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UMENO, Yoshikazu
Department of Internal Medicine, Saga Prefectural Koseikan Hospital

MATSUISHI, Eizyou
Department of Internal Medicine, Saga Prefectural Koseikan Hospital

MURAKAMI, Yoshikazu
Department of Internal Medicine, Saga Prefectural Koseikan Hospital

NAKAO, Takaaki
Department of Internal Medicine, Saga Prefectural Koseikan Hospital

他

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症　　例

An Autopsy Case of B-cell Lymphoma Associated with Macroglobulinemia (IgM-k)

Yoshikazu UMENO[1], Eizyou MATSUISHI[1], Yoshikazu MURAKAMI [1], Takaaki NAKAO[1], Yuichi MIYAMOTO[1], Seiko YOSHITOMI[2], Koji IRIE[2] and Yoshiro OHTA[1]

Departments of Internal Medicine[1] and Pathology[2] Saga Prefectural Koseikan Hospital, Saga 840

Abstract While he was treated for macroglobulinemia showing symptoms, a 65-year-old man developed an enlargement of the left lateral cervical lymph node. Biopsy specimens of the cervical lymph node revealed large-cell non-Hodgkin's lymphoma. The lymphoma cells had rearrangement in the immunoglobulin heavy chain and kappa light chain genes. There was osteolysis involving right metatarsal bones. And, a tumor appeared on the upper hard palate in the terminal stage.

Autopsy specimens showed infiltration of lymphoma cells into multiple organs. Production of monoclonal immunoglobulin M was detected only slightly and focally in the tumors. Plasmacytic differentiation as in Waldenström's macroglobulinemia was not seen in any organs except the tumor on the upper hard palate. From these findings, it is speculated that B-cell lymphoma might have developed in the course of macroglobulinemia.

Introduction

Macroglobulinemia is a monoclonal neoplasm which develops from mature B lymphocyte, producing a monoclonal IgM protein and characterized by lymphadenopathy, hepatosplenomegaly, and proliferation of lymphocytic-plasmacytic cells in the lymphoreticular tissues[6].

Macroglobulinemia and B-cell lymphoma are morphologically different malignancies, but represent different stages in the lymphoproliferative disorders.

We experienced an autopsy case of B-cell lymphoma initially presenting as macroglobulinemia, suggesting a close pathoetiologic relationship between these two lymphoproliferative disorders.

All correspondence to: Yoshikazu Umeno, M. D. Department of Internal Medicine, Saga Prefectural Koseikan Hospital, 1-12-9 Mizugae, Saga, 840

Case Report

This 65-year-old man helped the atomic bomb victims in Nagasaki city in August, 1945. So, he has gotten a physical check up at regular intervals. In 1980, liver dysfunction with unknown etiology was found by the physical check up. In April, 1990, he had an itch on the whole body, and was seen by a local medical doctor. Then, liver dysfunction was pointed out, again. He was then referred to our hospital for further examination in August 20, 1990.

Laboratory findings showed high level of colloid reaction and monoclonal gammopathy (IgM-k) (Fig. 1) as follows: total protein, 10.6

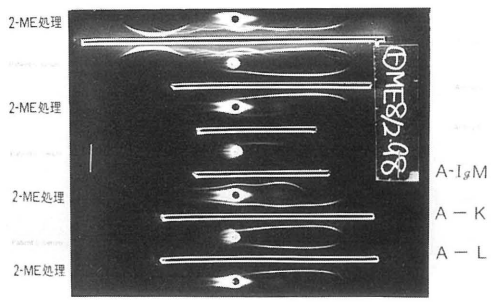


Fig. 1 Serum immunoelectrophoresis on the first admission.

g/dl; albumin, 2.9 g/dl; ZTT, 78.7 U; TTT, 39.9 U; IgG, 2,460 mg/dl (normal range, 800-1,800 mg/dl); IgA, 104 mg/dl (normal range, 95-450 mg/dl); IgM, 5,210 mg/dl (normal range, 60-280 mg/dl). In urinalysis, Bence-Jone's protein was positive. The hemoglobin level was 11.8 g/dl. WBC count was 4,800/μl with no atypical lymphocytes. RBC count was 3.55×10^6/μl with rouleaux formation. Bone marrow examination revealed normocellular marrow with localized infiltration of lymphoid cells. Ultrasonic study revealed paraaortic small lymph node enlargement. He felt tinnitus and dizziness. From these findings, Waldenström's macroglobulinemia was clinically diagnosed.

He was treated with melphalan (2mg/day) and prednisolone (10mg/day) (MP), which decreased the total protein level and the IgM level, moderately. Then, he was discharged in December 12, 1990. He continued to receive MP as an out patient. However, he noticed a hard cervical lymph node on the left side. In October 5, 1992, he was readmitted to our hospital for further examination and treatment.

The physical examination revealed slightly anemic conjunctiva. The ocular fundi showed no evidence of hyperviscosity. Some cervical lymph nodes on the left side and a inguinal lymph node on the right side were enlarged. The cervical lymph node biopsy showed diffuse large B non-Hodgkin's lymphoma (Fig. 2), which had rearrangement in the immunoglobulin heavy chain (Fig. 3) and kappa light chain genes (Fig. 4). Breath sound was decreased over the right base. There was no hepatosplenomegaly. Edema was slightly present on the lower extremities. The neurological examination revealed no abnormal findings.

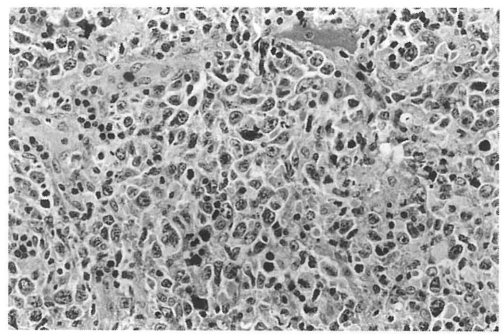


Fig. 2 Lymph node biopsy at onset shows diffuse infiltration of atypical large cells compatible with non-Hodgkin's disease, diffuse, large cell type. Hematoxylin-Eosin ×200.

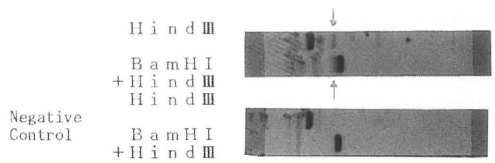


Fig. 3 Analysis of Ig heavy chain gene configuration. Arrows show the positions of rearranged restriction fragments in DNA.

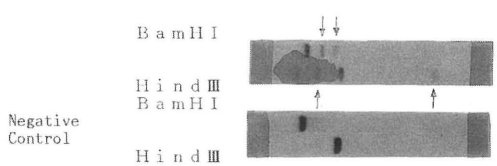


Fig. 4 Analysis of Ig light chain gene configuration. Arrows show the positions of rearranged restriction fragments in DNA.

The laboratory findings on the second admission are shown in Table 1. Urinalysis showed proteinuria, and Bence-Jone's protein (Kappa light chian) was detected on a urine immunoelectrophoresis. The hemoglobin level was 10.8 g/dl. WBC count was 7,700/μl with 2

Table 1 Laboratory data on admission

Urine :
Glu (−)
Prot (+)
Ubg (N)
Sed. RBC 1/4-5 Hpf
WBC 1/1-2 Hpf

Peripheral blood :

RBC	3.18 ×10⁶/μ l
Hb	10.8 g/dl
Ht	30.8 %
Plt	20.5 ×10⁴/μ l
WBC	7,700/μl
Myelo	0.0
Meta	0.0
St	4.0
Seg	77.0
Ly	17.0
Mo	0.0
Ba	0.0
Aty-Lym	2.0

Rouleaux formation(+)

Serological reaction :

CRP 7.3 mg/dl

React. for syphilis (−)

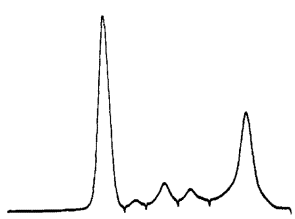
HBs-Ag (−)
HCV-Ab (+)
ATLA-Ab (−)
HIV-Ab (−)

IgG 1,580 mg/dl
IgA 57.1 mg/dl
IgM 3,370 mg/dl

Anti-DNA Ab 12 IU/ml
Anti-nuclear Ab (−)
RA test (+)

Blood Chemistry :

GOT	17	mIU/ml
GPT	11	mIU/ml
LDH	429	mIU/ml
Al.P	91	mIU/ml
ZTT	37.9	unit
TTT	20.2	unit
T-Chol	191	mg/dl
ChE	0.70	△ PH
Bil		
total	0.53	mg/dl
BUN	14.1	mg/dl
Cr	0.4	mg/dl
UA	5.3	mg/dl
Na	142	mEq/l
K	4.4	mEq/l
Cl	101	mEq/l
BS	132	mg/dl
TP	7.8	mg/dl
Alb	3.2	mg/dl
S-Amy	72	SU
A/G	0.88	



Serum immunoelectrophoresis
M-protein IgM-K

Urine immunoelectrophoresis
BJP(+) k type

% of atypical lymphocytes. RBC count was $3.18\times10^6/\mu l$, and rouleaux formation was seen. A bone marrow smear showed infiltration of the large atypical lymphocytes. The serum protein concentration was 7.8 g/dl. Increase in IgM level and a monoclonal IgM (k) band on a serum immunoelectrophoresis were noted. The IgG level was 1,580 mg/dl, IgA 57.1 mg/dl and IgM 3,370 mg/dl. The levels of ZTT and TTT were elevated to 37.9 U and 20.2 U, respectively. Chest X-ray film on admission showed right pleural effusion. Examination of the pleural fluid revealed chylothorax, but no evidence of lymphomatous infiltration. Osteolysis of the right metatarsal bones was noted with fracture on bone X-ray film, suggesting bone involvement. Ultrasonic study of the abdomen revealed paraaortic lymph node enlargement.

Chest CT scan revealed mediastinal lymph node enlargement with right pleural effusion, while abdominal CT scan showed paraaortic lymph node enlargement.

He received 4 cycles of combination chemotherapy consisting of prednisolone, cyclophosphamide, etoposide, pirarubicin and vincristine. After received the treatment, the bone marrow infiltration of the large atypical lymphocytes, the right pleural effusion and the lytic bone lesion nearly disappeared, and the IgM level decreased to 2,397 mg/dl. However, the treatment resulted in transient partial response with rapid recurrence of enlargement of the cervical lymph nodes. Then, he received salvage chemotherapy with cisplatin, mitoxantrone hydrochloride, etoposide and prednisolone. But, the salvage chemotherapy was also ineffective. In the terminal stage, IgM level decreased to 1,120 mg/dl, and a mass appeared on the upper hard palate. Finally, he died of the lymphoma approximately eight months after the admission.

He was submitted to autopsy after death. Autopsy specimens showed infiltration of lymphoma cells into multiple organs. Lymph nodes showed characteristics of non-Hodgikin's lymphoma, with diffuse expansion of large cells, while histolgical features of the tumor of the upper hard palate (Fig. 5) showed plasmacytic differentiation as in Waldenström's macroglobulinemia.

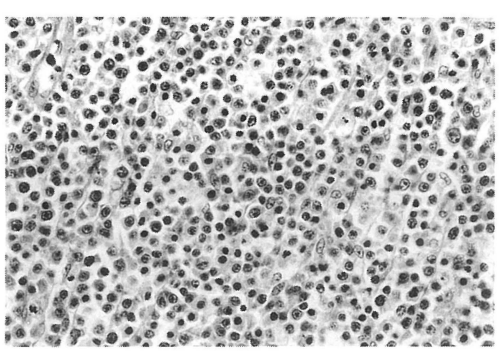


Fig. 5 Tumor of the upper hard palate shows infiltration of small lymphoid cells which show plasmacytoid feature. Hematoxylin-Eosin ×200.

Discussion

The prominent clinical features of this case were : initial presentation with macroglobulinemia ; subsequent development of cervical lymphadenopathy with right chylothorax : variable histological features of lymphoma cells.

The presence of a serum IgM M-component is not tantamount to a diagnosis of macroglobulinemia. There are other B-cell neoplasms in which serum IgM M-components are present, but, with the exception of macroglobulinemia and myeloma, the levels are generally lower than 1.0 g/dl and almost always lower than 2.0 g/dl[8]. In this patient, the IgM leval was more than 3.0 g/dl, and unlike myeloma, marrow plasmacytosis (>10%) was not seen. These findings are considered to be compatible with a diagnosis of macroglobulinemia.

Autopsy revealed widespread infiltration of lymphoma cells with hardly positive cytoplasmic IgM in various organs, and localized proliferation of lymphocytic-plasmacytic calls as in Waldenström's macroglobulinemia. These B-cell lymphoma and plasmocytoid lymphocyte are both regarded as cells of B-cell line in different stages of maturation. In the course of Waldenström's macroglobulinemia, complications of chronic lymphocytic leukemia, hairy-cell leukemia, malignant lymphoma and then related lymphoreticular proliferative disorders have been reported in the literature[1)2)3)4)5)7)9)10)11)]. In the present case, relationship between macroglobulinemia and B-cell lymphoma remains obscure. However, based on our clinical findings, we would consider that the development of B-cell lymphoma represents dedifferentiation from macroglobulinemia.

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(和文抄録)

マクログロブリン血症（IgM-k）の経過中に発症したB細胞性リンパ腫の一剖検例

佐賀県立病院好生館内科[1)]
臨床検査科[2)]
梅野美一[1)]・松石英城[1)]・村上嘉一[1)]・中尾多香昭[1)]
宮本祐一[1)]・吉富誠子[2)]・入江康司[2)]・太田善郎[1)]

興味ある経過をとったマクログロブリン血症の一剖検例を報告する．

症例は65歳の男性．1990年よりマクログロブリン血症の診断で外来治療中であったが，1992年，左側頚部に腫大したリンパ節が触知された．

頚部リンパ節の生検より得られた病理組織学的所見より大細胞型非ホジキンリンパ腫と診断された．遺伝子レベルの検索では、免疫グログリン重鎖およびk軽鎖に遺伝子の再構成が認められた．右中足骨には骨融解像が認められ，また，終末期には上硬口蓋に腫瘤が出現した．剖検の結果，リンパ腫細胞が多数の臓器に浸潤しているのが認められたが，単クローン性IgMは腫瘍中には極くわずかに，しかも局在して認められるにすぎなかった．Waldenströmマクログロブリン血症に認められる形質細胞様の細胞は、上硬口蓋の腫瘤を除いてはどの臓器にも見い出すことができなかった．

これらの所見より、経過中にマクログロブリン血症からB細胞性リンパ腫に移行したことが推察される．