Proceedings of Scientific Research Universidad Anáhuac, 2022, 2(4): 23-28.
ISSN-e: 2954-3541.

Case Report

AIDS-related disseminated Kaposi Sarcoma: a case report

Samanta Ruiz[a1*], Juan José Díaz-Vintimilla[b2], Maximiliano Trevilla-Viveros[c3], Rogelio Zapata-Arenas[c4], Tamara Monserrat Mejia-Alcantara[d5]

[a]Universidad Anáhuac México, Estado de México, México.
[b]Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez", Ciudad de México, México.
[c]Hospital General de México "Dr. Eduardo Liceaga", Ciudad de México, México.
[d]Universidad Autónoma de Guadalajara, Jalisco, México.

ID OCRID:
[1]https://orcid.org/0000-0001-5080-5059, [2]https://orcid.org/0000-0002-2985-1883, [3]https://orcid.org/0000-0001-5742-8292,
[4]https://orcid.org/0000-0003-4715-5643, [5]https://orcid.org/0000-0001-6890-8048

https://doi.org/10.36105/psrua.2022v2n4.03

ABSTRACT

Kaposi sarcoma (KS) is the most common malignant tumor in HIV-infected individuals. Although its most common form consists of skin and mucosal lesions, it can also present itself in a disseminated way affecting the gastrointestinal tract, lungs and eye structures. We present the case of a 27-year-old male patient with HIV infection and disseminated Kaposi sarcoma. Disseminated KS is an uncommon form of the disease. Therefore, it is important to take this into account, particularly in HIV-infected individuals with characteristic cutaneous lesions.

Key words: kaposi sarcoma; acquired immunodeficiency syndrome; human herpesvirus 8; human immunodeficiency virus.

RESUMEN

El Sarcoma de Kaposi es el tumor maligno más frecuente en las personas infectadas por el VIH. Puede presentarse de forma diseminada afectando no solo la piel y la mucosa oral sino también el tracto gastrointestinal, los pulmones y las estructuras oculares. En este artículo se presenta el caso de un paciente masculino de 27 años con infección por VIH y sarcoma de Kaposi diseminado. El KS diseminado es una forma poco común de la enfermedad y que raramente involucra estructuras oculares. Por lo tanto, es importante tener esto en cuenta, particularmente en individuos infectados por el VIH con lesiones cutáneas características.

Palabras clave: sarcoma de kaposi; síndrome de inmunodeficiencia adquirida; herpes virus humano 8; virus de inmunodeficiencia humana.

* *Corresponding author:* Samanta Ruiz. Universidad Anáhuac México. Address: Av. Universidad Anáhuac núm. 46, Lomas Anáhuac, 52786, Huixquilucan, Estado de México, México. Tel.: +52 55 5627 0210. Email: samanta.ruizl@hotmail.com

Received: June 23, 2022.
Accepted: August 23, 2022.

INTRODUCTION

Kaposi sarcoma (KS) is a malignant tumor of the vascular endothelium. In 1872 Moritz Kaposi, a Hungarian dermatologist described this pathology for the first time as a multicentric skin tumor consisting of hyperpigmented and nodular lesions in elderly European men.[1,2] Human Herpesvirus 8 (HHV8) also known as Kaposi Sarcoma Herpesvirus (KSHV) is regarded as the etiology of KS.[1] The different types of KS are: classic, endemic, iatrogenic and epidemic or AIDS-related. The latter two forms occur in immunosuppressed patients.[1]

In 1980 the first cases of Kaposi sarcoma in men who have sex with men (MSM) and that had acquired immunodeficiency syndrome (AIDS) were reported.[1] Of all four forms, epidemic KS is the most aggressive and it is also the most frequent malignant neoplasm in human immunodeficiency virus (HIV)-infected individuals.[3,4] It typically affects patients with a low CD4 cell count, usually below 200 cells/µl.[3]

Kaposi sarcoma can affect other organs besides the skin, mostly the gastrointestinal tract, lungs, liver, oral cavity and lymph nodes.[1,2] Disseminated KS, however, only very rarely affects ocular structures such as the conjunctiva, cornea, sclera and ocular adnexa.[3,4,5]

The HHV8 virus inhibits the p53 pathway on three levels: latency-associated nuclear antigen, suppressing transcription and transactivation and acting directly on p53 protein by inhibiting its ability to induce cell death. There are other pathogenic factors of HHV8, such as viral interferon (IFN) and regulatory factor 4 (VIRF4). The pathogenic process of HHV8-associated KS starts with stable genetic damage, followed by a promotor factor, this added to viruses and chemicals, acting as initiators as well as promoters, depending on their prevalent effects either mutagenic or epigenetic. Viruses can interact with co-carcinogens; these may act directly on the potential cancer cell or indirectly by affecting other tissues of the host. There is also an issue with the role of TNF-α; this factor appears to play an important role in reactivating the viral lysis cycle (HHV8 itself stimulates TNF-α production), thus creating an environment for disease development.[6]

In addition, cofactors with the ability to interact with HHV8 can affect the immune system, or act as vasoactive agents. For example, in AIDS-related KS, the use of large amounts of nitrite-rich inhalants by HIV-infected men who have sex with men was strongly associated with development of KS.[6]

KSHV encodes oncogenic proteins such as LANA-1, v-FLIP, v-cyclin, v-GPCR, v-IL6, v-CCL, v-MIP, v-IRF that can modulate cellular pathways leading to inhibition of apoptosis, cellular proliferation stimulation, angiogenesis, inflammation and immune escape; all involved in the development of KS. This virus infects B cells and endothelial cells primarily in vivo, next (KSHV) becomes latent, especially in B lymphocytes and monocytes. Typical infected spindle cells are of the endothelial cell lineage. In fact, spindle cells express markers from both vascular and lymphatic endothelial cells such as VEGF-3, LYVE-1, podoplanin, CD34, CD31, CD36 and have the phenotypic properties of those two cells. In other matters, their gene expression profiles do not accurately represent neither of these two endothelial lines. In the majority of Kaposi sarcoma cells, the virus remains dormant and indicates a central role for viral latency proteins in the development of this disease. Only a small portion of spindle cells undergo spontaneous reactivation of the lytic virus, leading to lytic protein expression and virion production, with secretion of pro-inflammatory molecules and angiogenesis-promoting factors that may be involved in cell proliferation suggest their important role in the process of tumorigenesis.[7]

There is a temporal regulation of viral gene expression in the lytic replication that is divided in three phases: immediate early (IE), early (E), and late (L). The first phase does not require protein synthesis and it creates viral trans activators involved in E gene expression; E viral proteins then replicate. The first and second phase genes do not depend on viral DNA synthesis, but E genes sometimes accumulate in the onset of replication. Late expression comes after viral DNA synthesis, consisting of components of virions with no infectious virus particles. Secondly, during viral latency a limited set of viral genes are expressed, the most important being latency-associated nuclear antigen (LANA), which joins viral genome to host chromosome for the latent viral DNA persistence. The fundamental origin binding proteins recognize oriLyt and enroll DNA replication proteins, they may also do so with enzymatic function. One of these is K-RTA that ties up to RRE and enrolls the polymerase processivity factor (ORF59).[8]

The transcription capacity of the viral DNA template is modulated by the interaction of the viral genome and cellular histones. Recruitment of different subtypes of histones, like H1 linker histone, induce progression employing states of the viral replication cycle.[8]

There is some controversy about the exact cause of KS, neurogenic and vascular etiologies have been described. Recent evidence, however, suggests that is not a true tumor, rather a dysregulation of the inflammatory response. Moreover, lesion growth depends on various cytokines and growth factors, including the Tat gene from the HIV genome.[9]

https://doi.org/10.36105/psrua.2022v2n4.03

We present the case of a 27-year-old male patient with newly diagnosed HIV infection and disseminated Kaposi sarcoma involving the skin, esophagus, stomach and probably, bulbar conjunctiva.

Case report

A 27-year-old man with previous history of unprotected male to male sexual intercourse exhibited a clinical picture of unintended weight loss of about 12 kg in the past four months, accompanied by purple lesions in his mouth and lower limbs. Three days prior to admission he developed dry cough and resting dyspnea which prompted him to seek medical attention. After initial evaluation in the emergency room, the patient was admitted to the internal medicine ward. On physical examination we noticed several purple, flesh-like lesions on the right bulbar conjunctiva, tongue, soft palate and feet. Also, cotton-white lesions were observed in his tongue, soft and hard palate and oropharynx (Figure 1).

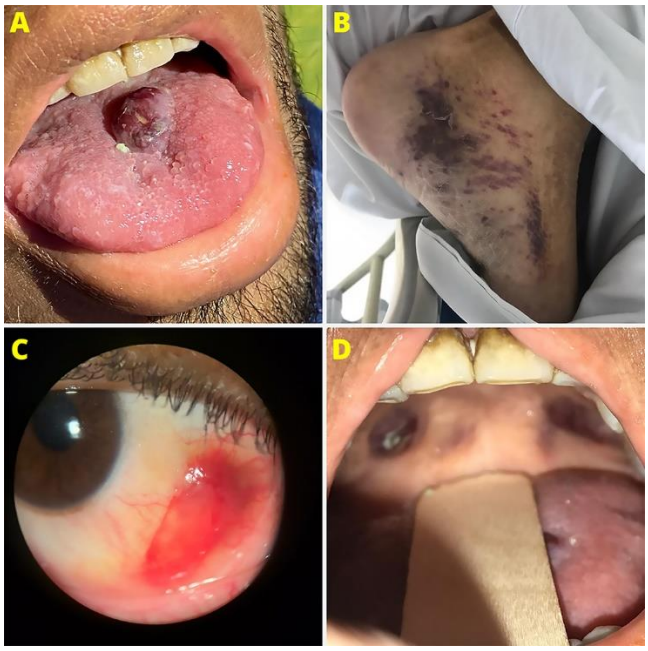

Figure 1. Disseminated Kaposi Sarcoma. (A-D) Classic purple, hypervascularized, flesh-like lesions on the tongue, feet, right bulbar conjunctiva and hard palate.

A high-resolution computed tomography (HRCT) of the chest was requested with non-specific interstitial infiltrates; a SARS-CoV-2 RT-PCR came out negative, but he tested positive for human immunodeficiency virus (HIV) infection, with a CD4+ count of 17 cells/µl. Empiric treatment with trimethoprim/sulfamethoxazole and fluconazole for *Pneumocystis jiroveci* pneumonia (PJP) and esophageal candidiasis, respectively, was started; along with azithromycin for *Mycobacterium avium* complex primary prophylaxis.

An upper gastrointestinal endoscopy reported abundant whitish, confluent plaques throughout the esophagus and several elevated, hypervascularized lesions with irregular borders close to the esophagogastric junction and the gastric fundus, body and pylorus; related with a Kodsi 3 esophageal candidiasis and probable Kaposi sarcoma (Figure 2).

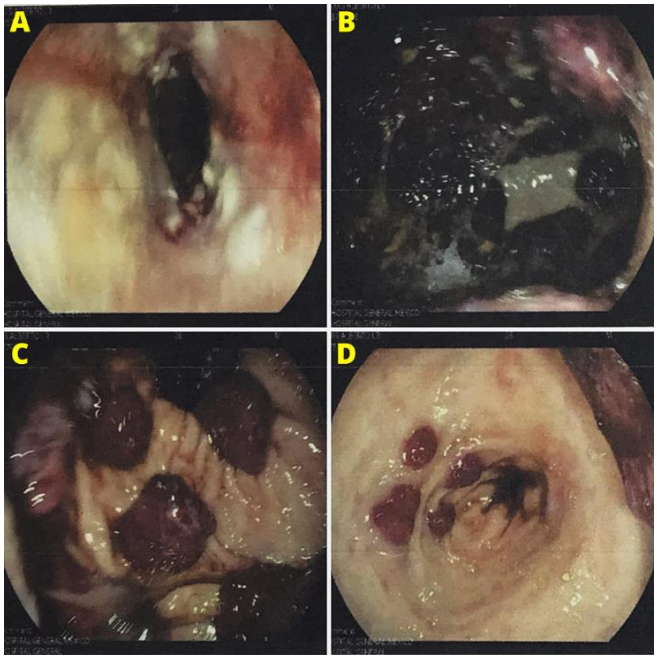

Figure 2. Upper gastrointestinal endoscopy. (A) Kodsi 3 esophageal candidiasis. (B-D) Elevated, hypervascularized lesions consistent with visceral Kaposi sarcoma located in the stomach and esophagogastric junction.

A biopsy of the previously mentioned skin lesions was performed, reporting findings consistent with nodular Kaposi sarcoma. Regarding his ocular lesions, although no biopsy was taken, a thorough ophthalmologic evaluation was carried out, with the lesions being described as a probable conjunctival Kaposi sarcoma. With all this, a diagnosis of AIDS-related disseminated Kaposi sarcoma was established. We consulted the case with the oncology department who decided against starting chemotherapy due to the patient's poor status at the time. During the next few days, his respiratory condition deteriorated despite empirical treatment for PJP, and the patient eventually died.

No autopsy was performed due to the COVID-19 pandemic biosafety protocols.

DISCUSSION

Kaposi sarcoma (KS) is a malignant neoplasm derived from the endothelium, characterized by vascular proliferation of multifocal origin. It was first described in 1872 by Moritz Kaposi as a type of idiopathic pigmented sarcoma of the skin, thought to be endemic to Eastern Europe and the Mediterranean in elderly Jewish men.[10]

It was thought to be rare until 1980 when a report of an epidemic of disseminated Kaposi sarcoma among men who have sex with men (MSM) would become one of the first studies to observe the beginning of the HIV pandemic and what would be known as an AIDS-related and defining disease.[11]

The observation at the beginning of the AIDS pandemic that the highest incidence of the disease between HIV patients was among MSM, led to the conclusion that an unidentified sexually- transmissible infectious agent could be present.[12]

In 1994 Chang et al. were the first to identify sequences of a Herpesvirus-like DNA in KS lesions which they named Kaposi Sarcoma Herpesvirus (KSHV) and afterwards became known as Human Herpesvirus 8 (HHV8).[13]

Since the original description, four types of KS have been described. The classical type, characterized by vascular-appearing plaques and nodules localized on the lower extremities, with single or multiple lesions, alone or in combination with visceral involvement. The African endemic form, first described in the 1950s. The iatrogenic form, described among renal allograft transplant recipients and immunosuppressed patients. The last form identified was the epidemic AIDS-related form, which was prevalent as the HIV pandemic progressed, preceding or occurring simultaneously to the development of HIV-related symptoms.[14]

HHV-8 infection is the common etiology among all forms of KS, being considered a necessary condition for the development of the disease, yet it requires other genetic, immunologic and environmental factors which determine the evolution of the different forms, the most important one being HIV co-infection, with ongoing debate about the role of HIV either through a direct or immunosuppressive effect, associated with CD4+ count and the degree of viremia.[1,4,5]

HHV-8 is a DNA oncogenic virus which mediates viral oncogenesis through interference at multiples levels of the tumor suppressor pathways which regulates DNA repair, senescence and apoptosis.[6]

AIDS-related Kaposi Sarcoma can be divided into two risk groups that determine prognosis: low-risk and high-risk diseases. These groups have been classified according to three main criteria regarding tumor burden, the patient's immune status and the presence of opportunistic infections. Low-risk patients have KS lesions confined to the skin and lymph nodes, a CD4+ count of >200 cells/µl and no history of opportunistic infections. High-risk KS on the other hand, is characterized by extensive cutaneous, oral and visceral lesions, <150 CD4+ and opportunistic infections.[1] Patients with <100 CD4+ and a viral load of >10,000 copies/ml have the worst prognosis.[1,2] The patient in our study falls under the second risk group due to KS lesions located in multiple organs, a very low CD4+ count, and the presence of *Candida*, and probably *P. jiroveci,* coinfection.[1]

Disseminated KS is not uncommon among HIV-positive individuals. Visceral involvement can be seen in up to 25% of HIV-infected KS patients. The gastrointestinal tract is affected in more than 50% of the patients with cutaneous lesions and HIV-infection as we were able to evidence in our case. The gastrointestinal tract can be compromised at any point, from the esophagus to the large intestine. Clinically, patients may be asymptomatic or present non-specific symptoms, such as nausea, vomiting, abdominal pain, diarrhea and weight loss. On upper gastrointestinal endoscopy, lesions can be seen as erythematous, maculopapular, nodular, or polypoid.[1,2]

Other organs less commonly involved include the lungs (45% of HIV-positive patients with cutaneous and gastrointestinal KS) with symptoms that cannot be distinguished from opportunistic infections; kidneys, particularly in renal transplant recipients but rarely in epidemic-KS, and adrenal glands.[1,2]

Skeletal involvement is relatively rare in KS, it worsens the patient´s prognosis and is more typically seen in the setting of locally aggressive head-and-neck lesions that erode through tissue planes into the underlying bony structures, as initially described by Kaposi. Lesions are characteristically osteolytic, with destruction of the bone cortex and less commonly, destruction of the entire bone can be seen. HIV-associated cases show a greater predilection for the axial skeleton compared to classic or endemic variants.[15] Prognosis depends heavily on the extent of the disease. Three-year survival rate has been reported as ranging from

https://doi.org/10.36105/psrua.2022v2n4.03

88% in localized disease, to 53% in the case of symptomatic visceral disease. Asymptomatic disease may be treated with immune reconstitution through initiating ART alone.[15]

Ocular KS is exceedingly rare with very few cases reported, mostly in HIV-infected individuals and solid organ transplant recipients, especially renal transplantation, and less commonly in bone marrow or peripheral blood stem cell transplantations; likely associated to the immunosuppressive therapy these patients receive prior to and after transplant surgery. It can affect any eye structure, especially eyelids and conjunctiva, most likely the case in our patient, and more rarely extend to the cornea or orbit. It manifests as violaceous, red or pink fleshy lesions with or without associated hemorrhage in the aforementioned sites, therefore it can easily be mistaken as a subconjunctival hemorrhage, conjunctival cysts, hemangioma or even lymphoma, melanoma and squamous cell carcinoma. Thus, highlighting the importance of an adequate ophthalmologic examination in AIDS patients.[3-5,16]

The KS incidence among HIV-infected patients has lowered greatly after the introduction of antiretroviral therapy. Worsening of previous KS lesions has been described as presence of immune reconstitution inflammatory syndrome (IRIS) after initiation of antiretroviral therapy.[17] There is some literature reporting concurrent Multicentric Castleman disease (MCD) and KS. Volkow-Fernandez et al., reported that up to 79% of patients with Castleman disease had coexistent KS.[17]

The identification of both diseases on pathology is crucial because the therapeutic targets may be different, and patients with untreated MCD are at higher risk of large B-cell lymphoma.[17]

Patients with a rare disease called Kaposi sarcoma inflammatory cytokine syndrome tend to have a lower CD4+ count (<100 cells/mm3) than those with Kaposi Sarcoma-Multicentric Castleman disease (>200 cells/mm3). These may appear when the levels of Kaposi Sarcoma Herpesvirus viral load, IL-6, and IL-10 are significantly elevated. The difference between these two pathologies can be established with a lymph node biopsy called Hence.[18]

The first line of treatment in AIDS-related KS consists of improving the patient's immune status with the use of antiretroviral therapy (ART); individuals with an early-stage disease will often respond to bolstering the immune system alone.[2,19] Nonetheless, there is always a considerable risk for the development KS-associated immune reconstitution inflammatory syndrome (IRIS), particularly in ART-naïve patients with a relatively high CD4+ count.[2] For patients with a more advanced disease the next step becomes tumor-directed treatment. Anthracyclines are considered to be the standard first-line chemotherapeutic agents for AIDS-related KS in an advanced stage.[19] Regarding ocular KS, treatment will depend on the extent of the lesions and associated comorbidities, such as HIV infection or iatrogenic immunosuppression. Localized lesions can be treated with surgical excision, intralesional chemotherapy or radiation therapy. For widespread disease, systemic chemotherapy or immunomodulatory agents are preferred. In the case of iatrogenic ocular KS, it is often required to discontinue immunosuppressive therapy.[16]

CONCLUSION

Kaposi sarcoma in HIV-positive individuals can present involvement of several organs including the skin, oral mucosa, viscera and ocular structures.

Poor prognostic factors include tumor extension and the patient's immune status. Treatment options include antiretroviral therapy and chemotherapy depending on the tumor stage. It is important to consider this condition in patients with a high suspicion or diagnosis of HIV infection in order to initiate an adequate therapy on a timely fashion and prevent severe complications and death.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

ACKNOWLEDGEMENTS

I would like to thank everybody involved in the development of this case report for their support and dedication.

FUNDING

The publication was supported by the authors themselves.

AUTHORS' CONTRIBUTIONS

All the authors have read and approved the final manuscript.

REFERENCES

1. Fardin RB, Leite LAC, Bezerra LMDS, Alves PMP, Dos Santos LL, Salvá M de A, et al. Fatal disseminated Kaposi's sarcoma in two patients with human immunodeficiency virus (HIV) infection. Am J Case Rep. 2018;19:868-74. https://doi.org/10.12659/AJCR.910004
2. Tang ASO, Teh YC, Chea CY, Yeo ST, Chua HH. Disseminated AIDS-related Kaposi's sarcoma. Oxf Med Case Reports. 2018;2018:omy107. https://doi.org/10.1093/omcr/omy107
3. Sousa Neves F, Braga J, Cardoso da Costa J, Sequeira J, Prazeres S. Kaposi's sarcoma of the conjunctiva and the eyelid leads to the diagnosis of human immunodeficiency virus infection: a case report. BMC Cancer. 2018;18. https://doi.org/10.1186/s12885-018-4611-3
4. Jin C, Minhas H, Kaur A, Kodali S, Gotlieb V. A case of Ocular Kaposi's sarcoma successfully treated with highly active antiretroviral therapy (HAART) combined with docetaxel. Am J Case Rep. 2018;19:1074-7. https://doi.org/10.12659/AJCR.910374
5. Yang J, Yin X-F, Li Y-P, Zhou S-Y. Case report of ocular Kaposi's sarcoma. BMC Ophthalmol. 2017;17. https://doi.org/10.1186/s12886-017-0525-0
6. Ruocco E, Ruocco V, Tornesello ML, Gambardella A, Wolf R, Buonaguro FM. Kaposi's sarcoma: etiology and pathogenesis, inducing factors, causal associations, and treatments: facts and controversies. Clin Dermatol. 2013;31:413-22. https://doi.org/0.1016/j.clindermatol.2013.01.008
7. Jary A, Veyri M, Gothland A, Leducq V, Calvez V, Marcelin A-G. Kaposi's sarcoma-associated Herpesvirus, the etiological agent of all epidemiological forms of Kaposi's sarcoma. Cancers (Basel). 2021;13:6208. https://doi.org/10.3390/cancers13246208
8. Gutierrez IV, Sarkar P, Rossetto CC. Kaposi's sarcoma-associated Herpesvirus processivity factor, ORF59, binds to canonical and linker histones, and its carboxy terminus is dispensable for viral DNA synthesis. J Virol. 2021;95. https://doi.org/10.1128/JVI.02169-20
9. Rossetto JD, Molles S, Gracitelli CPB. Extensive bulbar conjunctival Kaposi's sarcoma as initial symptom of human immunodeficiency virus. Arq Bras Oftalmol. 2019;82:429-31. https://doi.org/10.5935/0004-2749.20190083
10. Kaposi. Idiopathisches multiples Pigmentsarkom der Haut. Arch Derm Res. 1872;4:265-73. https://doi.org/10.4067/S0034-98872007000900011
11. Friedman-Kien AE. Disseminated Kaposi's sarcoma in homosexual men. Ann Intern Med. 1982;96:693. https://doi.org/10.7326/0003-4819-96-6-693
12. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet. 1990;335:123-8. https://doi.org/10.1016/0140-6736(90)90001-l
13. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266:1865-9. https://doi.org/10.1126/science.7997879
14. Friedman-Kien AE, Saltzman BR. Clinical manifestations of classical, endemic African, and epidemic AIDS-associated Kaposi's sarcoma. J Am Acad Dermatol. 1990;22:1237-50. https://doi.org/10.1016/0190-9622(90)70169-i
15. Rusu-Zota G, Manole OM, Galeș C, Porumb-Andrese E, Obadă O, Mocanu CV. Kaposi sarcoma, a trifecta of pathogenic mechanisms. Diagnostics (Basel). 2022;12:1242. https://doi.org/10.3390/diagnostics12051242
16. Venkateswaran N, Ramos JC, Cohen AK, Alvarez OP, Cohen NK, Galor A, et al. Spotlight on ocular Kaposi's sarcoma: an update on the presentation, diagnosis, and management options. Expert Rev Ophthalmol. 2021;16:477-89. https://doi.org/10.1080/17469899.2021.1962294
17. Lin IF, Lin JN, Tsai TH, Hsu CT, Wu YY, Lai CH. Coexistence of disseminated Kaposi sarcoma and multicentric Castleman disease in an HIV-infected patient under viral suppression. Int J STD AIDS. 2021;32:286-9. https://doi.org/10.1177/0956462420968385
18. Chang KM, Hsieh SL, Harris CA. Disseminated Kaposi sarcoma with cytokine release in an AIDS patient. J Microbiol Immunol Infect. 2022;55:344-6. https://doi.org/10.1016/j.jmii.2021.03.019
19. Cesarman E, Damania B, Krown SE, Martin J, Bower M, Whitby D. Kaposi sarcoma. Nat Rev Dis Primers. 2019;5-9. https://doi.org/10.1038/s41572-019-0060-9

https://doi.org/10.36105/psrua.2022v2n4.03