymphoid cells revaled distinct reactivty. CD11c, CD33 and CD68(Kp-1) were also negative on them. The immunohistochemical features of the major proliferating cells were summarized in Table 2.

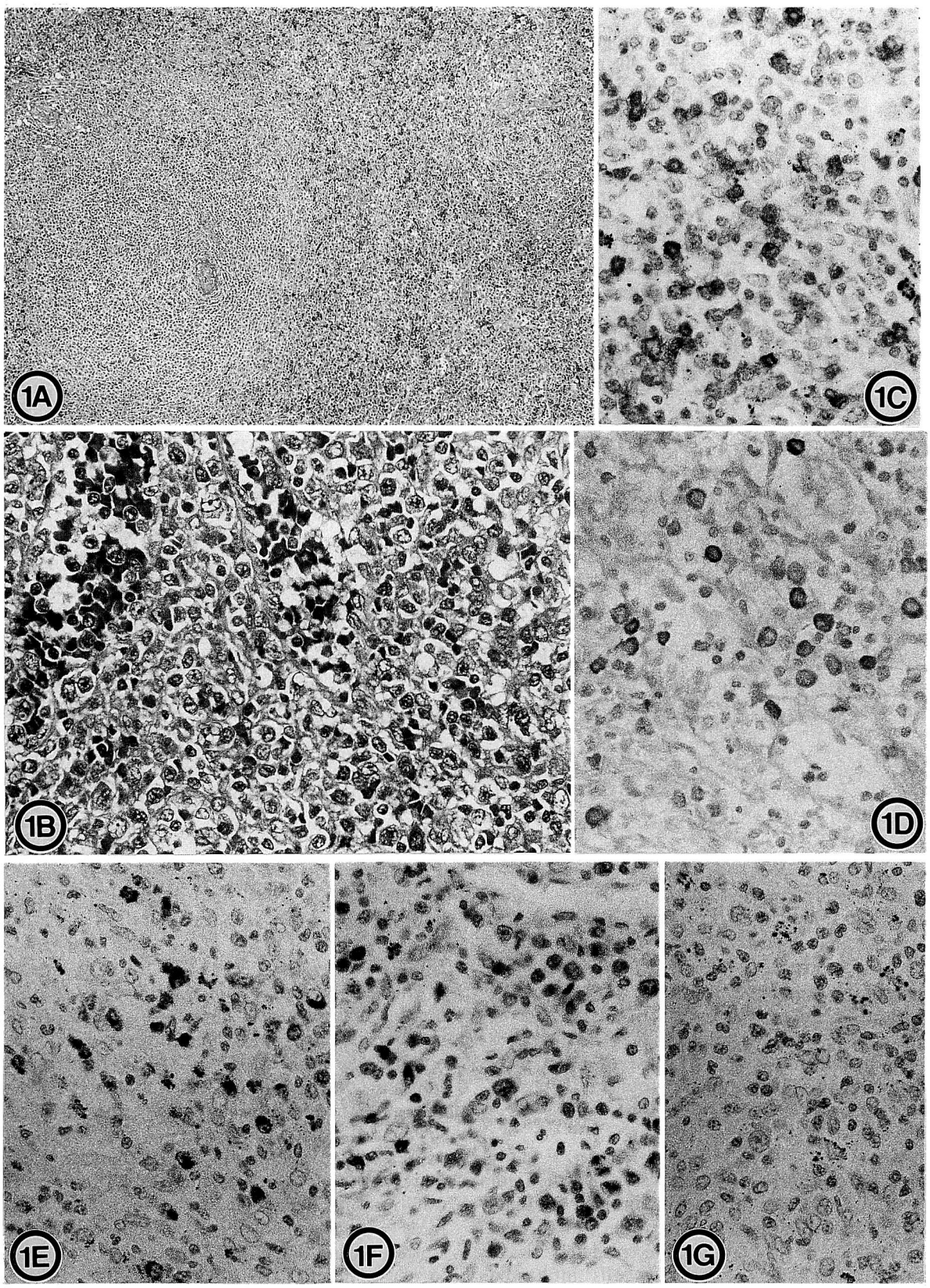

Fig. 1. Photomicrographs showing histological appearance of the spleen. Fig 1A and 1B demonstrate a low power view and a higher magnification of H&E (hematoxylin and eosin staining), respectively. Note marked expansion of both of red and white pulp and proliferation of immunoblastic cells accompanying plasmacytic differentiation in cords of red pulp and marginal zone. Fig.1C, 1D, 1E,1F and 1G indicate immunoreactivity with DBB42, B4 (CD19), anti-IgG, anti-λ-light chain and anti-κ-chain, respectively. Most of the proliferating cells revealed DBB42^{+}. CD19^{+}, cytoplasmic IgG^{+} andcytoplasmic λ-chain^{+}. (Fig.1A; X75 H&E, 1B; X300 H&E, H&E, 1C, 1D, 1E, 1F and 1G; X300 Indirect immunoperoxidase labeling with hematoxylin-counterstaining)

Table 2. Immunohistochemical characteristics of the major proliferating cells.

antibody (CD # or specificity)	reactivity
LCA (CD45)	++
B1 (CD20)	−
L26 (CD20cy)	−
B4 (CD19)	++
DBB42 (pan-Bcells)	++
DBA44 (subset of B-cells)	+/− (scattered cells)
LN-1 (CDw75)	+/− (scattered cells)
LN-2 (CD74)	+/− (only small cells)
LN-3 (HLA-DR)	−
MB-1 (CD45R)	−
MB-2 (subset of B-cells)	−
MB-3 (subset of B-cells)	+/− (small cells)
1F8 (CD21)	−
cytoplasmic IgG	++
CIgM	++
CIgA	−
CIgD	−
CIgE	−
C-lamda	++
C-kappa	−
CD2	−
CD3	−
UCHL-1 (CD45RO)	−
Leu22 (CD43)	+
IL-2R (CD25)	−
CD11a	−
CD11c	−
LeuM1 (CD15)	−
CD33	−
Kp-1 (CD68)	−

Splenic hilar lymph nodes

The enlarged splenic hilar lymph nodes, which were excised simultaneously at splenectomy, maintained their basic structures but the subcapsular and intermediated sinuses were markedly expanded by accumulation of the cells which had the same morphological and immunohistological features as mentioned in spleen except for most of them were containing μ-heavy chain in their cytoplasms (Fig. 2A, 2B, 2C and 2D).

Liver

The wedged resection of liver was performed for histological examination because certain liver dysfunctions were detected in his laboratory data as indicated in Table 1. The histology of the resected tissue demonstrated that many lymphoid cells infiltrated mainly in the hepatic sinusoids (Fig, 3A). These infiltrates consisted of medium-sized lymphocytes which expressed T-cell makers such as CD45RO, CD3 and CD43 (Leu22) (Fig,3B). Among these cells, DBB42 positive immunoblastic cells were seen only scatteredly (Fig, 3C). No nodular infiltration and periportal invasion was found.

Bone Marrow

The histological sections of BM clots revealed that normal hematopoietic elements were depressed and numbers of lymphoid cells infiltrated to form scattered nodular aggregations (Fig, 4A). The lymphoid aggregations are consisted of small and medium sized lymphoid cells and scattered transformed cells. In immunohistochemical staining, most of the lymphoid cells expressed conventional T-cell markers or B-cell markers (L26). Amongst these cells, some DBB42 + cells intermingled as shown in Fig, 4B. Cytoplasmic IgM + cells and λ-chain + cells were also found scatteredly in the lymphoid aggregations as correspond to above mentioned DBB42 + cells.

Peripheral Blood

Fig. 5 shows an atypical lymphoid cell appeared in peripheral blood. A few percent of large lymphoid cells having somewhat irregular nucleus with prominent

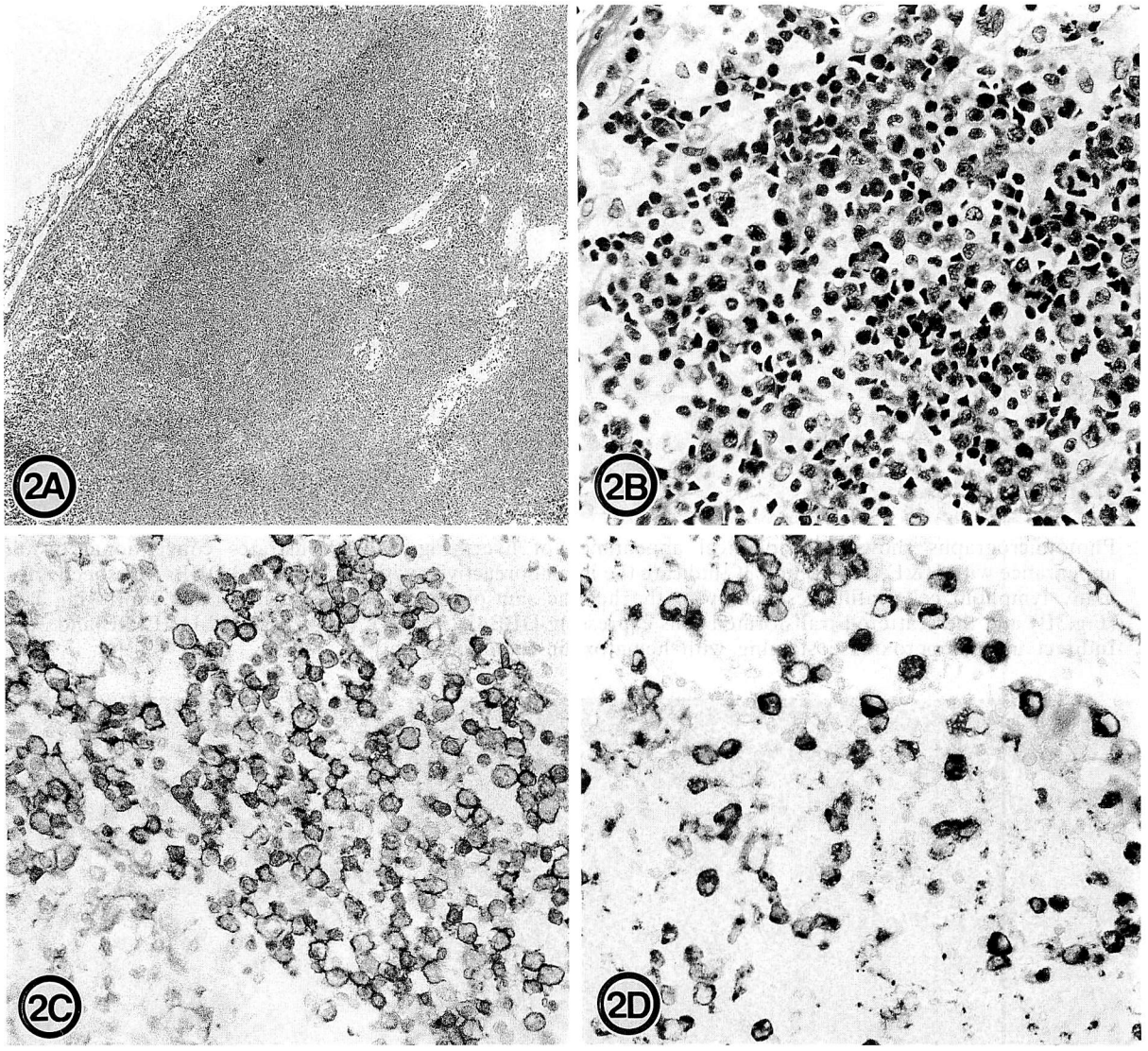

Fig. 2. Photomicrographs showing histological appearance of the splenic hilar lymph node. Fig. 2A and 2B demonstrate a low power view and the higher magnification of H&E, respectively. Note the marked cellular expanstion of the subcapsular sinus and prolifertion of immunoblastic cells with intermingled lymphocytes and plasma cells. These cells are positive for DBB42 and IgM as indicated in Fig.2C and 2D, respectively. (Fig.2A; X30 H&E, 2B; X300 H&E, 2C and 2D; X300 Indirect immunoperoxidase staining with hematoxylin-counterstaining)

nucleoli and relatively abundant basophilic cytoplasm were observed in the smear. These cells did not display any microvillous projections or hairy appearance as far as we examined.

Discussion

Concerning the present case, the following subjects are discussed: 1) phenotype and characteristics of the proliferating cells, 2) the most suitable histological diagnosis and classification, especially application of the updated Kiel classification, and 3) origin of the disease.

It seems to be certain that the major proliferating cells in the preesent case are of B-cell origin because they are positive for some of pan-B-cell markers (DAA42, CD19) and negative for any T-cell markers. Immunodetection of monotypic ligh chain (λ) or bitypic heavy chains (γ / μ) of immunoglobulins in their cytoplasms not only supports their B-cell nature but also suggests their monoclonal proliferation meaning neoplastic growth. Comparing other usual B-cell lymphomas, these cells are somewhat peculiar because most of them did not express the most general B-cell marker, CD20 (L26 and B1). Such peculiar immunophenotype of the prolierating cells can be explained that they are situated in the terminal stage of B-cell differentiation. Some other reports also mentioned that CD19 or DBB42 could be expressed on plasmablasts or plasma cells which already lost the

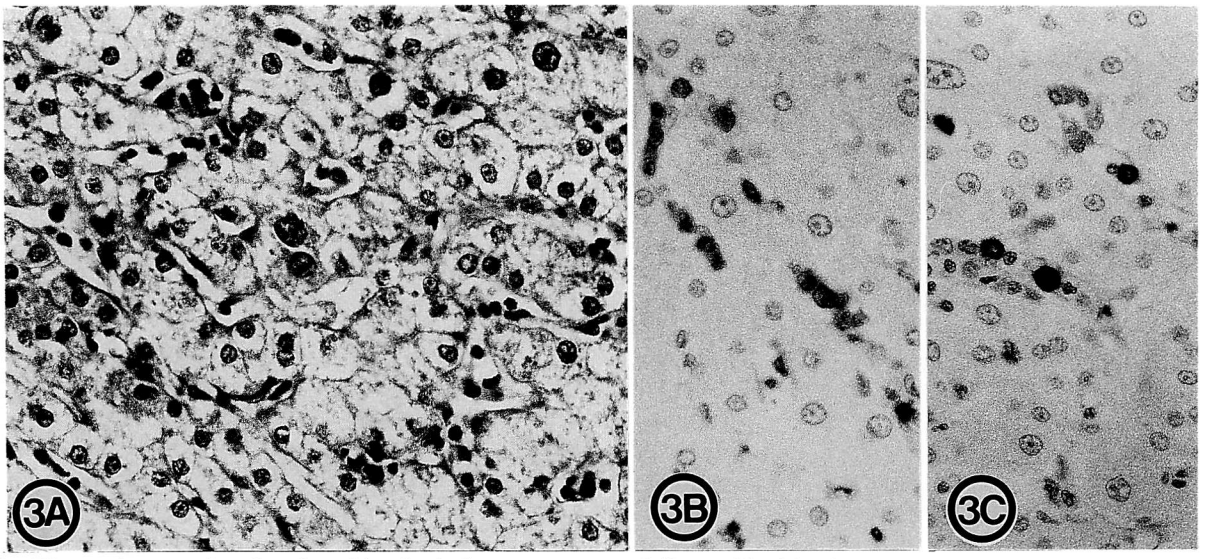

Fig. 3. Photomicrographs showing histological appearance of liver. Fig.3A demonstrates conventional histological appearance with H&E. Fig.3B and 3C indicate the immunoreactivity with UCHL-1 and DBB42, respectively. Note many lymphoid cells infiltrates mainly in the hepatic sinusoids, most of these infiltrates expressing UCHL-1 (Fig.3B) and the scattered transformed cells expressing DBB42 (Fig,3C). (Fig.3A: X300 H&E, 3B and 3C; X300 Indirect immunoperoxidase staining with hematoxylin-counterstaining)

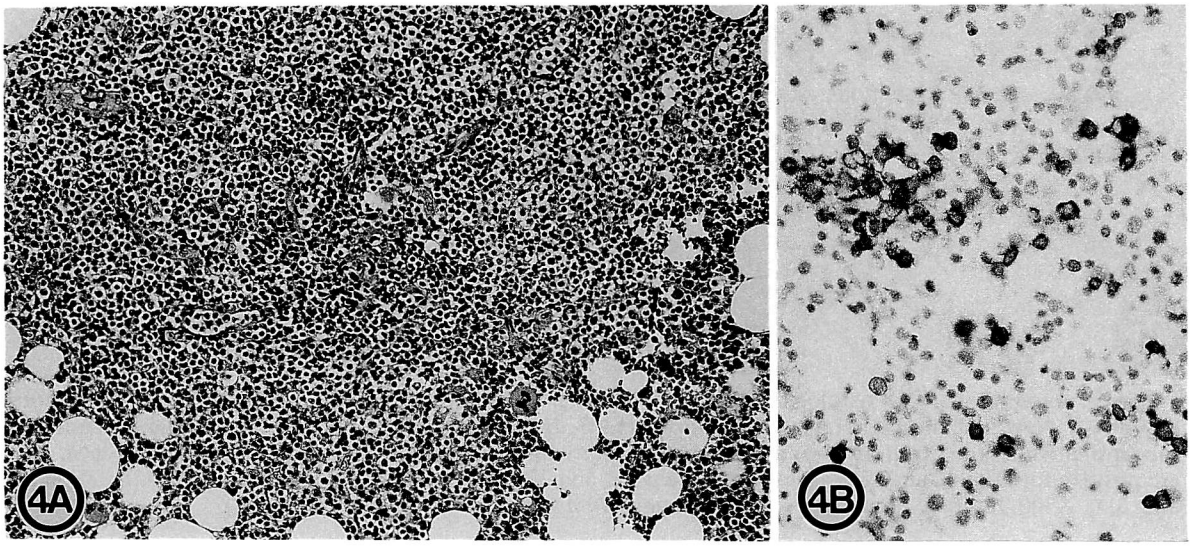

Fig. 4. Photomicrographs showing histological appearance of BM. Fig.4A demonstrates a conventional histological appearance with H&E staining. Note numbers of lymphoid cells forming a nodular aggregation. Amongst these cells, some DBB42 $^{+}$ cells intermingled as shown in Fig,4B. (Fig.4A; X150 H&E, 3B; X300 Indirect immunoperoxidase staining with hematoxylin-counterstaining)

surface CD20 expression in physiological or in neoplastic condition[6,7]. The morphological features of these cells such as immunoblastic appearance and accompanying plasmacytic differentiations were correspond to our explanation.

The morphological and immunohistocheical features of the lymphoma cells and their distribution pattern in spleen, the involved LNs, liver and BM can discriminate this case from the representative splenic lymphomas such as HCL, SLVL and PLL.Rather than these, the characteristics of the tumor cells seems to correspond to lymphoplasmacytic type of malignant lymphoma in the updated kiel classification. In this category, following three histological subtypes can be defined : 1) lymphoplasmacytoid subype, consisting of small lymphocytes and lymphoplasmacytic cells, 2) lymphoplasmacytic subtype, rich in plasma cells, and 3) polymorphic subtype consisting of varying numbers of lymphocytes, plasma cells, immunoblasts, plasmablasts and even transformed cells resembling Reed-Sternberg cells[8,9]. According to this concept, the present case seems to be classified in the last subtype (polymorphic

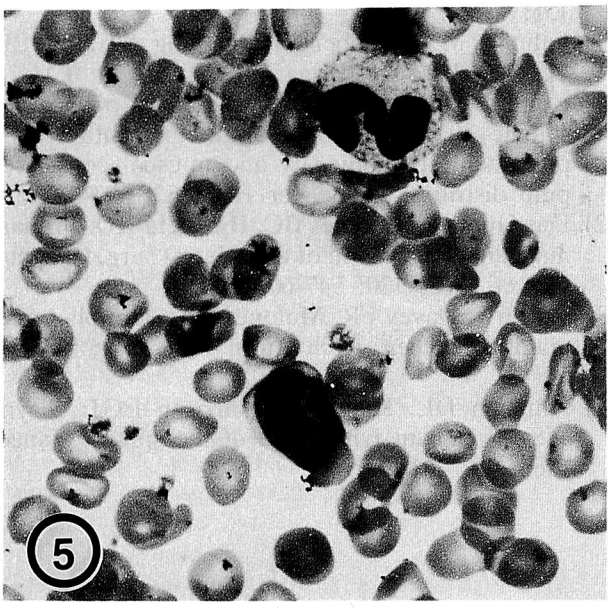

Fig. 5. A photomicrograph demonstrating an atypical lymphoid cell appearing in peripheral blood. This cells do not show any microvillous projections or hairy appearance.(X750, May-Gimsa)

subtype). In fact, Audouin et al[10] reported the eleven cases of lymphoplasmacytic lymphoma of spleen including 8 cases of polymorphic subtype whereas their growth pattern in spleen and their histological distribution in the involved LNs, liver and BM are not identical to those of this case.

On the other hand, Palutke et al[11] reported two unigue cases in which large cell type of lymphoma with B-cell properties involved predominantly in red pulp of spleen. They assumed these lymphoma might originate from marginal zone lymphocytes which were thought to represent a separate lineage from follicular B-lymphocytes. Although there are some discrepancies on the immunocytochemical features and the phagocytic activity between these reported cases and ours, their infiltration pattern and indolent behavior are alike to consider their common nature.

Lennert and Feller pointed out that T-cells, which were prominently infiltrating into BM, hepatic sinusoid and splenic white pulps in this case, also revealed some pleomorphic features and aberrant distribution pattern. They, therefore, suggested the possibility of co-existence of T-cell and B-cell neoplasms (composite lymphoma consisting of T-CLL and splenic B-large cell or lymphoplasmacytic lymphoma). Sothern blot analysis on rearrangements of both T-cell receptor genes and immunoglobulin genes should prove the possibility.

The definition of a primary splenic malignant lymphoma has varied from one publication to another. Thus, Das Gupta et al[12] suggested that diagnosis be made only if there was isolated splenomegary without any other tumor localization, in particular in the liver or in the mesenteric and para-aortic lymph nodes and if there was relapse-free period of at least 6 months after splenectomy whereas Skarin et al[13] suggested that primary malignant lymphoma of the spleen should comprise all malignant lymphomas essentially expressed by a predominant splenomegary. Ahmann et al[14] defined the following three stages of splenic lymphomas: I (malignant lymphoma localized in the spleen), II (involvement of the spleen and the splenic hilar lymph nodes) and III (splenic involvement associated with a hepatic localization with or without lymph node involvement). The present case is mostly satisfied with these definitions for primary splenic lymphoma because prominent splenomegary were noted and over 6 months of relaps-free period have been maintained after splenectomy and to be adapted into stage III.

In conclusion, an unusual type of malignant lymphoma possibly originate from spleen are reported in this article. Further analyses, especially using molecular biogical technigues or electron microscopic observations and careful follow-up of the patient will be necessary to elucidate the essential nature of the lymphoma cells, to establish the disease entity and to evaluate accurate prognosis.

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