



Diagnosis of Lymphadenopathic Kaposi Sarcoma by Fine Needle Aspiration in a non-HIV patient.

Case report with uncommon presentation and brief review of the literature

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Abstract

This report presents the diagnosis of Kaposi sarcoma by the minimally invasive procedure of fine needle aspiration. The patient, a 65-year-old HIV negative Mediterranean man with a history of colon cancer, presented with right inguinal lymphadenopathy. Biopsy of the lymph node showed histological morphology consistent with Kaposi sarcoma confirmed by HHV-8 positive immuno stain. We review the role of HHV-8 in the pathogenesis of Kaposi sarcoma. We also discuss how it presents differently than Multicentric Castlemans disease of the lymph node, caused by the same virus. How the latent and lytic pathways of the virus can influence the progression of the Kaposi sarcoma and Multicentric Castlemans disease, respectively. Also, we review various treatment modalities for Kaposi sarcoma.

Keywords: Sarcoma; Immunohistochemistry; Lymphadenopathy; Aspiration; Castlemans

Abbreviations

KS: Kaposi sarcoma, HHV-8: Human Herpes Virus 8, MCD: Multicentric Castlemans disease, IHC: Immunohistochemistry, FNA: Fine needle aspiration

Introduction

Kaposi sarcoma (KS) is the most common HIV associated malignancy and is induced by the Human Herpes Virus 8 (HHV-8). There are 4 main classes of KS; HIV-associated (AIDS), Iatrogenic (transplant), Classical (sporadic) and Men who have sex with men without HIV. KS most commonly appears on the dermis, oral cavity, GI tract, and respiratory tract, the latter 3 being more common with HIV associated KS rather than classical KS [1]. While these are the classic location of lesions, KS can occur nearly anywhere in the body as a primary neoplasm. This includes lymph nodes with a solitary presentation of lymphadenopathy. Lymphadenopathy has an extensive differential, so the diagnosis

of KS is vital in the determination of appropriate treatment¹. Ultrasound-guided biopsy of undiagnosed lymphadenopathies has been shown to greatly decrease the number of excisional surgeries of lymph nodes. This can be diagnostic and can allow for specific treatment for the cause of the lymphadenopathy, such as cancer, autoimmune diseases, and infections [2].

KS mechanism of invasion involves an elevated expression of cytokines/ angiogenic growth factors and DNA damage from viral replication. KS leads to an angiosarcomatous change of epithelial and mucosal connective tissue [1]. The clinical presentation of KS outside the setting of immune suppression most commonly occurs as cutaneous lesions in the lower extremities and may have a more indolent course. While post-transplantation KS and AIDS-associated KS are more likely to be diffuse in presentation involving visceral organs and lymph nodes [3].

HHV-8, like other herpes viruses, has a lifelong length of infection and is normally monitored by the cytotoxic T-lymphocytes¹. HHV-8 can infect several types of cells which can lead to the occurrence of two different primary neoplasms in a lymph node. These primary neoplasms are KS of the lymph node (non-metastatic form) and Multicentric Castlemans disease (MCD). However, it appears that the pathogenesis of these two conditions is dependent on whether the virus is latent or lytic, rather in addition to the cells being infected [4].

Castlemans disease (CD) is a rare disease of lymph nodes and related tissues. It was first described by Dr. Benjamin Castlemans in the 1950s. It is also known as Castlemans's disease, giant lymph node hyperplasia, and angiofollicular lymph node hyperplasia (AFH). CD is not a straight cancer. Instead, it is considered a lymphoproliferative disorder. This means there is an abnormal overgrowth of cells of the lymph system that is similar in many ways to lymphomas. Even though CD is not officially a cancer, one

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form of this disease, known as multicentric Castleman disease (MCD) acts very much like lymphoma. In fact, many people with this disease eventually develop lymphomas. And like lymphoma, MCD is often treated with chemotherapy or radiation therapy. Therefore, it is included in the American Cancer Society's cancer information. There are also MCD patients who are negative for the HHV-8 virus, and the cause is unknown. These cases are called HHV-8 negative or "idiopathic" MCD [5].

In this report, we present a case of non-HIV related Kaposi Sarcoma diagnosed entirely utilizing fine needle aspiration (FNA) of lymphadenopathy leading to a final diagnosis with no need to tissue biopsy. We review the role of HHV-8 in the pathogenesis of KS. Also, we review various treatment modalities of different types of KS.

Case Presentation

A 65-year-old Mediterranean man with history of colon cancer presented with right inguinal lymphadenopathy for several weeks. On physical exam, a 2.5 cm nontender, enlarged right inguinal lymph node was noted. Recurrent or metastatic colon cancer was suspected. Ultrasound guided fine needle aspiration (FNA) was performed (Figure 1A) and cytologic analysis demonstrated fragments of atypical spindle cells in a background of polymorphous lymphocytes and extravasated blood (Figure 1B). Cell block material prepared from the cytology specimen demonstrated a spindle cell neoplasm with hyperchromatic elongated nuclei infiltrating lymphoid tissue and no evidence

of carcinoma (Figure 1C). Immunohistochemical stains showed tumor cells positivity for HHV-8 (Figure 1D), CD31 (Figure 1E), CD34 and vimentin and were negative for cytokeratins, S100, p63, and desmin, all of which was consistent with a diagnosis of Kaposi Sarcoma. Testing for human immunodeficiency virus (HIV) was negative. Full body scan showed no evidence of dissemination or involvement of other lymph nodes. Lymph node was excised, follow up for three years showed no evidence of Kaposi Sarcoma after which the patient was lost for follow up

Discussion

The diagnosis of KS is traditionally through histological examination of biopsy with a positive HHV-8 immuno stain. KS most commonly presents as a cutaneous neoplasm with a non-blanching dark area of the dermis. Histologically, regardless of location KS presents with elongated spindle-shaped cells surrounding extravasated pools of blood [6].

The pathogenesis of KS can arise from several different sources due to the various cells HHV-8 infects. These cell lines include epithelial cells, monocytes, and B-lymphocytes [3]. Additionally, the spindle cells have characteristics of smooth muscle cells and vascular pericytes. This could indicate the KS is a mixed tumor of various cell lineages forming the neoplasm [6]. The infection of HHV-8 induces an environment ideal for neoplastic proliferation. This is done by enhancing glucose metabolism via the Warburg effect, where HHV-8 miRNAs increase glucose uptake and lactate

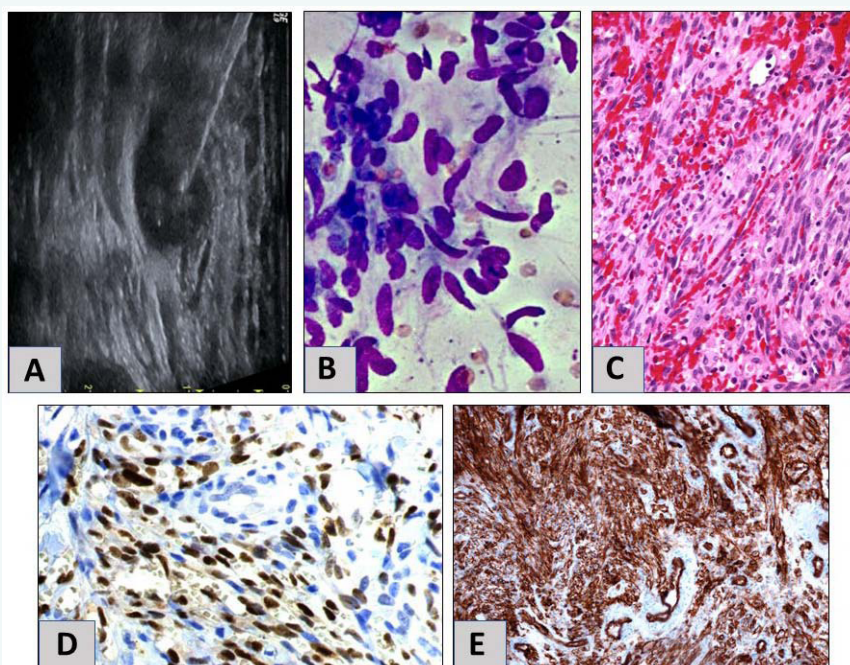


Figure 1 Ultrasound Guided Fine Needle Aspiration of the lymph node.

A: Ultrasound guided FNA of the lymph node, **B:** Cytology smear preparation showing atypical spindle cells in a background of polymorphous lymphocytes and extravasated blood (Diff Quick stain X100). **C:** Cell block material prepared from the cytology specimen demonstrated a spindle cell neoplasm with hyperchromatic elongated nuclei infiltrating lymphoid tissue and extravasated blood (H&E stain X40). **D:** Strong positive nuclear staining with HHV-8 (IHC). **E:** Strong positive membranous staining with CD31, (IHC)..



shuttle while viral proteins inhibit oxidative phosphorylation in mitochondria [7].

HHV-8 is one of many cancer-causing oncoviruses that most commonly occurs in an immunocompromised state such as AIDS or following transplant. Cancer from HHV-8 can also be caused in the absence of an immunocompromised state [1]. Before the AIDS epidemic in the 1970s the prevalence of KS in San Francisco was 0.5 per 100,000 people, peaked at 33.3 per 100,000 people in 1992, and decreased to 2.8 per 100,000 people in 1998 post-HAART therapy [8].

In addition to KS, HHV-8 can lead to lymph node Multicentric Castleman disease (MCD). MCD is lymphadenopathy with flairs of fevers and inflammation, which can occur in concert with or independent of KS⁴. The morphology of MCD has a relatively preserved LN architecture with infected cells resembling plasmablasts, without the characteristic spindle cells of KS [4]. Because both KS and MCD can be in the lymph node due to HHV-8, a biopsy and histological evaluation can be used to differentiate between the two conditions.

The recent integration of cytology and radiology has allowed for minimally invasive, safe, accurate, and cost-effective diagnosis of suspicious masses, previously accessible only by surgical biopsy techniques. As a result, cytologists are increasingly called upon to diagnose disease in specimens procured under image guidance for different organs. Rather than causing a delay, cytology facilitates timely diagnosis and management and is an integral part of a multimodal approach to various tumor diagnoses. Onsite cytology interpretation increases the diagnostic yield of the procedure by allowing for additional needle passes as necessary. The process culminates in a multidisciplinary conference such as tumor board where the results of clinical, radiologic, cytologic, and laboratory evaluations are discussed, and treatment is planned [9,10].

It has been shown that the use of fine-needle aspiration (FNA) as a diagnostic technique. With an extensive list of maladies for lymphadenopathy, FNA is a relatively fast and simple way to narrow a differential. This includes diagnoses such as KS, lymphoma, and metastatic cancers in addition to other causes of lymphoblastic reactions such as an active infection [11].

Previous cases have described an HIV positive man with symptoms of fever and lymphadenopathy. This patient presented with both KS spindled cells and MCD plasmablastic architecture induced by HHV-8 within the same lymph node. The patient was diagnosed via a cervical lymph node biopsy with no cutaneous lesions present [12]. This is significant in understanding that lymph node involvement of KS can occur even in the absence of cutaneous or mucous membrane involvement and can be the primary site of the malignancy.

In another case, an HIV negative patient with cutaneous Kaposi Sarcoma of the ear. This was confirmed with a negative HIV test and lesion characteristics of KS spindle cells, CD34, and HHV-8 positive. This indicates that although rare, KS should be on a differential in the absence of HIV infection [13].

HHV-8 is a lifelong latent herpes virus that is transmitted primarily via mucous membranes in adolescence [14]. HHV-8 has viral proteins mimic host signals such as Viral (v)GPCR promoting angiogenesis via VEGFr and cell survival via mTOR, vCyclin which promotes cell proliferation via activation cdk6, and vIL-6 inducing inflammation [3,4].

HHV-8 can infect several types of cells: endothelial, epithelial, B-cell, dendritic, monocyte, and epithelial cells. Molecular markers present on cells of KS neoplasm include endothelial markers CD31, CD34, Factor VIII, VEGFR3. Lymphatic markers lymphatic vessel endothelial hyaluronan 1 (LYVE1), D2-40, and podoplanin. Dendritic Factor XIII, macrophage CD68, and smooth muscle antigen (SMA) markers. This indicates a polyclonal population of cells [15].

HHV-8 has both lytic and latent cycles both of which are involved with KS and MCD. However, KS is more associated with the latent genes of HHV-8 like vCyclin and latency-associated nuclear antigen (LANA) in immunohistochemistry⁴. While the pathogenesis of MCD is closer associated with the lytic genes of HHV-8 like vIL6, vFLIP, and Replication and Transcriptional Activator (RTA) [4].

The treatment for Kaposi Sarcoma has various approaches depending on the mode of manifestation. All treatment approaches include surgical removal of the lesion. This is combined with systemic chemotherapy if the neoplasm is disseminated. AIDS-associated KS treatment includes combined anti-retroviral therapy (cART) therapy. This is to reconstitute the immune system and due to the proteinase inhibitor nelfinavir having direct anti-KS effects. In transplant-associated KS the primary goal is to decrease immunosuppression. In classical KS, the lack of immune surveillance is not the cause so anti-cancer drugs are required. These include DNA damaging agents. Liposomal formulations of doxorubicin or daunorubicin are effective in 2/3 patients [6]. Polychemotherapy with adriamycin, vinblastine, and bleomycin has been proposed for lymph node invasive KS [16]. Additionally, VEGF-receptor inhibitors (bevacizumab, imatinib) are effective due to KS's requirement for neovascularization, but this has a limited effect due to redundancy in vascular growth factors. Immune boosters such as pegylated IFN-alpha, have shown some efficacy in KS [6]. Imiquimod (TLR7 agonist) has shown some effect in cutaneous KS. Thalidomide and immune checkpoint regulators (CTLA-4 and PD-1) are growing attraction but have not yet been used clinically in KS [6].

Conclusion

In this report, the nodal tumor is cytologically consistent with KS, this was confirmed utilizing immunohistochemistry studies. This is despite no other KS lesions found. KS should be considered as a differential diagnosis for patients with lymphadenopathy of unknown etiology. It is also important to distinguish KS lymphadenopathy from MCD as they are both caused by HHV-8 even in those with a known HIV-negative status. The case also shows that the definitive diagnosis of Kaposi Sarcoma can be accomplished solely based on cytology preparation including cellblock.



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