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CASE REPORT

Multicentric Castleman's Disease, Non-Hodgkin's Lymphoma, and Kaposi's Sarcoma: A Rare Simultaneous Occurrence

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SUMMARY A rare simultaneous occurrence of multicentric Castleman's disease, non-Hodgkin's lymphoma, and Kaposi's sarcoma was diagnosed in a 70-year-old man who presented with fever, polyarthralgia, weight loss, vascular purpura, anemia, generalized lymphadenopathy, and hepatosplenomegaly. He had no risk of HIV infection and serological tests for HIV were negative twice, but a low number of T-cells and a reversed CD4/CD8 ratio were observed. During hospitalization, he developed Kaposi's sarcoma at the right sole. Lymph node biopsies revealed multicentric Castleman's disease together with a large B-cell lymphoma, which showed monotypic IgM-lambda lymphocytes. To our knowledge, this is the first report in which systemic manifestations of all three diseases occurred simultaneously prior to any specific treatment. The altered immune status and human herpesvirus-8 infection might have played a role in the pathogenesis of this occurrence.

Multicentric Castleman's disease (MCD) is a recently recognized entity among atypical lymphoproliferative disorders.[1-4] The protean clinical manifestations in MCD are mostly related to lymphoproliferation and polyclonal hypergammaglobulinemia secondary to elevated levels of interleukin-6.[5] The patients usually present with generalized lymphadenopathy, fever, anemia, skin rash, hepatosplenomegaly, and a number of abnormal laboratory findings including polyclonal hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), positive Coombs' test, hypoalbuminemia, impaired liver function test, elevated lactate dehydrogenase (LDH), and marrow plasmacytosis. Clinically, MCD cannot be distinguished from angioimmunoblastic lymphadenopathy with dysproteinemia.[6] The median survival in MCD is approximately 24 to 30 months and the main cause of death is infection.[1-4]

MCD is one of many diseases known to have an increased risk of developing concurrent malignancy.[1,3,4] The two most common types of malignancy occurring in MCD are Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL). In a review of MCD by Peterson and Frizzera,[3] KS and NHL were found in 13% and 18% of patients with MCD, respectively. KS may occur synchronously or metachronously with respect to MCD, but NHL usually occurs months or years subsequently to MCD. However, simultaneous occurrence of MCD, NHL, and KS is rare. We found only three cases reported in the English literature.[7-9] We hereby report another case of such a rare occurrence. The term "simultaneous occurrence" is used to describe two primary malignancies diagnosed within three months of each other. When we use this definition, the present case seems to be the first case who developed systemic manifestation of MCD, NHL, and KS simultaneously prior to any specific treatment while the first two previous cases developed second or third neoplasms after a period of immunosuppressive therapy.[7,8] The third case first developed MCD and then, 11 months later, NHL and KS.[9]

CASE REPORT

A 70-year-old Thai man presented at Siriraj Hospital in March 1994 with fever and vascular purpura at both lower legs for

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three days. Two months previously, he had developed intermittent low-grade fever, polyarthralgia, and lost 2 kg weight. He was previously healthy and had no history of cigarette, alcohol or drug abuse. He had no risk of HIV infection. Physical examination revealed an asthenic built man with moderate anemia, generalized lymphadenopathy, hepatosplenomegaly, a left retroperitoneal mass of approximately 8 cm in diameter, and palpable vascular purpura at both lower legs. Investigations revealed a moderate degree of hemolytic anemia according to a positive direct Coombs' test and homozygous hemoglobin E. Westergren ESR was 70 mm/hr. Urinalysis was unremarkable. Blood chemistry showed hypoalbuminemia (2.7 g/dl), hyperglobulinemia (5.8 g/dl), elevated LDH (691 U/l, normal 225-450 U/l), and slightly elevated creatinine (1.4 mg/dl). Other blood chemical findings, including fasting blood sugar, blood urea nitrogen, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, cholesterol, and triglycerides, were normal. Serological tests were negative for human immunodeficiency virus (twice), hepatitis B surface antigen, VDRL, anti-DNA and antinuclear antigen. LE test was negative. Total lymphocytes were 979 cells/mm^3 with CD4+ T-cells, 284 cells/mm^3 (29%), CD8+ T-cells, 329 cells/mm^3 (33.6%), and CD4/CD8 ratio was 0.86. Ultrasonography of the abdomen confirmed hepatosplenomegaly and revealed right renal calculi and bilateral hydronephrosis. The clinical impression was malignant lymphoma.

Skin biopsy of the vascular purpura revealed leukocytoclastic vasculitis. Without any specific treatment, vascular purpura and fever spontaneously disappeared after hospitalization for three days. Bone marrow examination revealed erythroid hyperplasia and reactive polyclonal plasmacytosis. On the fourth admission day, vesiculopapular lesions were observed on the medial aspect of the right sole. They progressively expanded and turned into a bluish purple plaque involving the medial half of the sole. Skin biopsy demonstrated KS. During hospitalization, the patient still had intermittent fever, persistent lymphadenopathy, and anemia. Left cervical lymph node biopsy was then performed; the diagnosis was MCD associated with NHL of the large B-cell type. These histologic findings were similar in a subsequent biopsy of a right cervical lymph node. No evidence of KS was detected in either lymph node. The patient received combination chemotherapy including cyclophosphamide, vincristine, and prednisolone (COP regimen) as treatment for NHL and additionally local radiotherapy to the KS of the right sole of 3,000 cGy. After the administration of chemotherapy for one week, the patient had defervescence and rapid reduction in size of

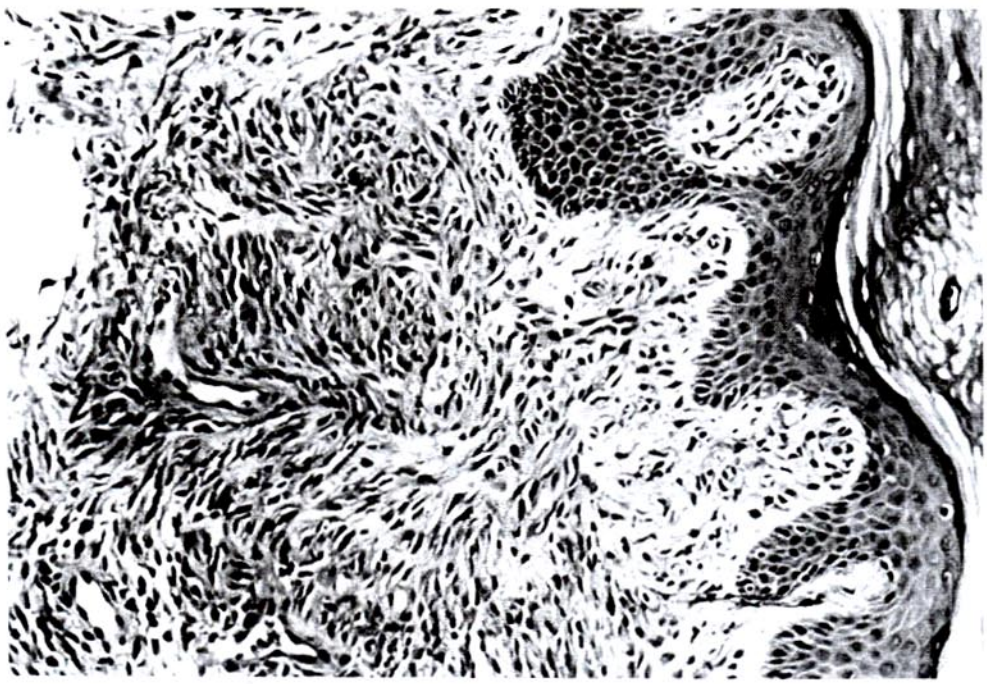

Fig. 1 Irregularly arranged slit-like vascular spaces located in the dermis of the lesion biopsied from the right sole, characteristic of Kaposi's sarcoma (hematoxylin-eosin, original magnification, x100).

the lymphadenopathy was observed. Two weeks after radiotherapy, the KS lesion appeared paler. Unfortunately, the patient was lost to further follow-ups after the first follow-up.

All specimens taken from the skin, lymph nodes, and bone marrow were fixed in neutral buffered formalin. They were conventionally examined, sampled, processed, embedded, sectioned and stained with hematoxylin-eosin, periodic-acid Schiff and methyl green pyronine. Paraffin section immunoperoxidase using the labeled streptavidin-biotin technique[10] was employed to study various markers including CD3, CD20 (L-26), CD45 (LCA), CD68 (KP-1), immunoglobulin G, A, M, kappa, and lambda light chains. The whole remaining skin biopsy and a representative area of each lymph node biopsy from paraffin-embedded tissue blocks were deparaffinized in xylene, rehydrated in descending concentrations of ethanol, fixed in 2% osmium tetroxide, dehydrated in ascending concentrations of ethanol, embedded in Epon, sectioned in 1 μg thick sections, stained with toluidine blue, and areas selected for ultrathin sections which were then stained with uranyl acetate and lead acetate for transmission electron microscopy (TEM).

The skin biopsy of the right sole demonstrated the characteristic features of KS. Irregularly arranged, spindle cell lined slit-like vascular spaces were confined in the dermis (Fig. 1). These spindle cells had plump elongated nuclei and showed some degree of atypia. Mitotic figures were infrequent. Extravasation of erythrocytes was prominent. The two biopsies of bilateral cervical lymph nodes revealed the same histologic findings- follicular hyperplasia accompanied by hypervascularity of postcapillary venules and some patent sinuses in the interfollicular areas. Each follicle had a small germinal center which was traversed by hyalinized blood vessels and contained variable amounts of hyaline material. The small lymphocytes in the mantle layer formed concentric arrangements (Fig. 2). Varying numbers of plasma cells were noted in the interfollicular areas and focally formed sheets of cells (Fig. 3). These plasma cells were polyclonal by staining with various types of immunoglobulins. In many areas, large transformed (noncleaved) lymphoid cells accumulated and definitely formed clusters; moreover, they were stained with CD20 (membranous pattern) and monotypically with IgM-lambda in their cytoplasm (Fig. 4). These histologic findings and immunoperoxidase staining results were consistent in both lymph node biopsies; the diagnosis of MCD associated with NHL of the large B-cell type was made. No areas of va-

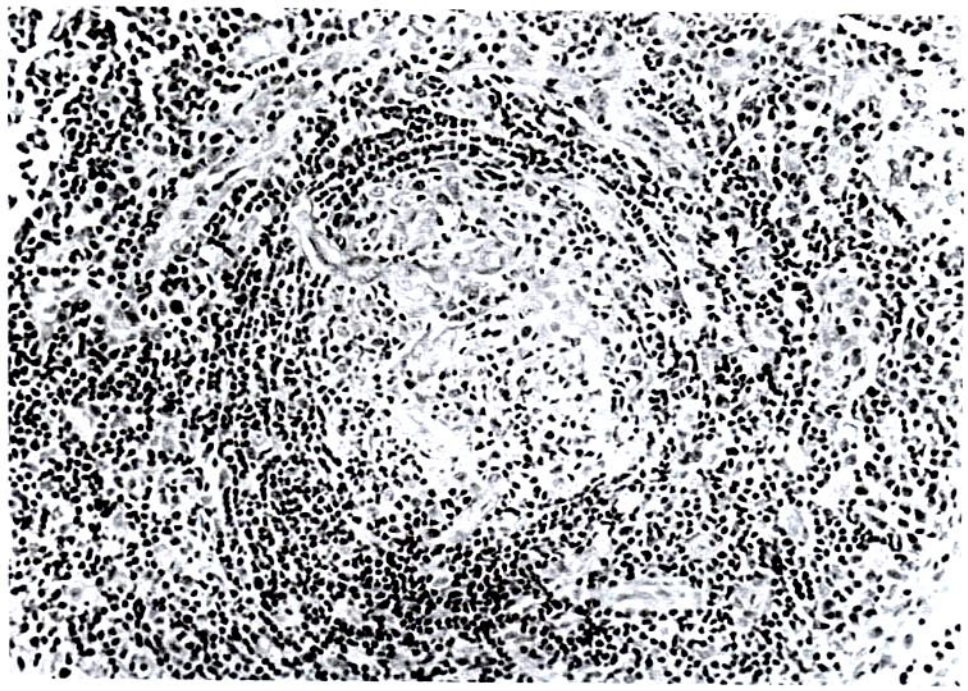

Fig. 2 Follicles with hyaline-vascular feature and hypervascularity in the interfollicular areas. Increase in hyaline material in the germinal center is noted. The interfollicular area shows hypervascularity admixed with lymphoplasmacytic proliferation (periodic-acid Schiff, original magnification, x100).

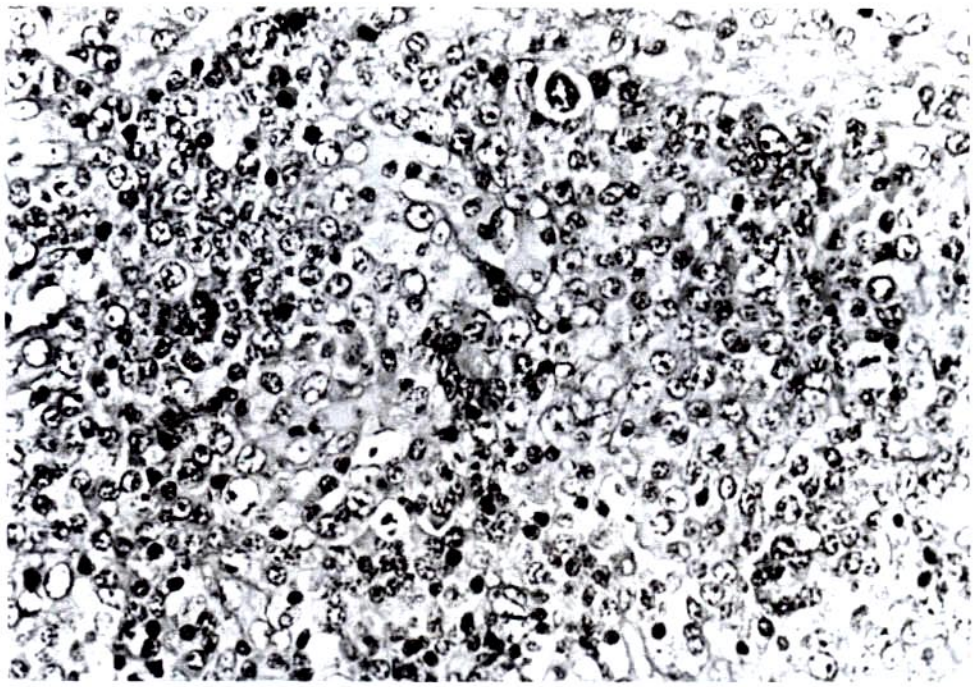

Fig. 3 Sheets of plasma cells found focally in the interfollicular areas of the lymph node (hematoxylin-eosin, original magnification, x200).

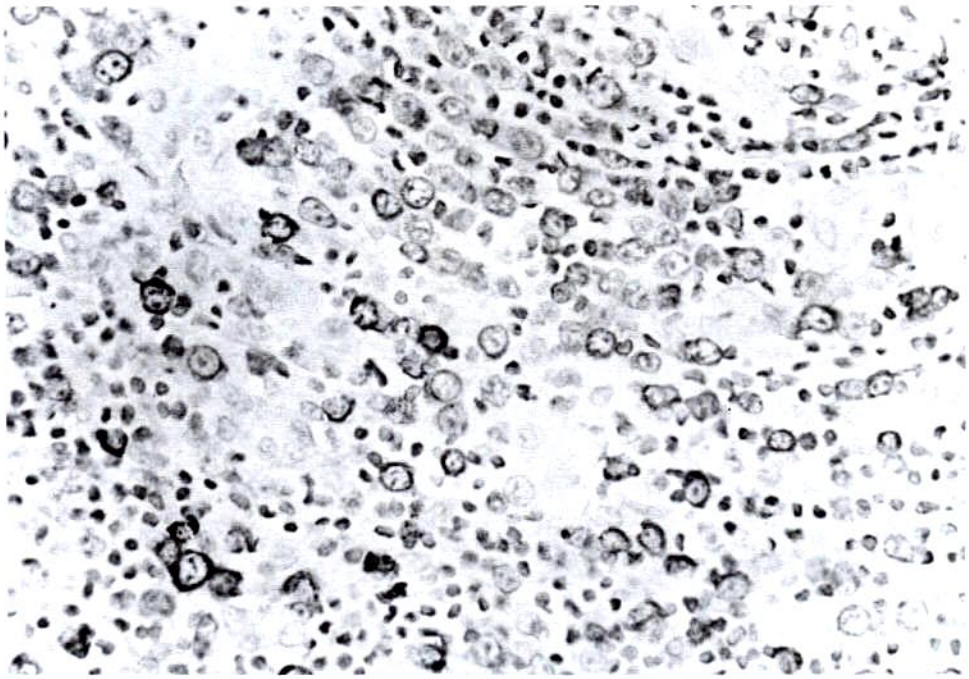

Fig. 4 Large transformed (noncleaved) lymphoid cells showing monotypic cytoplasmic immunoglobulin M (IgM). They also contain monotypic lambda light chains (not shown). (IgM; labeled streptavidin-biotin technique, hematoxylin counterstain, original magnification, x200).

soformative lesions of KS were found in the lymph nodes. Only some scattered polyclonal plasma cells were evident in bone marrow; no IgM-lambda bearing cells or vasoformative lesions were detected. No viral particles were demonstrated after scrutiny by TEM of the skin and lymph node biopsies.

DISCUSSION

The case reported here had clinical manifestations of a lymphoproliferative disorder which was proven to be MCD associated with NHL of the large B-cell type; the patient later developed KS within a 3-month period of the illness, establishing a simultaneous occurrence of MCD, NHL and Kaposi's sarcoma.

The histologic findings in MCD were described to be similar to those of the plasma cell variant of Castleman's disease.[1,3,4] But, in fact, typical hyaline-vascular follicles can be prominent and conversion between hyaline-vascular and plasma cell histologic types can be observed in subsequent biopsies.[2] Some investigators regarded these hyaline-vascular follicles as burned-out phase of the plasma cell variant.[3] However, we believe that the hyaline-vascular type or mixed type does exist in MCD, in fact, we placed the present case into the mixed type. Monoclonal plasma cells have been described in Castleman's disease.[11] But in the present case, the plasma cells were polyclonal while the large B-cells possessed monotypic IgM-lambda, thus confirmed the diagnosis of a large B-cell lymphoma arising in MCD.

The associations between MCD and KS, MCD and NHL, or KS and NHL are well recognized,[1,3,4,12] but simultaneous occurrence of all three diseases is rare because only three cases were previously reported (Table 1).[7-9] Only the present case developed all three diseases simultaneously prior to any specific treatment. The case reported by Perlow *et al.*[7] developed large cell lymphoma and KS after a

Table 1 Comparison of the present case with the three previously reported cases of rare simultaneous occurrence of multicentric Castleman's disease (MCD), non-Hodgkin's lymphoma (NHL), and Kaposi's sarcoma (KS)

Clinicopathologic features	The present case	Perlow *et al.*[7]	Dickson *et al.*[8]	Codish *et al.*[9]
Age (years)/**Sex**	70/Male	31/Male	72/Male	73/Female
Clinical manifestation	Fever, polyarthralgia, vascular purpura of both lower legs	Persistent headache, rhinitis, pharyngitis, sweating, fever	Abdominal pain and swelling	Hallucination and delusion due to hypoglycemia
Risk of HIV infection	No	High (homosexual)	No	No
Organ involvement	Lymph nodes (generalized), liver, spleen, skin	Lymph nodes (generalized), liver (late), skin (late)	Left axillary node, spleen, omentum, peritoneum, skin (late)	Left axillary node, ascites, lymph nodes (generalized), skin (late)
Sequence of disease*	MCD = NHL = KS	MCD > (NHL = KS)	(MCD = NHL) > KS	MCD > (NHL = KS)
Type of MCD	Mixed	Hyaline-vascular	Mixed	Mixed
Type of lymphoma	Large cell (IgMλ)	Large cell (IgMλ)	Small cleaved cell (IgAλ)	Primary effusion (CD30+, EMA+)
Anemia	Moderate	Slight	Slight	No
ESR (mm/hr)	70	126	95	Not available
Hypergammaglobulinemia	Yes	Yes	Not available	Not available
Serum LDH (U/l)	691	Not available	Not available	Not available
Numbers of T-cells	Low	Not available	Normal	Not available
CD4/CD8 ratio	0.86 (reversed)	Not available	0.75 (reversed)	Not available
Clinical course	Partial response (lost to follow-up)	Died	Died	Died

* = simultaneous occurrence within 3 months
> disease on the left occurred before the one on the right more than 3 months
EMA – epithelial membrane antigen

period of immunosuppressive treatment for MCD with prednisone. No evidence of MCD was found at the autopsy. The case reported by Dickson *et al.*[8] developed KS during combination chemotherapy for treatment of MCD and small cleaved cell lymphoma. It is noteworthy that the lymphomas in these cases, including the present case, were of B-cell phenotype except for the case reported by Codish *et al.*[9] whose NHL type was described as a primary effusion lymphoma of the null cell type (negative for B- and T-cell markers). The third case developed all three diseases prior to any specific treatment but NHL and KS developed 11 months after the diagnosis of MCD. Xerri *et al.*[13] described a case with a solitary inguinal nodal mass which showed nodular areas occupied by Castleman's disease or follicular lymphoma of the small cleaved cell type and a separate area of KS within the same mass; however, this was a localized disease and the patient was alive and well after removal of the mass.

An altered immune status in patients with MCD or KS, presumably resulting in impaired immunosurveillance, is usually proposed as a possible mechanism for the development of second neoplasm in these patients.[3] There were altered parameters in the immune status of the present case as previously described in MCD cases including a low number of T-cells and a reversed CD4/CD8 ratio. Other abnormal immune responses in MCD include T-cell unresponsiveness to mitogens, cell-mediated immunodeficiency, and reduced natural killer cell activity.[3] In the case reported by Dickson *et al.*,[8] reversed CD4/CD8 ratio was also found due to an increase in the CD8 subset. The cause of the decrease in the number of CD4+ T-cells in the present case was not due to HIV infection because serological tests by ELISA for anti-HIV antibody were negative at two different occasions and the patient had no risk of HIV infection.

Human Herpes virus type 8 (HHV-8), the Kaposi's sarcoma associated herpesvirus, has been reported to be associated with a group of patients with MCD, in addition to those with KS and primary effusion lymphoma.[14] The genome of this virus contains a gene homologue to the human IL-6 gene resulting in an elevation of IL-6 in these HHV-8 associated diseases.[15] The case reported by Codish *et al.*[9] was proven to have HHV-8 association in all three lesions by using antibody against the latent nuclear antigen 1 (LNA-1) of HHV-8 and polymerase chain reaction to amplify HHV-8 DNA sequences. Interestingly, the recent study on MCD and NHL associated with HHV-8 has demonstrated that HHV-8 was specifically associated with monotypic IgM-lambda large B-cells (so-called "plasmablasts") in both MCD and NHL.[16] In that study, two cases without HIV infection and six cases with HIV infection had MCD and NHL with monotypic IgM-lambda cells similar to the present case and the case reported by Perlow *et al.*[7] Moreover, these HHV-8 positive large B-cells did not harbor somatic mutations in the rearranged immunoglobulin gene, different from those normal large B-cells undergoing a germinal center reaction. The reason underlying this observation is not clear.[16] The seroprevalence of HHV-8 in Southeast Asia is low- less than 5%. In Thailand, the prevalence is only 4% in healthy individuals and 11.2% in HIV-1 positive individuals, much lower than that in comparable HIV-positive population in the USA or Africa.[17] It is possible that the rare simultaneous occurrence of MCD, NHL, and KS in the present case as well as the first two cases reported by Perlow *et al.*[7] and Dickson *et al.*[8] may be etiologically related to HHV-8. Although we failed to identify viral particles by TEM, the possibility of HHV-8 infection in the present case cannot be excluded. Certainly, further studies by molecular techniques that are more sensitive and more specific are needed.

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REFERENCES

1. Frizzera G, Peterson BA, Bayrd ED, Goldman A. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: clinical findings and clinicopathologic correlations in 15 patients. J Clin Oncol 1985; 3: 1202-16.
2. Weisenburger DD, Nathwani BN, Weinberg CD, Rappaport H. Multicentric angiofollicular lymph node hyperplasia: a clinicopathologic study of 16 cases. Hum Pathol 1985; 16: 162-72.
3. Peterson BA, Frizzera G. Multicentric Castleman's disease. Semin Oncol 1993; 20: 636-47.
4. Frizzera G. Atypical lymphoproliferative disorders. In: Knowles DM, ed. Neoplastic Hematopathology, 2nd edition. Lippincott Williams & Wilkins, Philadelphia, 2001; pp. 569-622.
5. Yoshizaki K, Matsuda T, Nishimoto N, *et al.* Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. Blood 1989; 74: 1360-7.
6. Upara S, Ruchutrakool T, Sukpanichnant S. Lymph node pathology in patients with a clinical diagnosis of angioimmunoblastic lymphadenopathy with dysproteinemia (AILD): an analysis of 37 cases. Asian Pacific J Allergy Immunol 1997; 15: 15-20.
7. Perlow LS, Taff ML, Orsini JM, *et al.* Kaposi's sarcoma in a young homosexual man. Association with angiofollicular

lymphoid hyperplasia and a malignant lymphoproliferative disorder. Arch Pathol Lab Med 1983; 107: 510-3.
8. Dickson D, Ben-Ezra JM, Reed J, Flax H, Janis R. Multicentric giant lymph node hyperplasia, Kaposi's sarcoma, and lymphoma. Arch Pathol Lab Med 1985; 109: 1013-8.
9. Codish S, Abu-Shakra M, Ariad S, *et al.* Manifestations of three HHV-8-related diseases in an HIV-negative patient: immunoblastic variant multicentric Castleman's disease, primary effusion lymphoma, and Kaposi's sarcoma. Am J Hematol 2000; 65: 310-4.
10. Sukpanichnant S, Sonakul D, Piankijagum A, *et al.* Malignant lymphoma in Thailand. Changes in the frequency of malignant lymphoma determined from a histopathologic and immunophenotypic analysis of 425 cases at Siriraj Hospital. Cancer 1998; 83: 1197-204.
11. Radaszkiewicz T, Hansmann ML, Lennert K. Monoclonality and polyclonality of plasma cells in Castleman's disease of the plasma cell variant. Histopathology 1989; 14: 11-24.
12. Ulbright TM, Santa Cruz DJ. Kaposi's sarcoma: relationship with hematologic, lymphoid and thymic neoplasia. Cancer 1981; 47: 963-73.
13. Xerri L, Gingou V, Lepidi H, *et al.* Lymphadenopathic tumor exhibiting intermingled features of Kaposi's sarcoma, malignant lymphoma and angiofollicular hyperplasia. Arch Pathol Lab Med 1991; 115: 1162-6.
14. Cesarman E, Knowles DM. Kaposi's sarcoma-associated herpesvirus: a lymphotropic human herpesvirus associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. Semin Diagn Pathol 1997; 14: 54-66.
15. Neipel F, Albrecht JC, Ensser A, *et al.* Human herpesvirus-8 encodes a homolog of interleukin-6. J Virol 1997; 71: 839-42.
16. Du M-Q, Liu H, Diss TC, *et al.* Kaposi's sarcoma-associated herpesvirus infects monotypic (IgMλ) but polyclonal naïve B cells in Castleman's disease and associated lymphoproliferative disorders. Blood 2001; 97: 2130-6.
17. Ablashi D, Chatlynne L, Cooper H, *et al.* Seroprevalence of human herpesvirus-8 (HHV-8) in countries of Southeast Asia compared to the USA, the Caribbean and Africa. Br J Cancer 1999; 81: 893-7.