□ CASE REPORT □

Malignant Lymphoma with Myxoid Change and Sarcomatous Features

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We report a case of unusual B-cell malignant lymphoma of the kidney and mediastinum. Renal biopsy showed prominent myxoid changes and sarcomatous features, leading to considerable difficulty in histologic diagnosis on routinely stained histologic sections. However, immunohistochemical staining for lymphocyte markers led to the final histologic diagnosis of B-cell malignant lymphoma. Although myxoid change is not generally found in malignant lymphoma, malignant lymphoma should not be excluded from consideration when one encounters a small round cell sarcoma with myxoid stroma, especially in extranodal soft tissue tumors.

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Key words: sarcoma, kidney, mediastinum, immunohistochemistry, Wilm's tumor, B-cell

Introduction

Although malignant lymphomas are usually readily recognizable by cytologic criteria, unusual histologic features, including spindle or bizarre polymorphic tumor cell appearances and myxoid stroma, create difficulties in differentiating malignant lymphomas from sarcomas (1, 2). Myxoid changes have only recently been recognized as occurring in malignant lymphoma (2–4). Although myxoid change is not common in malignant lymphoma (5), the presence of a myxoid histologic feature does not exclude the possibility of malignant lymphoma (2–4). The occurrence of myxoid features in malignant lymphoma is still not well recognized or understood. In the present report, a case of B-cell malignant lymphoma of the mediastinum and bilateral kidney is described. Renal biopsy showed sarcomatous features and myxoid stroma. Histologic diagnosis was difficult on routinely stained histologic sections. However, immunohistochemical staining for lymphocyte markers established a final diagnosis.

Case Report

A 16-year-old female presented in early August 1990 with neck and facial edema, and cough. She was hospitalized on August 22, 1990; an abnormal mediastinal mass, measuring about $10 \times 13 \times 5$ cm, and a left renal mass, measuring $7 \times 7 \times 13$ cm, and two right renal masses, measuring about 3 cm in diameter were noted. She was transferred to our hospital on August 31, 1990 for further evaluation. Physical examination revealed facial edema and slight distention of the jugular veins. Surface lymph nodes were not palpable. No hepatosplenomegaly was demonstrated. Laboratory data (Table 1) were all within normal limits, except erythrocyte sedimentation rates 33 mm/1 h and 75 mm/2 h, serum immunosuppressive acidic protein 685 μg/ml (normal, below 500), β_2-microglobulin 3.0 μg/ml (normal, 0.9–2.2) and a trace of proteinuria. Chest X-ray revealed a mediastinal mass (Fig. 1). Bone marrow aspiration was performed on August 31, and showed a slight hypocellular marrow with megakaryocytic and erythroid hypoplasia, and small number of atypical lymphocytes (Table 1). However, histologic examination of bone marrow needle biopsy showed a hypocellular marrow

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Table 1. Laboratory Findings on Admission

Peripheral blood		Biohemistry	
RBC	$3.6 \times 10^6/\mu l$	Total protein	7.0 g/dl
Hb	11.0 g/dl	Albumin	65.4%
Ht	31.9%	α1-Globulin	3.4%
WBC	4,700/μl	α2-Globulin	11.0%
Hemogram		β-Globulin	7.5%
Band neutrophils	7%	γ-Globulin	12.7%
Segmented neutrophils	62%	Total bilirubin	0.4 mg/dl
Lymphocytes	20%	GOT	16 IU/l
Monocytes	8%	GPT	4 IU/L
Eosinophils	3%	ZTT	6.1 U
Platelets	$262 \times 10^3/\mu l$	TTT	1.3 U
Reticulocytes	$4.0 \times 10^4/\mu l$	ALP	125 IU/l
Erythrocyte sedimentation rate		γ-GTP	16 IU/l
	33 mm/1 h, 75 mm/2 h	ChE	6.98 IU/l
Bone marrow		LAP	30 IU/l
NCC	$7.3 \times 10^4/\mu l$	LDH	227 IU/l
Megakaryocytes	0%	Amylase	131 IU/l
Erythroid	16.6%	CPK	51 IU/l
Myeloid		CRP	0.4 mg/dl
Myeloblasts	0%	Immunosupprressive acidic protein	
Promyelocytes	0.1%		685 μg/ml
Myelocytes	9.9%	β_2-Microglobulin	3.0 μg/ml
Metamyelocytes	5.9%	Uric acid	5.8 mg/dl
Band neutrophils	23.0%	Creatinine	0.8 mg/dl
Segmented neutrophils	19.6%	BUN	13 mg/dl
Eosinophils	2.0%	Ferritin	35 ng/ml
Basophils	0%	Fe	100 μg/dl
Monocytes	1.7%	TIBC	331 μg/dl
Lymphocytes	16.0%	Total cholesterol	143 mg/dl
Plasma cells	1.0%	Triglyceride	70 mg/dl
Atypical lymphoid cells	4.2%	Blood sugar	88 mg/dl
Coagulation		Immunology	
Prothrombin time	12.5 s	IgG	1,267 mg/dl
Fibrinogen	295 mg/dl	IgA	133 mg/dl
FDP	1.7 μg/ml	IgM	85 mg/dl
FDP-DD	1.1	C3c	61 mg/dl
ATIII	91.1%	C4	30 mg/dl
PLG	97.3%	Tumor markers	
α_2PI	100.7%	AFP	below 10.0 ng/ml
Protein C	78.2%	CEA	below 2.0 ng/ml
Urinalysis		HCG	below 8.0 mIU/ml
Protein	(±)	SCC	below 1.0 ng/ml
Glucose	(−)	CA19-9	13 U/ml
Occult blood	(−)		

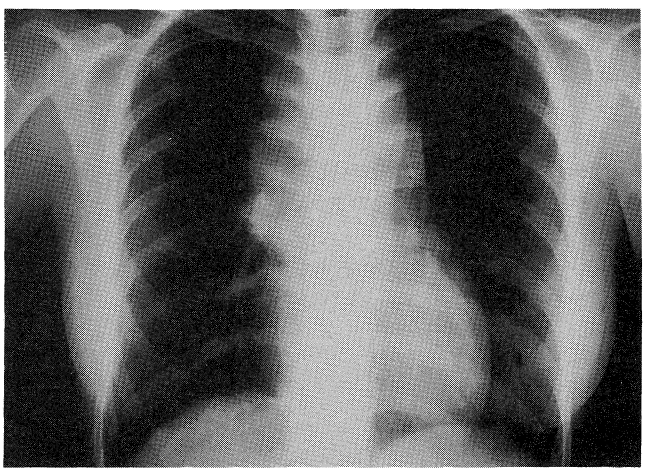

Fig. 1. Chest X-ray showing a mediastinal mass.

without lymphoma cells. Chest and abdominal CTs confirmed a large anterior mediastinal mass, a large left renal mass, and small right renal masses, which had been noted on admission to the first hospital (Fig. 2). Additionally, an abdominal CT revealed mild splenomegaly and hilar lymphadenopathy of the left kidney. The large mediastinal mass produced a marked stenosis of the trachea. The most likely clinical diagnosis was malignant lymphoma associated with superior vena cava syndrome. However, primary renal malignancy with mediastinal metastases could not be excluded. To make a final diagnosis, a left renal biopsy was performed on September 3, 1990.

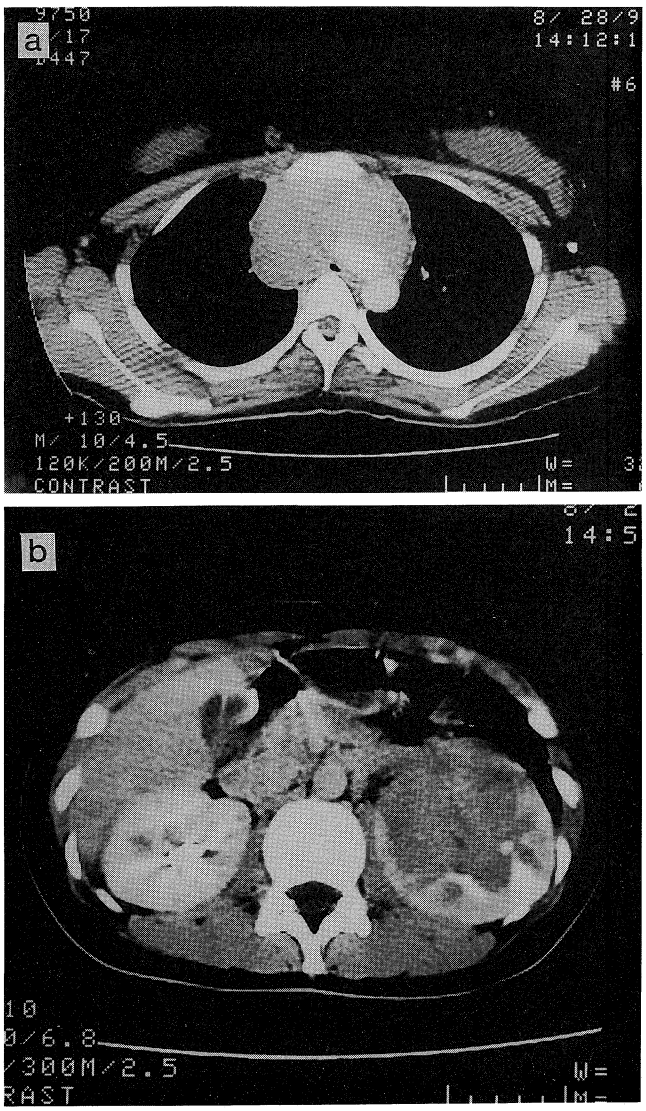

Fig. 2. Computed tomographies of the chest (a) and abdomen (b), showing a mediastinal mass with marked compression of the trachea (a), and bilateral renal masses (b).

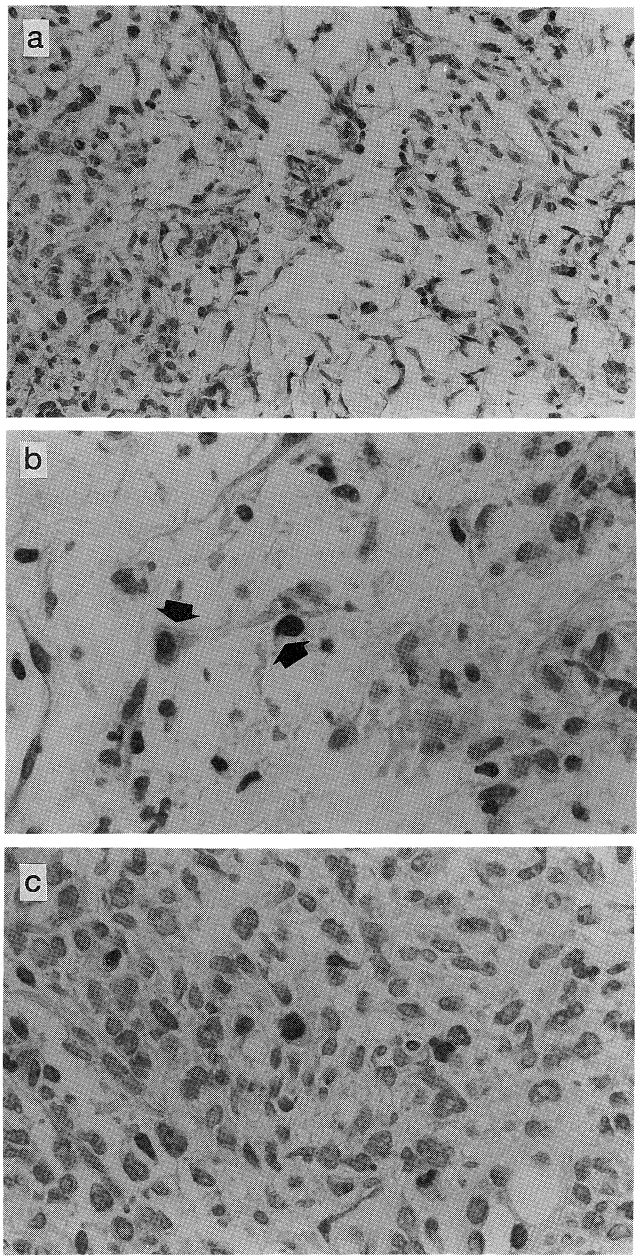

Fig. 3. Microphotographs of the renal tumor, showing spindle-shaped cell proliferation with marked myxoid stroma (a), bizarre tadpole-shaped cells with fibrillar cytoplasm (b, arrows), and solid growth of round, oval or fusiform tumor cells with occasional giant cells (c). (HE stain. a; ×400, b; ×800, c; ×800)

Materials and Methods

Biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin (HE), periodic acid-Schiff (PAS), Alcian blue, and silver impregnation. Immunohistochemical staining was performed by the avidin-biotin-peroxidase-complex method, as reported previously (6), using antibodies to leukocyte common antigen (CD45; Dakopatts, Copenhagen, Denmark), epithelial membrane antigen (Dakopatts), cytokeratin (Hybritech, La Jolla, CA, USA), myoglobin (Dakopatts), desmin (Dakopatts), vimentin (Dakopatts), S-100 (Dakopatts), L-26 (CD20; Dakopatts), LN-2 (B-cell marker; Technicolne, Santa Ana, CA, USA), MB-2 (B-cell marker; Biotest Diagnostics, Dreieich, Germany), Ber-H2 (Ki-1, CD30; Dakopatts), and UCHL1 (CD45RO; Dakopatts).

Pathologic Findings

The biopsy tissues were gray-white, and rubbery in consistency. Histologic examination revealed a diffuse growth of tumor cells with an abundant myxoid stroma (Fig. 3a). The tumor cells were suspended in a mucoid

stroma. They were spindle, oval and polymorphic, and possessed irregularly folded nuclei, coarse chromatin, and occasional large nucleoli. The cytoplasm was relatively abundant and amphophilic. Some cells were spindle-shaped and occasionally had eosinophilic cytoplasm. The appearance was somewhat rhabdomyoid, although cross striations and rhabdomyoblasts were not observed (Fig. 3b). Bizarre and multinucleated giants cells were occasionally found. Additionally, parts of the tumor showed areas of solid growth, where tumor cells with round, oval or irregularly folded nuclei were seen, together with occasional giant cells (Fig. 3c). The mitotic count averaged two per high power field. The myxoid stroma showed hyaluronidase-sensitive Alcian blue staining. Tumor cells were negative for PAS. Storiform pattern was not found. Lipoblasts and rhabdomyoblasts were not observed. Neither epithelial tumor cell nests nor chondroid or bone tissue was observed. The histologic features described above initially resulted in an erroneous exclusion of malignant lymphoma and led to a diagnosis of probable Wilm's tumor, even though the patient was older than is typical of Wilm's tumor, and the cytologic features in the more solid areas were rather compatible with malignant lymphoma. However, immunohistochemical staining revealed that the tumor cells were positive for LCA, L-26, and LN-2, but negative for Ber-H2, MB2, UCHL1, EMA, cytokeratin, vimentin, desmin, myoglobin, and S-100. The LCA staining was localized to the cell membrane, LN-2 to nuclear membrane and cytoplasm, and L-26 generally to the cell membrane (Figs. 4 and 5). A diagnosis of B-cell malignant lymphoma was finally established.

Clinical Course

After establishement of histologic diagnosis, the patient was treated with combined chemotherapy. The patient was free of symptoms until early April 1992, when she complained of nausea and headache, and was readmitted to the Kanazawa University Hospital. Abnormal laboratory tests were as follows: RBC 2×10^6/mm^3, γ-GTP 71 IU/l, and LDH 88 IU/l. Throughout the clinical course, abnormally elevated serum LDH levels were not observed, but occasionally abnormal low LDH

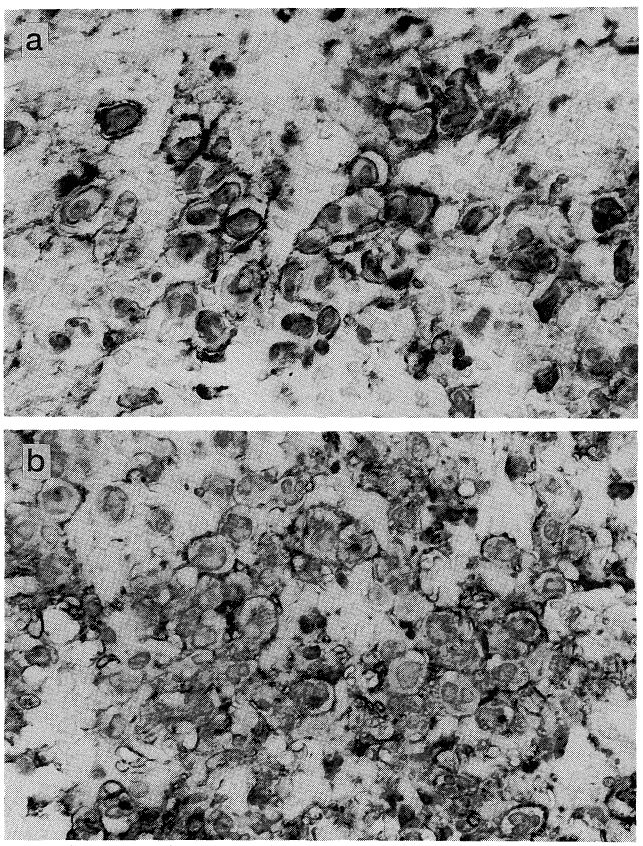

Fig. 4. Immunohistochemical staining for leukocyte common antigen (LCA) and L-26 of tumor cells in solid area. The majority of tumor cells are positive for both antigens; LCA reacting with the cell surface membrane (a), and L-26 reacting with the cytoplasmic membrane (b). (ABC immunohistochemical stain counterstained with hematoxylin. ×800)

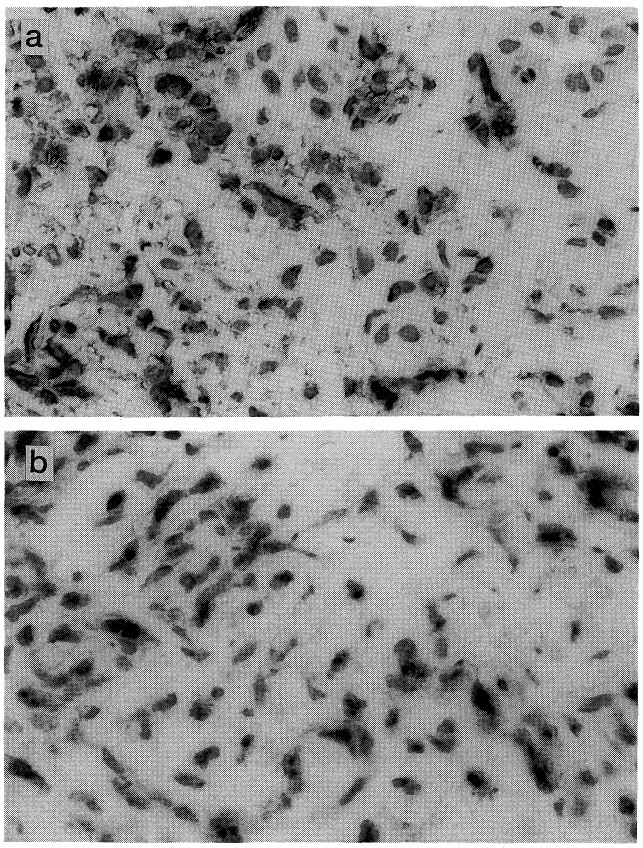

Fig. 5. Immunohistochemical staining for LN-2 of spindle-shaped tumor cells in myxoid area; LN-2 reacting with the nuclear membrane and cytoplasm (a). A section of negative control in which phosphate-buffered saline in place of primary antibody was applied, shows no positively staining (b). (ABC immunoperoxidase stain counterstained with hematoxylin. ×800)

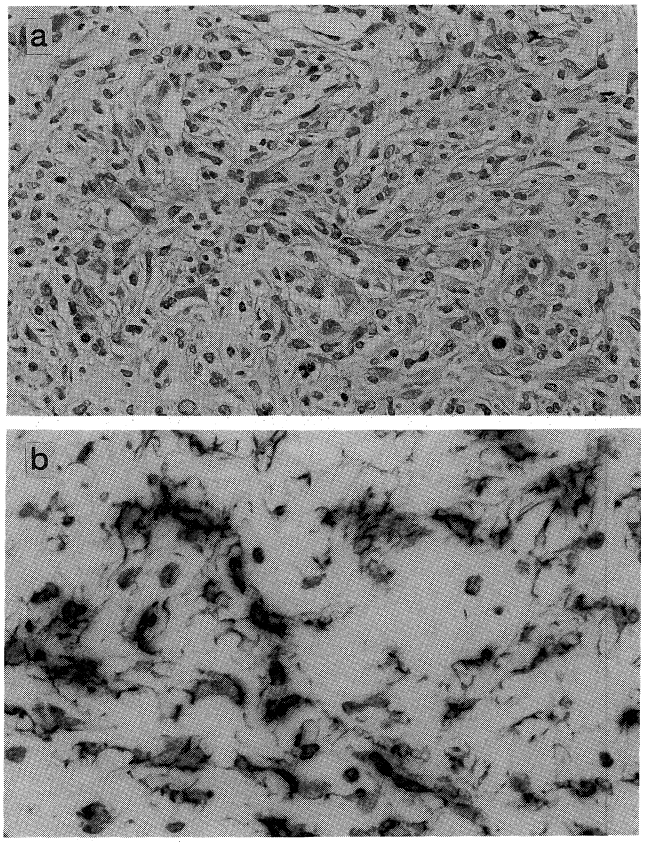

Fig. 6. Recurrent tumor cells of the meninges showing sarcomatous growth (a), and immunoperoxidase staining for L-26 (b). Cytoplasmic membranes of spindle-shaped tumor cells are positive for L-26 (b) (a: HE stain, ×400. b: ABC immunoperoxidase stain counterstained with hematoxylin ×800)

Table 2. Surface Marker Analysis by FACScan

T cell-associated antigens	
CD2(T11, Leu5)	6%
CD3(T3, Leu4)	2%
CD4(T4, Leu3)	3%
CD5(T1, Leu1)	5%
CD7(Leu9)	3%
CD8(T8, Leu2)	3%
B cell-associated antigens	
CD10(J5, CALLA)	1%
CD19(B4, Leu12)	99%
CD20(B1, Leu16)	98%
CD21(B2)	2%
CD22(B3)	95%
Myelomonocyte-associated antigens	
CD13(My7)	6%
CD33(LeuM9)	2%
CD34(MY10)	19%
Unspecified antigens	
HLA-DR	98%
CD16(Leu11)	3%
CD56(NHK1, Leu19)	8%
CD57(Leu7)	2%

levels were found. CT scan of the brain revealed a tumor in the right frontal lobe of the brain. Neither extracranial tumor nor surface or inner lymphadenopathy was found. On April 14, resection of the brain tumor was performed, followed by radiation therapy. Resected tissues contained brain parenchyma and meninges, both of which were involved with the malignant lymphoma. Lymphoma cells in the meninges exhibited a sarcomatous growth with partially myxoid stroma with B-cell markers (L-26$^+$ and LN-2$^+$) (Fig. 6), similar to that of the renal biopsy. Flow cytometrical analysis of the brain tumor tissue showed typical B-cell markers (Table 2). In mid May, the patient complained of muscle weakness in the lower legs. CT scan revealed an intramedullary mass of the lumbosacral region. Extramedullary lesions, however, were not found. She was treated with local radiation therapy. She is still hospitalized and her present condition is not good.

Discussion

Myxoid changes are characterized by the presence of a myxoid, or mucoid background of glycosaminoglycans (acid mucopolysaccharides) or glycoproteins that show a basophilic stain with hematoxylin and eosin. Myxoid changes are found in both epithelial and mesenchymal tumors (7). Myxoid areas, a storiform pattern, bizarre giant cells, and spindling are generally absent in lymphoma, and these features did not support the diagnosis of malignant lymphoma (5). However, with recent advances in immunohistochemical and molecular biological techniques, the morphologic spectrum of malignant lymphoma has become broader than that previously recognized (3). Examples are soft tissue large cell pleomorphic lymphoma which sometimes simulates pleomorphic sarcoma such as malignant fibrous histiocytoma, pleomorphic rhabdomyosarcoma, and pleomorphic liposarcoma (2, 5). Soft tissue lymphomas composed primarily of small round cells or mixed populations may sometimes be confused with small round cell tumors such as neuroepithelioma, Ewing's sarcoma, and rhabdomyosarcoma (5). Other examples, which might previously have been erroneously recognized as non-lymphoid tumors, are angiotropic large cell lymphoma (8), filiform large cell lymphoma (9), lymphoma with rosette formation (10), signet ring cell lymphoma (11), lymphoma with desmosome-like cell junctions (12), and sinusoidal large cell lymphoma (13). Myxoid change in malignant lymphoma has only recently been recognized (2–4). It is most likely that extranodal lymphoma with marked stromal myxoid change in addition to polymorphic or spindle cell features are more easily confused with myxoid soft tissue tumors (7). To date, only three cases of malignant lymphoma exhibiting stromal myxoid change have been reported, and all are reported from a single institute in Hong Kong (2–4). Therefore, it would

be useful to confirm and extend the findings in other laboratories.

The case presented herein had simultaneous mediastinal and bilateral renal masses, together with lymphadenopathy of the left renal hilus. Clinical features and CT and MRI findings indicated a malignant neoplasm, most likely malignant lymphoma. However, primary renal tumor with mediastinal and other metastases could not be excluded. Histologic examination of the left renal tumor was extremely challenging and led to considerable diagnostic difficulty on routinely stained histologic sections because the tumor consisted of pleomorphic cells with occasional spindle or bizarre giant cells together with a marked stromal myxoid change. Included for differential diagnosis were lymphoma, nephroblastoma (Wilm's tumor), renal cell carcinoma, and rare renal sarcomas, such as rhabdomyosarcoma, liposarcoma and malignant fibrous histiocytoma. Renal cell carcinoma rarely simulates sarcomas, such as fibrosarcoma or rhabdomyosarcoma, which are called fibrosarcomatoid or rhabdomyomatoid renal cell carcinoma, respectively (14). The renal tumor histology in the present case did not reveal as much pleomorphism as pleomorphic sarcomas such as pleomorphic malignant fibrous histiocytoma and pleomorphic rhabdomyosarcoma. Absence of lipoblasts and rhabdomyoblasts ruled out the possibility of liposarcoma and rhabdomyosarcoma. Our initial probable diagnosis on routine histologic sections was Wilm's tumor with mediastinal metastases, although the patient was older than the reported age group for Wilm's tumor (14). Subsequent immunohistochemical staining clearly revealed that the tumor was B-cell malignant lymphoma, diffuse type. Based on the tumor localization and the age of the present case, diffuse lymphoblastic lymphoma and Burkitt lymphoma were not excluded. However, later these were definitely ruled out by surface marker analysis of tumor cells by flow cytometry, because the tumor cells had characteristic B-lymphocyte surface markers ($CD19^+$, $CD20^+$, $CD22^+$, $HLA\text{-}DR^+$, $CD10^-$, $CD21^-$) and no T-cell markers ($CD2^-$, $CD3^-$, $CD4^-$, $CD5^-$, $CD7^-$, $CD8^-$). These results of tumor cell surface markers indicate that the tumor cells originate from non-follicular peripheral B-cells.

The pathogenesis of myxoid change in malignant lymphoma is not well understood. Since myxoid malignant lymphomas are mainly seen in soft tissues where fibroblasts are normally abundant (2, 3), some local factors, such as tissue edema, stimulating proliferation of fibroblasts and myofibroblasts must be considered (4).

In conclusion, the present case emphasizes that myxoid change may occur in malignant lymphoma, especially in tissues where fibroblasts are normally abundant. The presence of myxoid change does not exclude the possibility of malignant lymphoma.

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