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A case report : 34 y.o male with incidental histopathological findings of Kaposi sarcoma without clinical history of human immunodeficiency virus (HIV)

Relato de caso: Homem de 34 anos com achados histopatológicos incidentais de sarcoma de Kaposi sem história clínica de vírus da imunodeficiência humana (HIV)

Relato de un caso: Hombre de 34 años con hallazgos histopatológicos incidentales de sarcoma de Kaposi sin antecedentes clínicos del virus de la inmunodeficiencia humana (VIH)

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Abstract
Introduction: Kaposi sarcoma is a rare and challenging case especially in immunosuppressed patients that frequently doesn't have specific manifestation. It usually caused by human herpes virus 8 virus infection and male patient with multiple lesion has high mortality rates. The aim of this study is to report 34 y.o Male with incidental histopathological findings of kaposi sarcoma without clinical history of Human Immunodeficiency Virus (HIV). Methodology: Descriptive study of the case report type, whose data were obtained from the patient's medical record. Result: This paper will report 34-year-old young adult male with clinically diagnosed with poroma and differential diagnosis of squamous cell carcinoma and pyogenic granuloma. The clinical sign was multiple skin lesion appear on his right nose and thumb in the last 6 months. The nodules are solitary with oval shape, erythema, firm borders and the nodule surface covered with brownish-yellow squama. In addition, imaging examination suspicious for soft tissue mass. The biopsy was performed, and histopathological finding exhibit a tumor mass consists of Kaposi sarcoma. Discussion: Furthermore, after pathological report revealed the diagnosis of Kaposi sarcoma then a provider-initiated HIV testing and counseling (PITC) examination is carried out and the test result showed reactive for HIV infection. So that, patient concluded to have predisposition of HIV infection with Kaposi sarcoma and treated for antiretrovirals (ARV), chemotherapy and routine clinical follow up. Conclusion : Kaposi sarcoma is a rare cancer caused by infection with the human herpesvirus 8 (HHV8). These lesions are often found in immunosuppressed patients such as HIV sufferers characterized by vascular proliferation. Through the incidental findings of Kaposi's sarcoma in patients who are not clinically suspected of having HIV, clinicopathological correlation is highly recommended. Therefore, the purpose of this writing can be a strong reference so that clinicians are more thorough in reviewing clinical patients and more detailed physical examinations.
Keywords: Kaposi sarcoma; Skin lesion; Incidental histopathological findings.

Resumo
Introdução: O sarcoma de Kaposi é um caso raro e desafiador especialmente em pacientes imunossuprimidos que frequentemente não apresenta manifestação específica. Geralmente é causada pela infecção pelo vírus herpes humano 8 e pacientes do sexo masculino com lesões múltiplas apresentam altas taxas de mortalidade. O objetivo deste estudo é relatar um homem de 34 anos com achados histopatológicos incidentais de sarcoma de Kaposi sem história clínica de Vírus da Imunodeficiência Humana (HIV). Metodologia: Estudo descritivo do tipo relato de caso, cujos dados foram obtidos do prontuário do paciente. Resultado: Este trabalho relatará um homem adulto jovem, 34 anos, com diagnóstico clínico de poroma e diagnóstico diferencial de carcinoma espinocelular e granuloma piogênico. O sinal clínico foi múltiplas lesões cutâneas no nariz e polegar direito nos últimos 6 meses. Os nódulos são solitários, com formato oval,

eritema, bordas firmes e superfície nodular coberta por escama amarelo-acastanhada. Além disso, exame de imagem suspeita de massa de partes moles. A biópsia foi realizada e o achado histopatológico exibiu uma massa tumoral constituída por sarcoma de Kaposi. Discussão: Além disso, após o relatório patológico ter revelado o diagnóstico de sarcoma de Kaposi, é realizado um exame de teste e aconselhamento sobre VIH (PITC) iniciado pelo prestador e o resultado do teste mostrou-se reativo para a infecção por VIH. Assim sendo, o paciente concluiu ter predisposição à infecção pelo HIV com sarcoma de Kaposi e foi tratado com antirretrovirais (ARV), quimioterapia e acompanhamento clínico de rotina. Conclusão: O sarcoma de Kaposi é um câncer raro causado pela infecção pelo herpesvírus humano 8 (HHV8). Estas lesões são frequentemente encontradas em pacientes imunossuprimidos, como portadores de HIV, caracterizados por proliferação vascular. Através dos achados incidentais do sarcoma de Kaposi em pacientes sem suspeita clínica de terem HIV, a correlação clinicopatológica é altamente recomendada. Portanto, o objetivo deste escrito pode ser uma forte referência para que os médicos sejam mais minuciosos na revisão dos pacientes clínicos e nos exames físicos mais detalhados.
Palavras-chave: Sarcoma de Kaposi; Lesão na pele; Achados histopatológicos incidentais.

Resumen
Introducción: El sarcoma de Kaposi es un caso raro y desafiante especialmente en pacientes inmunodeprimidos que frecuentemente no presenta una manifestación específica. Generalmente es causada por una infección por el virus del herpes humano 8 y los pacientes masculinos con lesiones múltiples tienen altas tasas de mortalidad. El objetivo de este estudio es reportar un hombre de 34 años con hallazgos histopatológicos incidentales de sarcoma de Kaposi sin antecedentes clínicos de Virus de Inmunodeficiencia Humana (VIH). Metodología: Estudio descriptivo del tipo reporte de caso, cuyos datos se obtuvieron de la historia clínica del paciente. Resultado: En este trabajo se reporta un varón adulto joven de 34 años con diagnóstico clínico de poroma y diagnóstico diferencial de carcinoma de células escamosas y granuloma piógeno. El signo clínico fue lesión cutánea múltiple de aparición en nariz y pulgar derechos en los últimos 6 meses. Los nódulos son solitarios con forma ovalada, eritema, bordes firmes y la superficie del nódulo cubierta de escama de color amarillo parduzco. Además, el examen de imagen sospechosa de masa de tejidos blandos. Se realizó biopsia y el hallazgo histopatológico fue una masa tumoral consistente en sarcoma de Kaposi. Discusión: Además, después de que el informe patológico reveló el diagnóstico de sarcoma de Kaposi, se realiza un examen de asesoramiento y prueba de VIH (PITC) iniciado por el proveedor y el resultado de la prueba mostró reactivo para la infección por VIH. Así, el paciente concluyó que tenía predisposición a la infección por VIH con sarcoma de Kaposi y recibió tratamiento con antirretrovirales (ARV), quimioterapia y seguimiento clínico de rutina. Conclusión: el sarcoma de Kaposi es un cáncer poco común causado por la infección por el herpesvirus humano 8 (HHV8). Estas lesiones se encuentran a menudo en pacientes inmunodeprimidos, como los que padecen VIH, caracterizados por proliferación vascular. A través de los hallazgos incidentales del sarcoma de Kaposi en pacientes en los que no se sospecha clínicamente que tengan VIH, se recomienda encarecidamente la correlación clínico-patológica. Por lo tanto, el propósito de este escrito puede ser una fuerte referencia para que los médicos sean más exhaustivos en la revisión clínica de los pacientes y en exámenes físicos más detallados.
Palabras clave: Sarcoma de Kaposi; Lesion de piel; Hallazgos histopatológicos incidentales.

1. Introduction

Kaposi sarcoma is vascular neoplasm caused by human herpesvirus 8 (HHV8) infection, and it usually affect immunosuppressed patients (Billings, 2011; Landman, 2018; Geraminejad et all, 2002). According to Globocan data in 2020, Kaposi sarcoma cases rank 31 of all cancer cases in the world. While the ratio of male and female are 1.9: 1. Furthermore, the number of deaths due to Kaposi sarcoma is 68.3%, dominated in male rather than female patient. The mortality rate is 0.4 deaths per 100,000 people/year. Moreover, the epidemiology of Kaposi sarcoma in Indonesia is rare cases which only count for 0.03% of all cancers in 2020 (Globocan, 2021). Based on risk predisposition factor data, Kaposi sarcoma related to the homosexuals is 5.7 cases per 100 people/year and a person who infected by HIV are 100 to 300 times more likely to develop Kaposi sarcoma than the HIV-negative population. The 5-year survival rate in Kaposi sarcoma patients whose lesions have spread to multiple sites of the body is 40% (Cancer.NET, 2023).

2. Methodology

This is a descriptive study of the case report type. The case study approach is particular useful to employ when there is a need to obtain an in-depth appreciation of an issues which presenting any unique, rare clinical or pathological case and illustrate broader lessons that may be learnt (Crowe et al., 2011; Pereira et al.,2018). Analytical aspect of this study was

obtained from complete history taking, clinical examination and confirmed by pathological examination. The case report study approved by research ethics committee did not conduct any ethical clearance for case report due to the case already discusses at clinicopathological conference sand approve by clinician, patient, and pathologist. Following ethical principles, the patient consented to disseminating the data and displaying images of his case for academic purpose trough signing of a free and informed consent form.

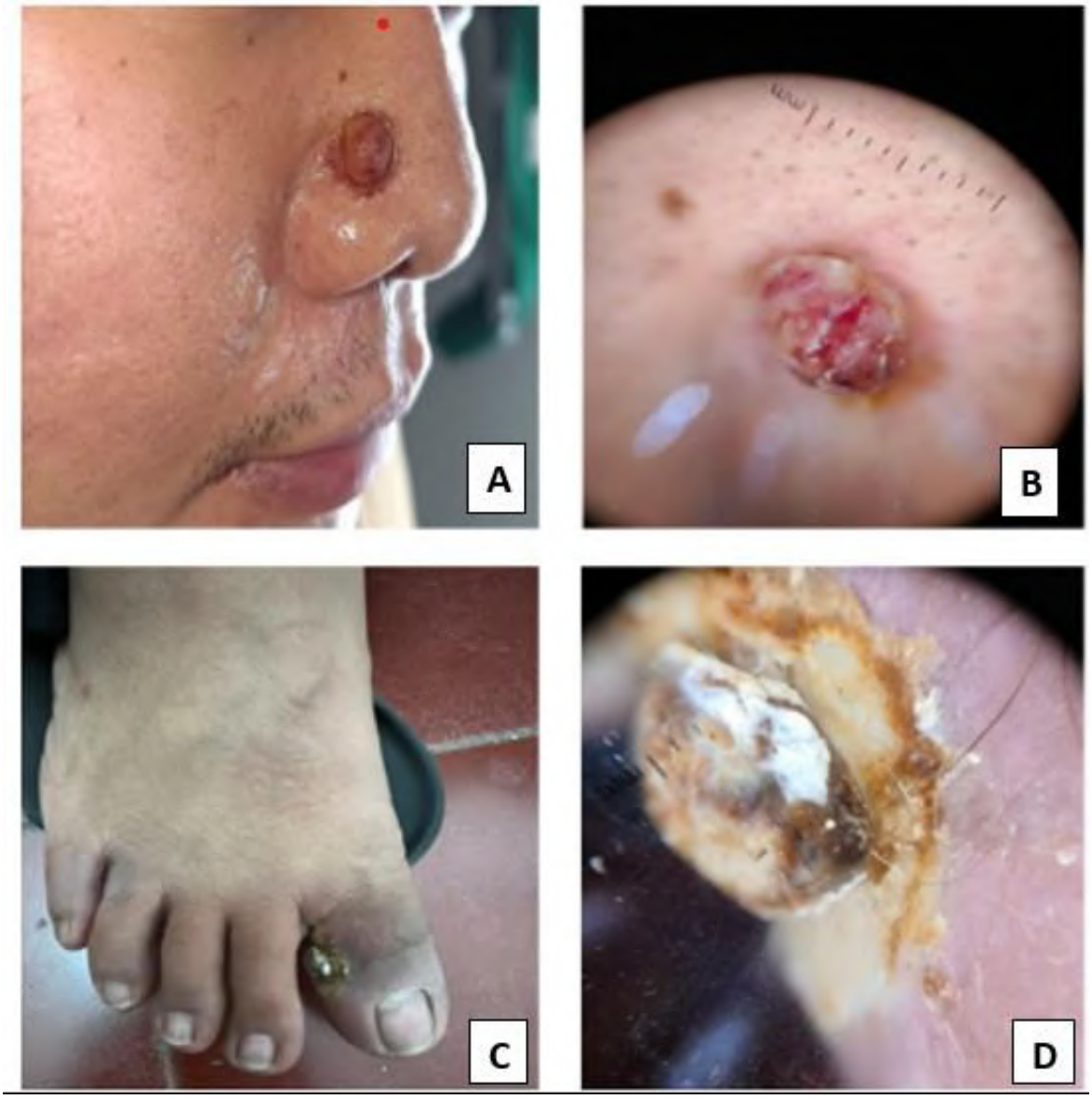
3. Case Presentation

A man, aged 34 years came to policlinic in mid-October 2022, with a chief complaint multiple lump appearing on his right nose and thumb since 1 month before. The lump feels enlarged and bleeds easily when exposed to friction. The patient said that he had experienced a similar lesion 4 months earlier on his toe, however the lump had disappear without any specific treatment. There is no other history of systemic and chronic disease. Clinical examination exhibits a nodule on his right nostril is pink, solitary, well defined, oval in shape, 1 x 0.8 cm in size and there are erosions and brownish yellow scales over the nodules (picture 1A and 1B). In addition, other nodules appear on the right lateral side of the first digiti pedis which appear as solitary erythema nodules with firm boundaries, round shape, 1 x 1 cm in diameter (Picture 1C and 1D). Moreover, x-ray examination results in the dextra lateral aspect of the pedis region showed a round opacity with a size of -/+ 0.9 x 0.6 cm, with soft tissue density in the first digit region, suspected soft tissue mass. The clinical diagnoses suspected poroma with differential diagnosis of squamous cell carcinoma and pyogenic granuloma.

The nodules were biopsied and tissues are continue for histopathological examination. Microscopic findings show nodular tumor mass consists of a proliferation of neoplastic cells that spread diffusely in the dermis through the epidermis in a storiform pattern. Blood vessels with vessel in vessel (promontory sign) can be observed among the tumor cells. These cells has semi-oval spindle morphology, eosinophilic cytoplasm, increased N/C ratio, irregular nuclear membrane, rounded oval nucleus, pleomorphic and vesicular to hyperchromatic chromatin, with invisible to prominent nuclei. Mitoses are easily found, and some abnormal mitosis are spotted. The surface layers of the epidermis some appear to be ulcerated (Picture 2A-C). Based on clinical data, and histopathological findings then it is concluded as malignant spindle cell tumor and suspicious for Kaposi sarcoma.

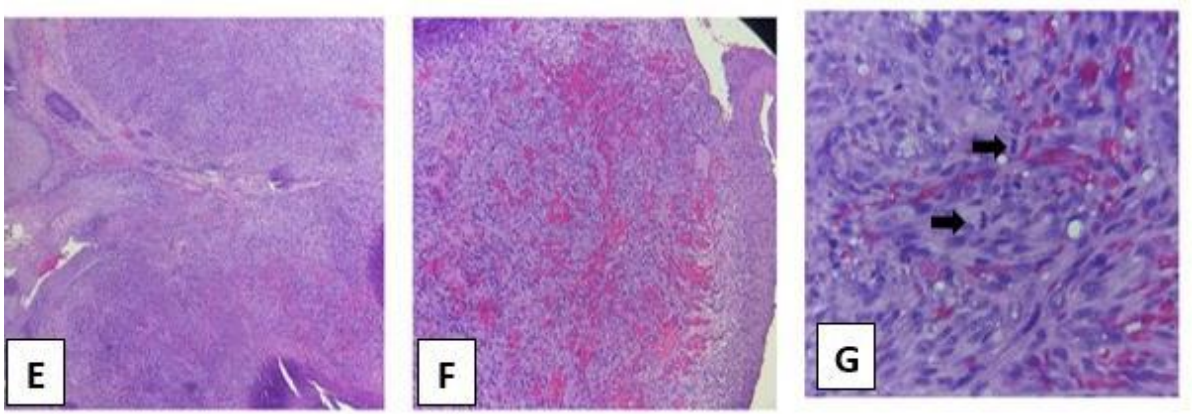
After the clinician gets a histopathological diagnosis, additional anamnesis and other investigations to look for risk factors are carried out.The patient has a history of risky sexual relations with multiple partners in the last 5 years and Provider-initiated HIV testing and counselling (PITC) obtained reactive results. Defined this patient with HIV diagnosis with Kaposi sarcoma.The patient is then given therapy antiretrovirals (ARV), chemotherapy and routine follow up.

Figure 1 - Macroscopic findings. A-B. Anodule on the right side of the nose pink, solitary, well demarcated, oval shape, size 1x 0.8 cm. Figure B shows erosion and brownish yellow scales on it. C-D nodule on the right side of the right digiti I pedis, solitary erythema nodule, well defined, round shape, 1 x 1 cm in diameter.



Fonte: Autores.

Figure 2 - Microscopic findings. E. The nodular tumor mass consists of a proliferation of neoplastic cells that spread diffusely in the dermis to the epidermis in a storiform pattern (40x, H&E stain). F. Blood vessels with promontory sign can be observed among tumor cells (100x, H&E stain). G. Cells with oval spindle morphology, eosinophilic cytoplasm, increased N/C ratio, irregular nuclear membrane, round oval nucleus, vesicular to hyperchromatic chromatin, incopicous to prominent nuclei, heavily pleomorphic. Mitoses are easy to find (black arrows).(400x, H&E stain).



Fonte: Autores.

4. Discussion

The pathogenesis of Kaposi sarcoma as an angioproliferative disease caused by a virus is multifactorial (Billings, 2011; Landman, 2018; Geraminejad et al, 2002). The disease is multifocal, where the course is slow at first manifesting only on the skin, until it becomes fulminant involving a large visceral area. The name Kaposi sarcoma was first introduced by Moritz Kaposi (1837–1902) when he discovered a case of multiple idiopathic hemangiosarcoma in elderly men at the University of Vienna in 1872 (Geraminejad et al, 2002). At that time Moritz Kaposi defined Kaposi sarcoma as a malignant neoplasm of the blood vessels or lymph vessels that appears with the appearance of vascular nodules in the skin or other organs (Ruocco et al, 2013).

The virus as the cause is thought to have appeared since the 1950 and then in the 1970, the role of the herpes virus was put forward by Giraldo and coresearching of patients in Africa with Kaposi sarcoma, they found herpes-type virus in five of eight tissue cultures (Wen & Damania,2010; Cheng, 2012). In 1994, Chang and colleagues identified the herpes virus HHV-8, detecting this virus in more than 90% of cases of Kaposi sarcoma, including those not associated with HIV. HHV-8 memhas a double-stranded DNA genome, and has distinctive morphological characteristics, namely the herpes virus with a diameter of between 100-150 nm, the particle is surrounded by a lipid envelope, and an electron-rich core[9]. HHV-8, found in saliva and semen, but can be spread through contact with saliva and kissing, and sexual activity, similar to other herpes viruses. Prevalence antibody HHV-8 increases with age (Grayson & Pantanowitz, 2008; Bergman et all, 2008) Manifestations can be in the form of chronic infections and a small proportion develop into cancer, the differences in clinical symptoms that appear are influenced by various cofactors, such as genetic, immunological and environmental factors. Rolecofactors can be attributed to their ability to interact with HHV-8, both influencing the immune system, to act as vasoactive agents (Wen & Damania,2010; Mancuso et all, 2008). HIV wasting syndromebeing one of the stages of HIV development in the patient's body becomes AIDS, where the sufferer will experience an emaciated body and no strength. The advanced stages are opportunistic infections (infections that have the opportunity to attack because the immune system has been undermined by HIV), such as lung infections, shortness of breath, severe and persistent headaches, or injuries to the genitals and anus (Whisman et al, 2019). In this case, physically the patient's body is athletic without other chronic disease complaints, so the clinician does not suspect a disease that arises due to an immunosuppression condition.

In 1989 until 1991, the prevalence of Kaposi's sarcoma in male cancer patients increased to 48.6% (incidence 30.1/100,000), becoming the most frequently reported cancer in men, while the prevalence in female cancer patients increased to 17.9% (incidence 11/100,000). People infected with HIV have a 100 to 300 times greater risk of developing Kaposi sarcoma and the prevalence of Kaposi sarcoma is much higher in post-transplant and AIDS patients, 500 times and 20,000 times, respectively. In this case it happened to a man with risky sexual behavior (Landman, 2018; Geraminejad et al, 2002 ;Whisman et al., 2019).

Table 1 - Conventional histopathological subtypes and the differential diagnosis of Kaposi sarcoma.

Histopathological subtypes	Differential diagnosis
stage patch	Early microvenular haemangiomas Interstitial (so called incomplete) granuloma annulare Mild inflammatory dermatoses
Plaque stage	Microvenular haemangiomas Tufted haemangiomas Hobnail haemangioma (Largetoid haemosiderotic haemangioma) Acroangiodermatitis (so called pseudo KS)
Well developed Nodular	Vascular lumps composed of spindle cells. Variant dermatofibroma Spindle cell sarcoma Spindle cell amelanotic melanoma Dermal fasciitis Bacillary syringomatosis

Table Sources from the WHO Book: Classification of Skin Tumors: IARC; 2018. h. 341-343.

The appearance of the skin lesions of the four subtypes is similar, divided into 3 stages: stage patch with findings in the form of macules or red or purple spots, Plaque stage in the form of thickened red, purple or brown plaques and Tumor stage in the form of nodule formation (Landman, 2018; Geraminejad et al, 2002). Microscopically, the patch stage is characterized by abnormal vascular or endothelial proliferation within the collagen dermis, particularly around the skin adnexa. Plaque stage with features of abnormal blood vessels or endothelial proliferation, increased cellulity with spindle cell proliferation. Tumor stage is a nodular lesion of Kaposi sarcoma which shows an even higher degree of cellularity, with spindle cells forming a storiform pattern or short fascicles that intersect each other randomly, often accompanied by inflammatory cells, which are dominated by plasma cells, mitosis, and squamous cells. atypical can also be found (Geraminejad et al, 2002; Cheng 2012). In this case, a nodular tumor mass was found consisting of proliferation of neoplastic cells that spread diffusely in the dermis to the epidermis to form a storiform pattern, partially scattered randomly. Blood vessels with vessel in vessel (promontory sign) can be observed among the tumor cells. These cells with oval spindle morphology, eosinophilic cytoplasm, increased N/C ratio, irregular nuclear membrane, round oval nucleus, vesicular chromatin to hyperchromatic, nuclei not visible to prominent, heavily pleomorphic. Mitoses are easy to find. Abnormal mitosis may be found. Part of the hyalinized tissue stroma is also visible. Erythrocyte extravasation and distribution of lymphocyte inflammatory cells can be observed scattered among the tumor cells.

It is known that the histopathologic variants of Kaposi's sarcoma are highly variable and should be differentiate to rule out differential diagnosis for each subtype. In this case, the clinical findings are suspicious of squamous cell carcinoma and can also be suspected as a benign lesion in the form of a poroma with a clinical well-defined period. Squamous cell carcinoma appears as a tumor mass that is partially ulcerated and occurs over a long period of time, but from the histopathological picture of squamous epithelial cell proliferation in the form of extensive cytoplasmic polygonal cells with or without keratin pearls around tumor cells (Whisman et al, 2019). Poroma is a benign tumor of the skin adnexa that usually originates from cells of the

outer layer of the acrosyringium and terminal eccrine ducts appearing as a single, slow-growing, asymptomatic, well-demarcated, smooth, red skin, slightly scaly papules or nodules. It commonly occurs on the palms and soles or sides of the feet. However, microscopically, a well-demarcated tumor mass of sebaceous differentiation with follicular differentiation and foci of apocrine-like features with anastomosing trabeculae pattern is obtained, appearing as precursor points of the epidermis and mostly located in the papillary and reticular upper dermis. The cells are small and uniform with scant cytoplasm and round to oval nuclei held together by inconspicuous intercellular bridges. Although clinically similar to Kaposi's sarcoma, it is microscopically distinguishable (Geraminejad et all, 2002; Cheng 2012).

Kaposi sarcoma is an interesting soft tissue tumor occurring in several distinct populations with a variety of presentations and courses. In its most well-known form, Kaposi sarcoma occurs in patients with immunosuppression, such as those with acquired immunodeficiency syndrome (AIDs) or those undergoing immunosuppression due to an organ transplant. Histologic variants of Kaposi sarcoma include: in situ Kaposi sarcoma, anaplastic Kaposi sarcoma, lymphangiectatic Kaposi sarcoma, bullous Kaposi sarcoma, ecchymotic Kaposi sarcoma, glomeruloid Kaposi sarcoma, and hyperkeratotic Kaposi sarcoma. Although the apparent histogenesis of some of these morphologic variants is known, the pathogenesis of others is uncertain. Hyperkeratotic Kaposi sarcoma, by way of example, frequently occurs as a result of Kaposi sarcoma-associated chronic lymph-edema of the lower extremities. Intravascular Kaposi sarcoma could either originate primarily as an intravascular proliferation, or alternatively develop as a consequence of intravascular extension of a lesion breaching the vessel wall.[16] The variant histopathology of Kaposi's sarcoma itself must be differentiated from similar or mimicking lesions so that immunorecative testing can be used. Kaposi's sarcoma shows immunoreactive reaction to LANA-1 in relation to HHV8, CD34, CD31 and Podoplanin (Wen & Damania, 2010; Cheng, 2012; Globocan, 2021). Immunoreactive testing was not performed in this case.

In administering therapy to Kaposi sarcoma patients, the tumor growth rate, clinical symptoms, immune system conditions, and HIV-related complications in the patient must be considered. Classic Kaposi sarcoma is the subtype that shows the best response to local therapy. Endemic Kaposi sarcoma requires systemic therapy with cytostatic agents. The prevalence of epidemic Kaposi sarcoma has decreased dramatically since the introduction of anti-retroviral (ARV) therapy. Electrochemotherapy (ECT) is an emerging treatment for skin lesions from a variety of tumor types. The combination of chemotherapy and electroporation increases drug absorption into tumor cells. Radiotherapy is effective and often the best local treatment for relief of pain, bleeding or edema. with a response rate of over 90% and a complete remission of over 70%. Systemic therapy with ARVs are indispensable in the treatment of all cases of epidemic Kaposi sarcoma, either single dose or in combination with systemic chemotherapy and local therapy. Systemic chemotherapy is usually reserved for patients who do not respond to ARV in this patient given systemic therapy with antiretrovirals, chemotherapy and routine follow-up (Bergman et all, 2008; Mancusor et al, 2008; Cheng, 2012). In these patients are given systemic therapy with ARVs, chemotherapy and routine follow-up.

5. Conclusion

Kaposi sarcoma is a rare cancer caused by infection with the human herpesvirus 8 (HHV8). These lesions are often found in immunosuppressed patients such as HIV sufferers characterized by vascular proliferation. Incidence in at-risk sex offenders and HIV-positive homosexuals are known to be more at risk of developing Kaposi sarcoma. Globocan data for 2020 reports that cases of Kaposi sarcoma rank 31 of all cancer cases in the world. The incidence ratio in males is higher. The low 5-year survival rate in Kaposi sarcoma patients with metastasized lesions resulting in a high mortality rate from this lesion.Through the incidental findings of Kaposi's sarcoma in patients who are not clinically suspected of having HIV, clinicopathological correlation is highly recommended.

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