Case Report

Orbital Kaposi Sarcoma in an Adult Filipino Male: A Case Report

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ABSTRACT: A distinctive case of orbital Kaposi sarcoma is reported to: (a) describe the unique presentation of the tumor, (b) identify key histomorphologic and immunohistochemical characteristics, and (c) discuss the challenges and issues in management. A 33-year-old Filipino male presented with a 5-month history of progressive proptosis of the left eye with associated blurring of vision, diplopia, and discomfort in eye movement. Magnetic resonance imaging (MRI) showed an abnormally enhancing intraconal mass in the left retro-orbital area with mass effects. Excision biopsy revealed a low-grade vasoformative neoplasm with positive CD34 immunostaining consistent with Kaposi sarcoma. Serologic test for HIV was positive. HIV-associated Kaposi sarcoma can occur in unusual locations including the orbit and should be considered in young, high-risk individuals presenting with ocular complaints.
Keywords: *AIDS, HIV, Kaposi sarcoma, orbit, proptosis*

INTRODUCTION

Kaposi sarcoma (KS) is a vasoproliferative disease of endothelial origin. It has four epidemiologic variants: classic (sporadic or Mediterranean), endemic (African), iatrogenic (post-transplant), and epidemic (acquired immunodeficiency syndrome or AIDS-associated).[1,2] KS is an AIDS-defining illness, and is considered to be the most frequently observed AIDS-associated malignancy worldwide.[3] The advent of antiretroviral therapy in 1996 has led to a decline in the incidence of AIDS-associated KS. The HIV/AIDS Cancer Match Study reported an average yearly decline of 6% during 2000 to 2010 in the United States. Nonetheless, the risk of KS among HIV-positive individuals remains elevated 800-fold compared to the general population.[3] There are no published data on the epidemiology of KS in the Philippines. We present a case of AIDS-associated KS with a distinctive clinical manifestation.

CASE REPORT

A 33-year old male admitted at The Medical City due to perianal abscess was referred to ophthalmology for proptosis of the left eye.

Five months prior to admission, the patient noted discomfort, blurring of vision, and slight proptosis of the left eye. He had palpitations and heat intolerance but denied tremors and weight loss. He was assessed to have Graves Disease and was started on methimazole with poor compliance. Three months prior to admission, progression of symptoms on the left eye prompted consult with an ophthalmologist. Thyroid eye disease was entertained at this time. Magnetic resonance imaging (MRI) of the orbits was requested, but the patient was lost to follow-up. Persistence of proptosis on the left eye with deterioration of vision, pain on eye movement, and diplopia prompted a subsequent ophthalmologic consult.

Review of systems was unremarkable. The patient had no history of trauma, eye surgeries, medications or spectacle use. Other medical conditions included untreated hepatitis B, bronchial asthma, and allergy to seafood and ibuprofen. There was family history of diabetes and hypertension.

The patient attained a college degree and worked as a call center agent. He was a previous smoker and occasional alcohol beverage drinker, and denied illicit drug use. He reported prior sexual relations with a male partner.

At the time of referral, vital signs were stable: blood pressure was 100-110/60-80 mmHg, heart rate 91 beats per minute, respiratory rate 20 cycles per minute, and temperature 37.5^{o}C. Body mass index was normal at 18.7 kg/m^2. There was a 10 cm x 5 cm abscess palpable on the right perianal area. The rest of the physical examination was unremarkable.

Distance visual acuity was 20/25 corrected to 20/20 on the right eye and counting fingers at 1-foot on the left eye. Near visual acuity was J+ on the right eye and >J16 on the left eye. Grossly, the left eye was proptosed by 11mm and exotropic by 30 prism diopters via Hirschberg with minimal conjunctival hyperemia and clear discharge. The right eye was grossly unremarkable. The right pupil was 2-3 mm, round, and briskly reactive to light with no relative afferent defect. The left pupil was 3-4 mm, sluggishly reactive to light, with a relative afferent defect. There were limitations in the extraocular muscles of the left eye on all gazes (-2), which was worst on abduction (-3). Binocular diplopia and occasional discomfort on the left eye was noted in all positions of gaze. The cornea was clear, the anterior chamber was deep, and the lens was clear on both eyes. Fundus exam on the left eye through clear media showed a hyperemic disc with indistinct borders, a cup-to-disc ratio of 0.3, and choroidal folds. There were no retinal vasculature changes, hemorrhages, exudates, or chorioretinal scars. The fundus of the right eye was unremarkable.

Laboratory tests including a complete blood count, thyroid panel including thyroid-stimulating hormone (TSH), FT3, and FT4, sodium, potassium, creatinine, capillary blood glucose, chest x-ray, and 12-lead electrocardiogram were all within normal limits. The TSH receptor antibody was elevated at 3.26 U/L (normal values: 1.10-1.5 U/L), which is consistent with Graves disease.

MRI of the orbits revealed a left retro-orbital, intraconal mass measuring 3.0 cm x 2.4 cm x 3.3 cm (volume x width x anterior-posterior). The lesion was isointense to gray matter in T1-weighted image (Figure 1A) and predominantly hyperintense in T2-weighted image (Figure 1B). The mass displaced the left optic nerve medially. The left lateral rectus muscle was also compressed and appeared to be infiltrated by the lesion. The patient was advised to undergo orbitotomy with excision biopsy of the left retro-orbital mass.

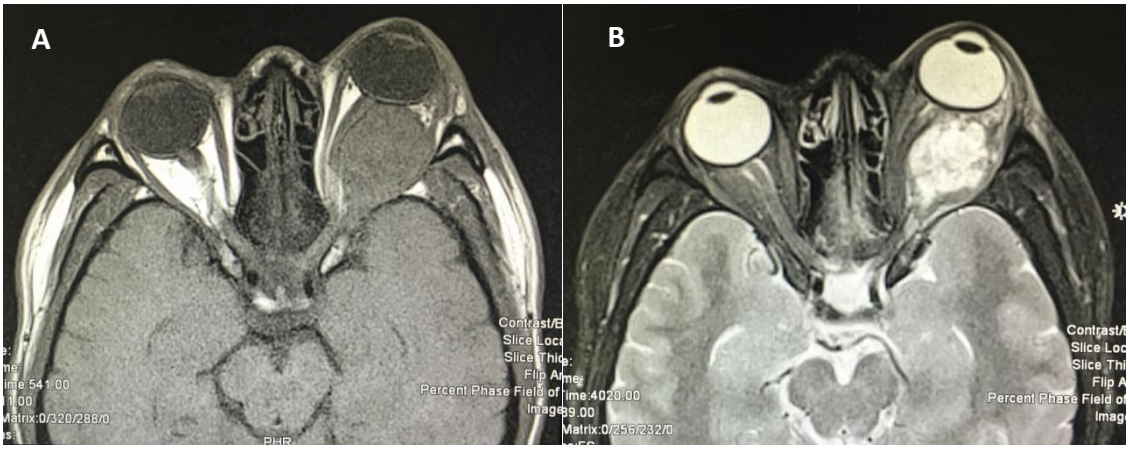

Figure 1: (A) T1-weighted and (B) T2-weighted MRI images of the orbit

Orbitotomy via transconjunctival approach with excision of the lesion and orbital exploration on the left eye was performed under general anesthesia. Intra-operatively, piecemeal excision of a pseudo-encapsulated mass measuring 2.75 cm x 2.75 cm was done. Microsections revealed spindle cells arranged in fascicles. The spindle cells formed slits, which contained extravasated red blood cells. Mitotic activity was low at 0-1/10 high power field. The individual tumor cells showed elongated, almost uniform nuclei with darkly colored and even chromatin, inconspicuous nucleoli, and tapered eosinophilic cytoplasm. Admixed with the tumor were lymphocytes and few eosinophils (Figure 2A, 2B). The histomorphologic features showed a round to spindle cell neoplasm, with mild nuclear pleomorphism, atypia and low mitotic count, suggesting a benign process. However, because of the cellularity, infiltrative nature, and geographic necrosis, a low-grade malignant neoplasm, possibly Kaposiform hemangioendothelioma was considered. Immunohistochemistry with CD3, CD20, CD21, CD1a, CD34, S-100 and Ki-67 was done. The tumor showed CD34 expression (Figure 3A) and a low Ki-67 expression (Figure 3B), which supports the diagnosis of a low-grade vasoformative neoplasm.

Five days after the surgery, uncorrected distance visual acuity on the left eye was 20/40 and uncorrected near visual acuity was J6. The patient developed fever and was advised intravenous antibiotics. However, the patient was lost to follow-up before further work-up, including HIV testing, could be done.

Two months after the surgery, the patient experienced headaches and had two episodes of generalized tonic-clonic seizures. A cranial MRI was done, which showed new multiple intracranial masses. HIV test was reactive. In the setting of HIV infection, the diagnosis of Kaposi sarcoma was made.

Four months after the surgery, the patient was admitted due to severe headaches accompanied by generalized body weakness, nausea, and vomiting. Near visual acuity on the left eye deteriorated to J16. The left pupil was dilated at 5 mm, non-reactive, with a relative afferent defect. Repeat cranial MRI demonstrated an "interval increase in the size of the enhancing left posterior temporal lobe intra-axial metastatic mass with development of intralesional micro hemorrhages and with slight progression of the perilesional edema, as well as interval increase in the sizes of the smaller nodules in the left cavernous sinus and right middle cranial fossa".

DISCUSSION

The clinical behavior of AIDS-associated Kaposi sarcoma (KS) has evolved in terms of onset and organ involvement. AIDS-associated KS usually appears in the late stage of the disease, when there is significant immune dysregulation and low CD4 lymphocyte counts (<150 – 200 cells/mm^3). However, recent studies have shown that KS can also occur as the initial manifestation of an HIV infection, particularly in young individuals aged between 20 to 50 years old.[5,6]

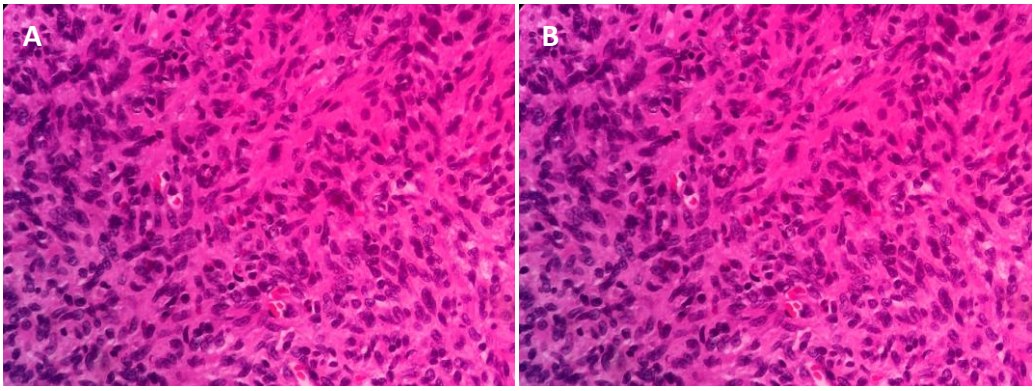

Figure 2: (A) Tumor cells are elongated with bland nuclei, inconspicuous nuclei, and tapered eosinophilic cytoplasm; High power view (40x, H&E stain), (B) Some areas show round tumor cells with ovoid nuclei, small nucleoli, irregular nuclear borders and variable eosinophilic cytoplasm; Extravasated red blood cells are seen in between tumor cells; High power view (40x, H&E stain)

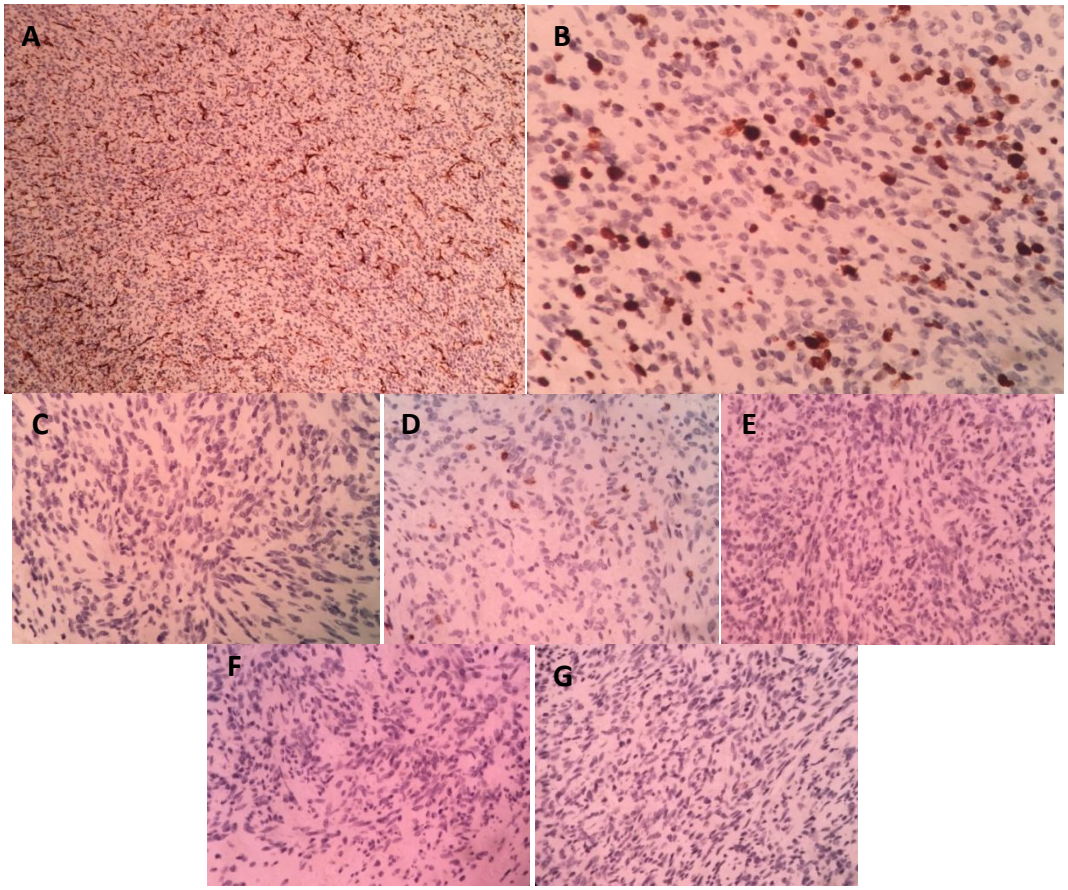

Figure 3: (A) CD34- focally positive; CD34 is expressed in endothelial cells; It is also an indicator for vascular differentiation; CD34 expression is seen in 86% of Kaposi sarcoma, (B) Ki67- positive 20%; Ki67 highlights the proliferative portion of the cell cycle; Ki67 expression roughly correlates with tumor grade, (C) S100- negative; S100 is expressed in cells of neural origin, (D) CD3- negative; CD3 is a marker for T-cell derivation, (E) CD20- negative; CD20 is a marker for mature B-cell neoplasms, (F) CD21- negative; CD21 is a follicular dendritic cell marker, (G) CD1a- negative; CD1a is expressed in Langerhans cells and cortical thymocytes

AIDS-related KS tends to be multifocal or anatomically disseminated in contrast to the localized behavior of classic KS.[7,8] It can occur in unusual locations such as the oral cavity, face, genital mucosa, lungs and gastrointestinal tract.[6] In fact, one of the most common manifestations of AIDS is KS in the head and neck.[8]

While ocular lesions usually arise in the ocular adnexa, specifically the eyelid, the lacrimal gland, and the conjunctiva, orbital involvement is an uncommon presentation.[9] In 2000, a case of AIDS-associated KS manifesting as an anterior orbital mass was reported.[10] Since then, our patient is the only documented case of AIDS-associated KS presenting similarly.

Table 1. Differential diagnoses characterized by histomorphologic and immunohistochemical features

Differential Diagnoses	Histomorphologic Features	Immunohistochemical Features
Kaposi sarcoma	• Spindle cells forming slits containing red blood cells • Low mitotic activity • Mild nuclear pleomorphism • Admixed lymphocytes, hemosiderin-laden macrophages and other inflammatory	• HHV-8 – positive nuclear expression • CD31, CD34 - positive in blood vessels
Kaposiform hemangioendothelioma	• Irregular vascular lobules that infiltrate soft tissue in a cannonball fashion	• CD31, CD34 - positive in capillary vessels • HHV-8 - negative
Ancient schwannoma	• Truly encapsulated neoplasms and almost always solitary • Cellular neoplasm composed of spindle cells often arranged in a palisading fashion or in an organoid arrangement • Mitoses are usually absent or extremely scanty • Blood vessels can be of such prominence as to simulate a vascular neoplasm	• S100 - positive
Malignant peripheral nerve sheath tumor	• Extremely cellular spindle cell neoplasm • Mitoses are usually abundant • Serpentine shape of the tumor cells arranged in palisades or whorls • Epithelioid appearance of the endothelial • cells of these vessels; presence of large gaping vascular spaces • Geographic areas of necrosis, with tumor palisading at the edges • Metaplastic tissues such as cartilage, bone, muscle, or blood vessels are present in approximately 15% of the cases	• S100 - positive
Hodgkin's lymphoma	• Monoclonal lymphoid neoplasm composed of mononuclear Hodgkin cells and multinucleated Reed Sternberg cells • Variable mixture of inflammatory infiltrates such as lymphocytes and eosinophils	• CD3 – negative • CD20 – positive in 40% of cases
Langerhans cell histiocytosis	• Presence of Langerhans cells with indented and grooved nuclei, inconspicuous nucleoli and fine chromatin. • Background contains variable amounts of eosinophils, histiocytes, lymphocytes, and neutrophils. • Mitosis is variable	• CD21 – positive • CD1a – positive

Due to its broad morphologic characteristics and similarities to several vasoproliferative lesions and spindle cell neoplasms, the histopathologic diagnosis of Kaposi sarcoma can be challenging.[1,12] The differential diagnoses considered in this case were Kaposi sarcoma, Kaposiform hemangioendothelioma (KHE), ancient schwannoma, malignant peripheral nerve sheath tumor, Hodgkin's lymphoma, and Langerhans cell histiocytosis. The likelihood of KS is exponentially increased in the setting of an HIV infection.[8]

Tissue biopsy with immunohistochemistry is utilized in the diagnosis of Kaposi sarcoma.[9,12] The histomorphologic features of KS include spindle cells forming slits containing red blood cells. The cells have mild nuclear pleomorphism, low mitotic activity and are admixed with lym-

phocytes, hemosiderin-laden macrophages, and other inflammatory cells.[13] These findings are all present in the specimen obtained from our case.

CD34 expression and a low Ki-67 expression support the diagnosis of a low-grade vasoformative neoplasm. Kaposiform hemangioendothelioma shares almost the same histologic characteristics as KS, but it is seen almost exclusively in children.[14] Immunostaining for HHV-8-latent nuclear antigen-1 (LNA-1) can differentiate KHE from KS, with KS being HHV-8-LNA-1 positive.[1] This highly sensitive and specific test, however, is not available in the Philippines. Given that the patient is an adult male with HIV infection, the clinical, histologic, and immunologic features is more consistent with Kaposi sarcoma.

Immunohistochemistry also ruled out other disease entities. S100 expression was not observed, thereby removing ancient schwannoma and malignant peripheral nerve sheath tumor from the differentials (Figure 3C). The lymphoma markers (CD3, CD20 and CD21) were also negative, ruling out Hodgkin's lymphoma (Figure 3D, 3E, 3F). Langerhans cell histiocytosis was also ruled out since CD1a was negative (Figure 3G). Table 1 contains the histomorphologic and immunohistochemical features of the disease entities considered in the case.[13,16] Table 2 summarizes the immunohistochemical features of the differential diagnoses and the specimen obtained from the patient.

Imaging also plays a role in the diagnosis of Kaposi sarcoma. With MRI, KS is seen as an abnormal enhancing tissue with low signal intensity on T1-weighted images and high signal intensity on turbo inversion recovery magnitude (TIRM) or T2-weighted images. This is consistent with the MRI findings of our case.

AIDS-associated KS tends to be a multifocal disease and therapy should be directed systemically.[10,16] Chemotherapy and/or radiotherapy alone, despite having some palliative value, portends a poorer prognosis and less overall survival in AIDS-associated KS.[11]

The use of highly active antiretroviral therapy (HAART) in AIDS-associated KS has been linked to disease regression 80% of the time and an increase in overall survival. The median time to response ranged from 3 to 9 months.[11] KS flare, a phenomenon wherein there is a paradoxical worsening of KS while undergoing HAART, has also been described.[12] HAART has decreased the incidence of KS among HIV patients in developed countries.[3] Further research is still required to determine the impact of HAART on KS in developing countries.[11]

Unfortunately, our patient was lost to follow-up before further work-up and treatment with HAART could be initiated.

Table 2. Summary of immunochemistry results

	CD3	CD20	CD34	CD1a	CD21	S100
Kaposi sarcoma	-	-	+	-	-	-
Kaposiform hemangioendothelioma	-	-	+	-	-	-
Ancient schwannoma	-	-	-	-	-	+
Malignant peripheral nerve sheath tumor	-	-	-	-	-	+
Hodgkin's lymphoma	-	+	-	-	-	-
Langerhans cell histiocytosis	-	-	-	+	-	-
Patient	-	-	+	-	-	-

CONCLUSION

Kaposi sarcoma is a low-grade vasoformative neoplasm with morphologic similarities to other vasoproliferative lesions and spindle cell neoplasms. This characteristic along with the atypical location and multifocal behavior of AIDS-associated KS can lead to challenges in diagnosis and management. In this case, determining the HIV status of the patient was essential in the diagnosis of KS given its unusual orbital presentation. HHV-8 LNA-1 staining can distinguish KS in patients with unknown HIV status; however, this test is currently not available in the Philippines. Therefore, Kaposi sarcoma should always be considered as a differential diagnosis in young, high-risk individuals presenting with ocular complaints.

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