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Case Report

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HHV-8 Linked to Kaposi's Sarcoma and Castleman's Disease in HIV-1-infected patient: Case Report and Review of the Literature

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ABSTRACT

Kaposi's sarcoma (KS) and multicentric Castleman's disease (MCD) are both linked to human herpesvirus-8 (HHV-8) infection which most commonly affects people living with human immunodeficiency virus (HIV). Herein, we describe the case of a 57-year-old patient who has been admitted for fever, night sweats, weight loss, and diffuse lymphadenopathy with abdominal pain. HIV status was confirmed by a positive Western blot test. His initial CD4 cell count was equal to 270 cells/µL. A histological study of a peripheral lymph node concluded that KS is associated with MCD. These two conditions found in the same patient highlight the malignant potential of HHV-8, particularly in the case of HIV-induced immunodeficiency.

Keywords: Human herpesvirus-8 (HHV-8); Kaposi's sarcoma; Multicentric castleman's disease (MCD); HIV

INTRODUCTION

In the era of highly active antiretroviral therapy (HAART), people living with HIV are less likely to develop opportunistic infections and less likely to be diagnosed with an AIDS-defining neoplasm such KS or MCD. However, these malignancies remain a significant cause of morbidity and mortality for individuals who are not on HAART, especially in developing countries. Clinical suspicion and histological study are important to make an early diagnosis and initiate the adequate treatment along with HAART.

Case presentation

We report a case of a 57-year-old patient with diabetes mellitus and no risk factors for sexually transmitted infections, who was admitted to our department for fever, night sweats, weight loss and diffuse lymphadenopathy with abdominal pain. On physical examination, hepatosplenomegaly and a right axillar lymph node measuring 3cm were found. Complete blood cells count showed pancytopenia. He also had a moderate hepatic cytolysis and an elevated C reactive protein (240mg/l).

There was hypoalbuminemia and polyclonal hypergamma globulin on serum protein electrophoresis, not disseminated tuberculosis or lymphoma. Computed tomography scan showed axillar, mediastinal, intraperitoneal, and inguinal lymphadenopathies with hepatosplenomegaly. An axillar node biopsy was performed. Histological study concluded to KS with positive immunostaining for HHV-8; latency-associated nuclear antigen in the nuclei of multiple spindle cells were seen (Figure 1). Clusters of CD20 + cells were also present with rare lymphocytes stained for HHV-8. This aspect was compatible with MCD (Figures 2, 3). There was no Hodgkin's lymphoma proliferation associated, Plasma HHV-8 PCR was positive. HIV status was confirmed by a positive Western blot test. Initial CD4 cell count was equal to 270 cells/µL and the viral load to 4560 copies/ml. Upper gastrointestinal endoscopy showed Barrett's esophagus with no KS lesions. The bronchoscopy was also normal. HAART was rapidly initiated. However, the patient presented a massive gastrointestinal hemorrhage and did not survive.

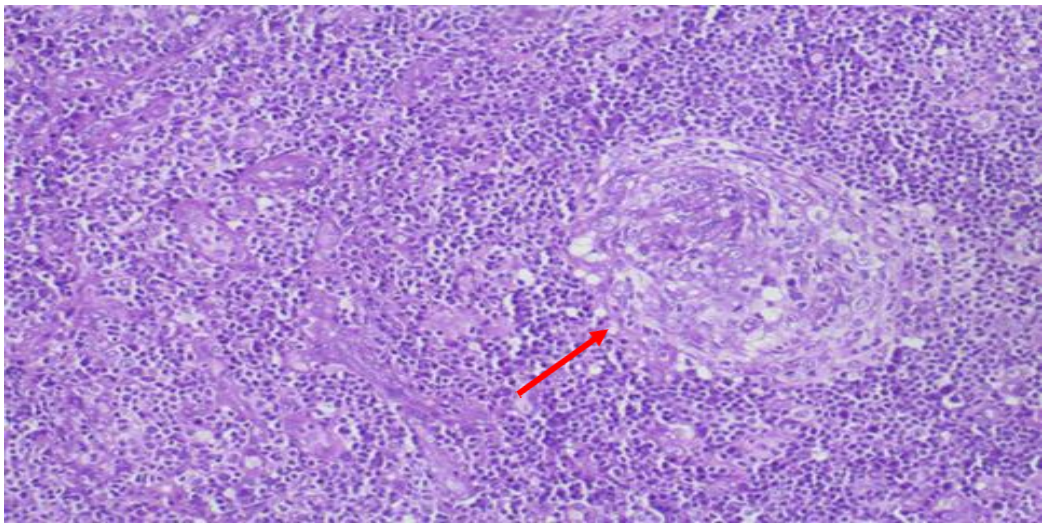

Figure 1: Concentric rings of lymphocytes around germinal center « onion skinning » (arrow)

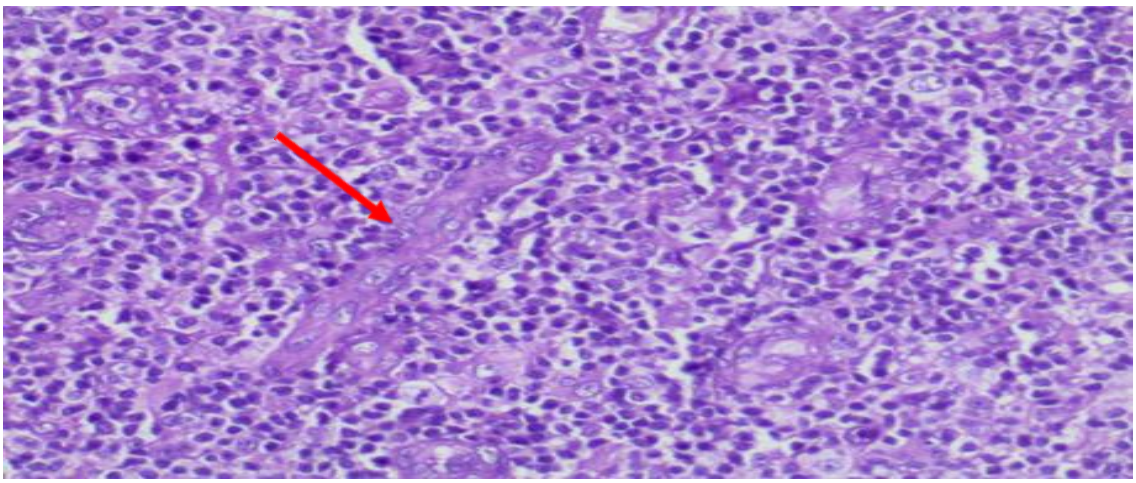

Figure 2: Proliferation of capillaries and small vessels in the germinal center and intrafollicular space (arrow)

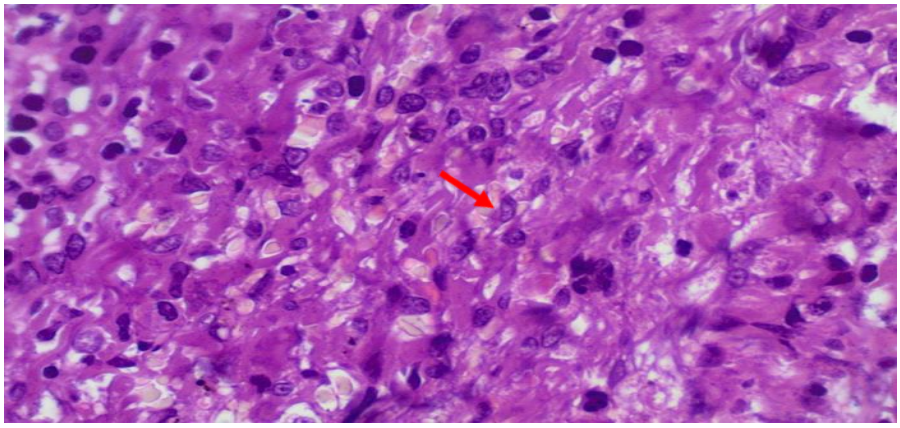

Figure 3: Proliferation of spindle cells (arrow)

DISCUSSION

Castleman's disease was first described in 1950 as a constellation of histological findings in one region of lymph nodes [1]. In 1970s, it was reported in more than one affected region of lymph nodes[2]. This observation gave rise to an entity MCD. An increase in reported cases of MCD emerged in the 1980s, in HIV-infected individuals[3]. In these patients, the disease was frequently associated with KS. Later, (HHV-8 also known as Kaposi's sarcoma-associated herpesvirus, was discovered in skin tumor biopsy of an AIDS-related KS [4].

HHV-8 is the etiological agent of KS, primary effusion lymphoma as well as most MCD and related lymphomas[5].The geographical distribution of the virus is not ubiquitous and is roughly parallel to that of HIV. Indeed, it is highly endemic in sub-Saharan Africa and in the Mediterranean region. HHV-8 is also endemic in the northwestern part of China and in South America [6].

In widely endemic areas, multiple studies have shown that HHV-8 infection mainly occurs during childhood and is transmitted between siblings or from mother to child. Transmission between adults seems to be less frequent [7]. However , it is common among men who have sex with men[8].

HHV-8 is part of the herpesvirus group. Like other herpesviruses, HHV-8 evades the immune system through its ability to use viral immunomodulators that interfere with host immune response[9]. One of the evading mechanisms consists of diverting the host immune response from Th1 to Th2 response[10].

HHV-8 also encodes proteins that inhibit several complements and downregulate the adaptive immune response. In fact, HHV-8 genome encodes for proteins with homology to human proteins, including an interleukin-6 (IL-6) homologue[11]. IL-6 has multiple systemic effects and when excessively expressed, it may contribute to immunity dysregulations. Besides its effect on immune system, HHV-8 has also an oncogenic potential. It causes chromosomal instability, compromises gene expression, increases telomerase activity and promotes cell proliferation and survival[12].

Coexistence of MCD and KS in the same tissue is commonly seen. This association may be caused by the lysis of B lymphoid cells during HHV-8 infection, which exposes endothelial cells at vulnerable sites[13].

The overall median survival of these patients is generally limited to a few months but there are exceptions[14]. Patients on HAART with regressing KS had lower HHV8 DNA load and higher CD4 cell counts. Thus, maintaining high levels of cellular immunity using effective HAART is essential to suppress HHV8 multiplication[15].

Treatment of KS and MCD in people living with HIV is based on HAART along with chemotherapy, immunomodulatory agents or monoclonal antibodies against the IL-6 or anti-CD20 receptors (rituximab)[16]. Rituximab has shown promising results of sustainable remission, but it has also been associated to reactivation cases.

CONCLUSION

Given the findings of this case study and the previous date, practitioners should always consider the diagnosis of KS associated MCD in HIV-positive patients with diffuse lymphadenopathy. Definitive diagnosis requires tissue biopsy with immunostaining. Randomized studies should be performed to establish precise treatment guidelines.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

Ethical approval

Ethical approval was waived by the local Ethics Committee of the Faculty of Medicine of Tunis in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Abbreviations

HIV: Human immunodeficiency virus
HHV-8: Human Herpesvirus-8
KS: Kaposi's sarcoma
Metacentric Castleman's disease: MCD
HAART: Highly active antiretroviral therapy

REFERENCES

1. Castleman B, Towne VW. Case records of the Massachusetts general hospital; weekly clinicopathological exercises; Case No.40351. N Engl J Med. 1954; 251(10):396-400.
2. Gaba AR, Stein RS, Sweet DL, et al. Multicentric giant lymph node hyperplasia. Am J Clin Pathol. 1978;69(1):86-90.
3. Lachant NA, Sun NCJ, Leong LA, et al. Multicentric angiofollicular lymph node hyperplasia (Castleman's disease) followed by Kaposi's sarcoma in two homosexual males with the acquired immunodeficiency syndrome (AIDS). Am J Clin Pathol. 1985;83(1):27–33.
4. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994;266(5192):1865–9.
5. Mamimandjiami AI, Mouinga-Ondémé A, Ramassamy JL, et al. Epidemiology and Genetic Variability of HHV-8/KSHV among Rural Populations and Kaposi's Sarcoma Patients in Gabon, Central Africa. Review of the Geographical Distribution of HHV-8 K1 Genotypes in Africa. Viruses. 2021;13(2):175.
6. De Souza VAUF, Sumita LM, Nascimento MC, et al. Human herpesvirus-8 infection and oral shedding in Amerindian and non-Amerindian populations in the Brazilian Amazon Region. J Infect Dis. 2007;196(6):844–52.
7. Dow DE, Cunningham CK, Buchanan AM. A review of human herpesvirus 8, the Kaposi's sarcoma-associated herpesvirus, in the pediatric population. J Pediatric Infect Dis Soc. 2014;3(1):66-76.
8. Casper C, Wald A, Pauk J, et al. Correlates of prevalent and incident Kaposi's sarcoma-associated herpesvirus infection in men who have sex with men. J Infect Dis. 2002;185(7):990-3.
9. Coscoy L. Immune evasion by Kaposi's sarcoma-associated herpesvirus. Future Microbiol. 2010;5(9):1349-65.
10. Diehl S, Rincón M. The two faces of IL-6 on Th1/Th2 differentiation. Mol Immunol. 2002;39(9):531-6.
11. Neipel F, Albrecht JC, Ensser A, et al. Human Herpesvirus 8 Encodes a Homolog of Interleukin-6. J Virol. 1997;71(1):839-42.
12. Wen KW, Damania B. Kaposi sarcoma-associated herpesvirus (KSHV): Molecular biology and oncogenesis. Cancer Lett. 2010;289(2):140-50.
13. Castillo J, Pantanowitz L, Dezube BJ. HIV-associated plasmablastic lymphoma: Lessons learned from 112 published cases. Am J Hematol. 2008 Oct;83(10):804-9.
14. Eaton C, Dorer R, Aboulafia DM. Human Herpesvirus-8 Infection Associated with Kaposi Sarcoma, Multicentric Castleman's Disease, and Plasmablastic Microlymphoma in a Man with AIDS: A Case Report with Review of Pathophysiologic Processes. Patholog Res Int. 2010;2011: 647518.
15. Boivin G, Gaudreau A, Routy JP. Evaluation of the human herpesvirus 8 DNA load in blood and Kaposi's sarcoma skin lesions from AIDS patients on highly active antiretroviral therapy. AIDS. 2000;14(13):1907-10.
16. Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood. 2010; 115(15):3008–16.