Chula Med J Vol. 46 No. 5 May 2002

Kaposi's sarcoma of a lymph node with Castleman's disease-like lesions in HIV-infected patient: A case report

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Assanasen T, Wannakrairot P. Kaposi's sarcoma of a lymph node with Castleman's disease-like lesions in HIV-infected patient: A case report. Chula Med J 2002 May; 46(5): 409 - 17

The histomorphology of Castleman's disease of lymph nodes is not specific only for Castleman's disease. Kaposi's sarcomas (KS) and HIV infection of lymph nodes are also found in a number of diseases. We, herein, report the rare characteristics found in the same lymph node of an HIV-infected patient, to remind pathologists about the existence of this histomorphology. The case report was of a Thai patient, admitted at King Chulalongkorn Memorial Hospital, who presented with multiple cervical lymphadenopathy. A lymph node biopsy and a routine histopathological examination were done. A coexistence, a Castleman's disease-like lesion and Kaposi's sarcoma, was observed in the same lymph node. The backgrounds of both lesions were reviewed with a discussion about their association and the roles of Human herpes virus 8 (HHV-8). According to the findings and reviewed papers, one should not diagnoses Castleman's disease without a prior extensive exclusion of other diseases.

Key words: *Kaposi's sarcoma, Castleman's disease, Lymph node, HIV, HHV-8.*

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Received for publication. February 12, 2002.

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ธรรมธร อาศนะเสน, พงษ์ศักดิ์ วรรณไกรโรจน์. มะเร็งต่อมน้ำเหลืองชนิด Kaposi's sarcoma ที่มีลักษณะรูปร่างทางกล้องจุลทรรศน์ ของต่อมน้ำเหลืองคล้ายโรค Castleman ในผู้ป่วยติดเชื้อ HIV: รายงานผู้ป่วย 1 ราย. จุฬาลงกรณ์เวชสาร 2545 พ.ค; 46(5): 409 – 17

ลักษณะทางกล้องจุลทรรศน์ ของต่อมน้ำเหลืองในโรค Castleman นั้นไม่ได้จำเพาะเฉพาะโรคนี้ อาจพบได้ในโรคอื่น ๆ รวมทั้ง Kaposi's sarcoma ของต่อมน้ำเหลือง และผู้ป่วยที่ติดเชื้อ HIV การรายงานผู้ป่วยรายนี้ มีเจตนาจะให้พยาธิแพทย์ระลึกถึงความจริงดังกล่าว ผู้ป่วยรายนี้ เป็นคนไข้ในโรงพยาบาลจุฬาลงกรณ์ ที่มาด้วยต่อมน้ำเหลืองที่คอโตหลายต่อม และได้ถูกตัดออกแล้วนำไปตรวจทางพยาธิวิทยา การรายงานนี้ยังรวมถึงการศึกษาลักษณะของทั้ง 2 โรคโดยละเอียด พร้อมกับความสัมพันธ์ซึ่งกันและกัน และความเกี่ยวข้องของ Herpes simplex virus 8 จากการศึกษาการจะวินิจฉัยถึงโรค Castleman นั้นต้องทำการแยกโรคอื่น ๆ ออกให้หมดก่อนจึงจะวินิจฉัย มิใช่ดูจากลักษณะทางกล้องจุลทรรศน์แต่เพียงอย่างเดียว

Kaposi's sarcoma (KS) was relatively rare in Asian countries, until the outbreak of AIDS epidemic. It has become the most common AIDS-related cancer reported internationally.[1]

The pandemic of Kaposi's sarcoma of lymphadenopathic type among homosexual men[2] and those who acquired immunodeficiency syndrome (AIDS),[3] has pushed this, once a rare disorder among developed countries, (it was a common tumor in several parts of Africa) into the forefront of global medical interest.

We hereby report a case of KS with Castleman's disease-like features of a lymph node in Human Immunodeficiency Virus (HIV), taken from an infected patient (at King Chulalongkorn Memorial Hospital). Our purpose is to illustrate histopathological features of Castleman's disease-like lesion and KS, which coexisted in a lymph node and the difficulties in establishing the diagnosis.

Case report

A 34-year-old Thai male, presented at King Chulalongkorn Memorial Hospital in May 2000, with multiple cervical lymphadenopathy hepatosplenomegaly and skin rash without fever. His serum anti-HIV was positive. A cervical lymph node biopsy was taken and sent to Department of Pathology, Faculty of Medicine, Chulalongkorn University for histological examination. The macroscopic appearance of the lymph node was as follows: a well-circumscribed firm ovoid brown mass, measured 1.5x1x0.5 cm. Its cut surfaces were pinkish brown with multiple red brown spots. Its microscopic examination revealed a preserved nodal architecture with scattered multiple discrete angiomatous lesions and slit-like vascular spaces; extravasated erythrocytes and an intervening spindle cells' components were found in the lymph node with some areas adjacent to its capsule. Involvement of sinuses was seen with focal parenchymal replacement. The spindle cells possessed elongated nuclei with pale to dark chromatin, inconspicuous nucleoli, and lightly stained cytoplasm. Nuclear pleomorphism was mild, and mitosis was rarely seen (Fig.1). There were some hyaline globules (2 - 10 μm) that were PAS-positive and diastase-resistant. Most of them were located within the cytoplasm of the spindle cells or histiocytes, surrounded by clear halos. Occasionally, the globules were extra-cellular. The residual lymphoid tissue displayed abnormal follicles and interfollicular vascularity. The follicles were increased, and varied in sizes, from barely perceptible

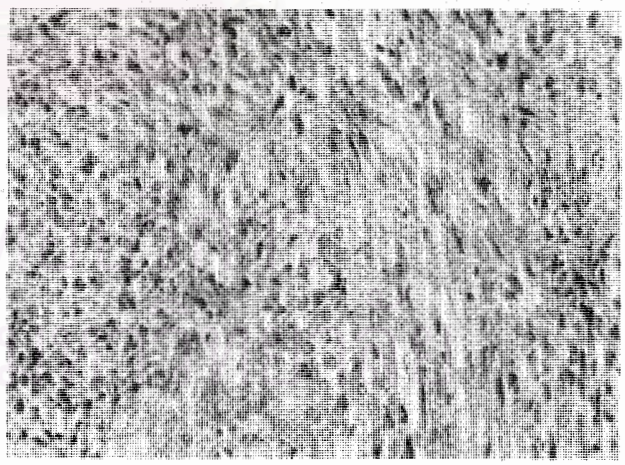

Figure 1. Kaposi's sarcoma in lymph node: A high magification shows typical criss-crossing pattern, with longitudinal sectioned fascicles alternated with tranversely sectioned fascicles. Note sieve-like pattern in the latter. Nuclear pleomorphism is minimal and red blood cells are seen in vascular slits (H&E, x 200).

to medium, but most of them were small. Many follicles contained small blood vessels that often radiated from the perifollicular vessels through the germinal centers. The capillaries had thick hyalinized walls, which gave rise to thickened hyaline in the follicles. Other follicles were characterized by concentric layering of cells within germinal centers, thus superficially resembling Hassle's corpuscles of the thymus. Some of the follicular centers were surrounded by concentric zones ("onion skin"), small lymphocytes (Fig. 2) which were prominent with completely obscured germinal centers and presence of more than one small germinal center within a single follicle in few follicles. The inter-follicular areas consisted of extensive networks of capillaries. The majority of the cells among these capillaries were plasma cells (Fig.3), with occasional immunoblasts. Few small fibrotic areas were also noted. The acid-fast stain showed no positive acid-fast bacilli. The neoplastic spindle cells showed focally positive staining for factor VIII, actin and CD34. The final anatomical diagnosis of the lymph node was Kaposi's sarcoma of the lymph node with Castleman's disease-like features. The study for HHV-8 was not available at our institute.

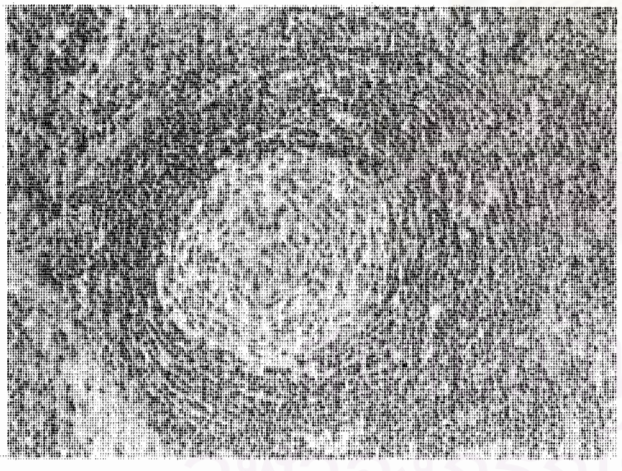

Figure 2. Hyaline-vascular type of Castleman's like features: There is concentric layering of small lymphocytes around a compact germinal center, devoid of follicle center cells, which superficially resembling a Hassal's corpuscle. A capillary from the vascular interfollicular area penetrates the follicle (H&E, x100).

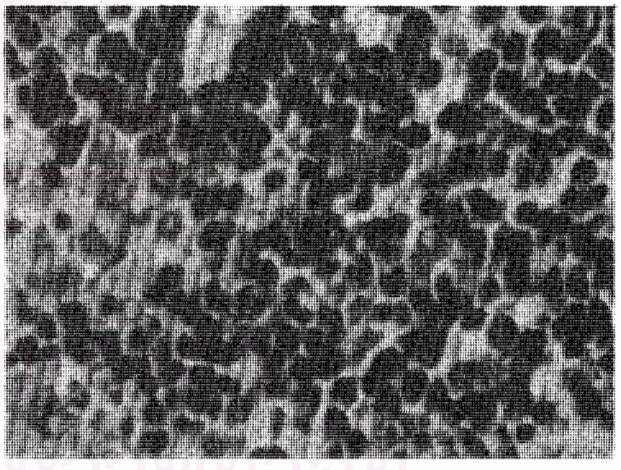

Figure 3. The interfollicular area contains an almost pure population of plasma cells (H&E, x 400).

Discussion

Kaposi's sarcoma (KS) is a distinctive tumor of probable vascular nature. Histologically, it is characterized by an admixture of spindle cells and narrow vascular spaces, and frequently showing multicentric growths.[4] In the case, there was no involvement of other organ, except the lymph node. It was controversy concerning the nature of KS, whether it was a hyperplastic lesion or a neoplasm.[5] The multifocal growth, which did not conform to a metaplastic pattern, the heterogeneous cellular composition, and the lack of DNA aneuploidy were cited to support the probable hyperplastic nature of KS.[6] On the other hand, in vitro studies demonstrated transforming genes in KS.[7] DNA obtained from NIH/3T3, when the transfected cells were injected into nude mice; a tumor that was histologically similar to KS was formed. It was possible that early KS was a hyperplastic state that might progress into a true neoplasm, when a secondary genetic change occurred.[8] Kaposi's sarcoma occurred in a variety of clinical settings, but it was rare among the non-Africans until the recent epidemic of AIDS.[9] KS occurred in approximately 30 percent of patients with AIDS, primarily among homosexual men; however, it was uncommon among patients who contracted HIV infection through parenteral route.[10] The risk of developing KS was fairly constant after HIV seroconversion, unlike the risk of opportunistic infections or lymphoma which increased as the immunodeficiency became worsen. The disorder was often disseminated, involving mucocutaneous sites, lymph nodes, and visceral organs (especially the gastrointestinal tract and lungs). AIDS-related KS also had a fulminant course, with less than 20 percent survival in 2 years, if it had opportunistic infection.[11] A recent study revealed human herpes virus 8 (HHV-8) in early lesions supporting a role for HHV-8 in the pathogenesis of KS.[12] Furthermore, detection of HHV-8 in HIV-positive patients without KS was often predictive of a subsequent development of KS. A serologic study showed that 52% of patients with KS had seroconversion of antibody to HHV-8, with the median time of 33 months before the diagnosis of KS. The mechanism of oncogenesis of HHV-8 might be related to the ability of HHV-8 to encode homology of Bcl-2 chemokine receptor, interleukin-6,and cycline D.

Castleman's disease was first described by Castleman and associates.[13] It had many synonyms,[14] namely: = lymph nodal hamartoma, angiofollicular mediastinal lymph node hyperplasia, angiomatous lymphoid hamartoma, follicular lymphoreticuloma, and benign giant lymphoma. In the first accounts of giant lymph node hyperplasia, the lesions were described as solitary and localized to the mediastinum, which was still the most frequent site of its involvement. Giant lymph node hyperplasia was reported as a solitary lesion in other locations, .eg., cervical and axillary regions, skeletal muscle, pulmonary parenchyma, abdomen, and retroperitoneum.[15] There appeared to be no sex preference, and the age of patients ranged from 8 to 70 years. Two distinct clinical manifestations were recognized. Solitary Castleman's disease and Multicentric Castleman's disease (MCD). The former seemed to be non-specific; and its symptoms were usually due to its mass effects. It usually consisted of a rounded mass ranging in size from 1.5 - 16.0 cm[17] MCD, on the other hand, was a systemic lymphoproliferative disorder with morphologic features of Castleman's

disease. The diagnosis of this disease came out of exclusionof other disorders that had similar histological patterns. Its patients were older (57 years, median age) than those with the localized disease, most of them were male, and their peripheral lymph nodes were always involved, and the development of malignancy was common, and its clinical course of the disorder varied. It might behave like a chronic disease with persistent or relapsing pattern, otherwise like an unremitting aggressive lymphoproliferative disorder that might be fatal. The disorder might associate with KS, POEMS, or Crow Fukase syndrome. Lymph nodes with similar histologic changes were also reported in patients with AIDS. Other organs frequently involved by systemic disorder included bone marrow, liver, kidney, skin, spleen, and central and peripheral nervous system.[16] Histologically, there were two distinct types of lesions described: hyaline-vascular and plasma cell. A transitional or an intermediate form of pathology with similar features of both was also reported.[16] The hyaline-vascular type of lesions was much more common than the plasma cell type. The majority of patients with the hyaline-vascular type of lesion were asymptomatic except for mass effects. In contrast, patients with plasma cell type of giant lymph node hyperplasia, which constituted about 10 -20 percent of the lesions, often had associated systemic clinical manifestations, such as fever, anemia, and hypergammaglobulimenia.[17] The symptoms were reported to disappear after the removal of the lesions. The transitional or mixed type of Cantleman's disease was to be the least common.[14] Clinically, the majority of patients were similar with those who had hyaline vascular type in that they were asymptomatic at their presentation. Histologically, most of the lesions were of the hyaline-vascular type with focal areas of plasmacytosis. The etiology of the lesions was not known. The changes in hyaline vascular type suggested an inflammatory or infectious process, perhaps a later stage of the plasma cell type.[14] Excessive interleukin-6 (IL-6)-like actively was found. The data suggested that Castleman's disease was a syndrome of multiple etiologies with aberrant IL-6 activity from either endogenous or viral sources.[18] HHV-8 was also associated with MCD. HHV-8 was found in most cases of HIV-positive MCD. Even in HIV-negative patients HHV-8 appeared to have significant association with MCD, though the findings were not striking. The role of HHV-8 in pathogenesis of MCD remained unclear.[19]

HHV-8 played a striking role in the pathogenesis of both KS and MCD. HHV-8 was first isolated by Chang et al, 1994. The unique DNA sequences were isolated from KS tissue from AIDS patients. The KS-associated herpes-virus like sequences (KSHV) had significant homology to sequences of two gamma herpes viruses; EBV and herpes virus saimiri, then was named Human herpes virus 8 (HHV-8). In the subsequent studies, HHV-8 appeared to be associated with all types of KS, whether the patients were antiHIV –positive or negative, or the patients were antiHIV- positive via homosexual transmission, or other routes. [20-22]

The association between MCD and KS was studied. In antiHIV-negative patients with MCD, there was 13 % chance of KS during the course of the disease, but in antiHIV-positive patients with MCD, 75 % developed KS.[23] It was unclear whether KS was a consequence of immunological alterations associated with MCD, or whether both processes

were caused by a primary disorder of immune regulation. [24] In the case, only one lymph node was examined. Multicentricity was not verified as though investigation of the whole body were not carried out. The study of HHV-8 was not available at our institute.

It is worth to mention that features that characterize Castleman's disease, especially hyaline vascular type, which could be found in other conditions, such as AIDS-related lymphadenopathy, systemic lupus ery the matosus, angioimmunoblastic lymphadenopathy, and single follicle, otherwise in non-specific reactive lymph nodes.[8,14,25,26] There was an example of uninvolved areas of lymph nodes in KS which showed features of giant lymph node hyperplasia of Castleman (hyaline-vascular type).[27,28] The term Castleman's disease-like lesion might be applied to a node without any obvious clinical manifestation of Castleman's disease.

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