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Case Report

Kaposi's sarcoma in a male with human immunodeficiency virus and condyloma acuminata: A case report

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Abstract Kaposi's sarcoma (KS) is an angioproliferative cancer originating from endothelial cells. Usually occurs in immunocompromised conditions such as human immunodeficiency virus (HIV). Condyloma acuminata (CA) are papules on the genitals caused by the human papillomavirus (HPV). This case report aims to describe the diagnosis of KS and CA in HIV patients. A 23-year-old man with HIV came with a red swollen face and purplish red bumps on his face and body, and dark brown lumps on his anus. Dermato-venereological examination revealed multiple well-defined erythematous papules and nodules on the face, lower extremities, trunk, and inguinal. There are multiple dark brown papules with a verrucous surface that is partially erosive. Immunohistochemistry revealed positive CD-31. Facial skin biopsy showed spindle cells whereas anal skin biopsy showed polypoid, hyperplasia, acanthosis, and koilocytosis dominant in the epidermis. The acetowhite test on the anus is positive. We diagnosed this patient with KS and CA. KSis an angioproliferative cancer that often occurs in immunocompromised patients such as HIV. The risk factor of KS is having a CD4+ count below 200 cells/mL and CD4+ count in this patient with HIV is 7 cells/mL, which led to the manifestation of SK. HIV patients with low CD4+ count are susceptible to KS and CA. Biopsy and immunohistochemistry of KS shows positive spindle cells and CD-31 whereas biopsy of CA shows polypoid, hyperplasia, acanthosis, and a dominant koilocytosis of the epidermis.

Keywords
Human immunodeficiency virus, condyloma acuminata, Kaposi's sarcoma.

Introduction

Kaposi's sarcoma (KS) is a malignant soft tissue mesenchymal tumor originating from the proliferation of vascular endothelial spindle cells that was first reported by Moritz Kaposi in 1872.[1,2] Incidence in Europe in 2017 was 180 per 100,000 people per year while in Asia Pacific 52 per 100,000 persons/ year.[2] Incidence in men is 2-3 times higher than in women and six times higher in male who has sex with male (MSM). This group also has a very high prevalence of HPV infection and is very susceptible to the spread of Human Immunodeficiency Virus (HIV) infection.[3] Until now there are no specific guidelines for the management of KS, the treatment for KS only aims to improve symptoms, prevent progression and improve psychological stress.[4,5] Condyloma acuminata (CA) is a disease caused by Human Papillomavirus (HPV) 6 and 11 in anogenital areas with clinical manifestations in the form of epidermal and dermal papules/nodules.[6,7] The diagnosis of CA can be established based on the history, physical examination and supporting

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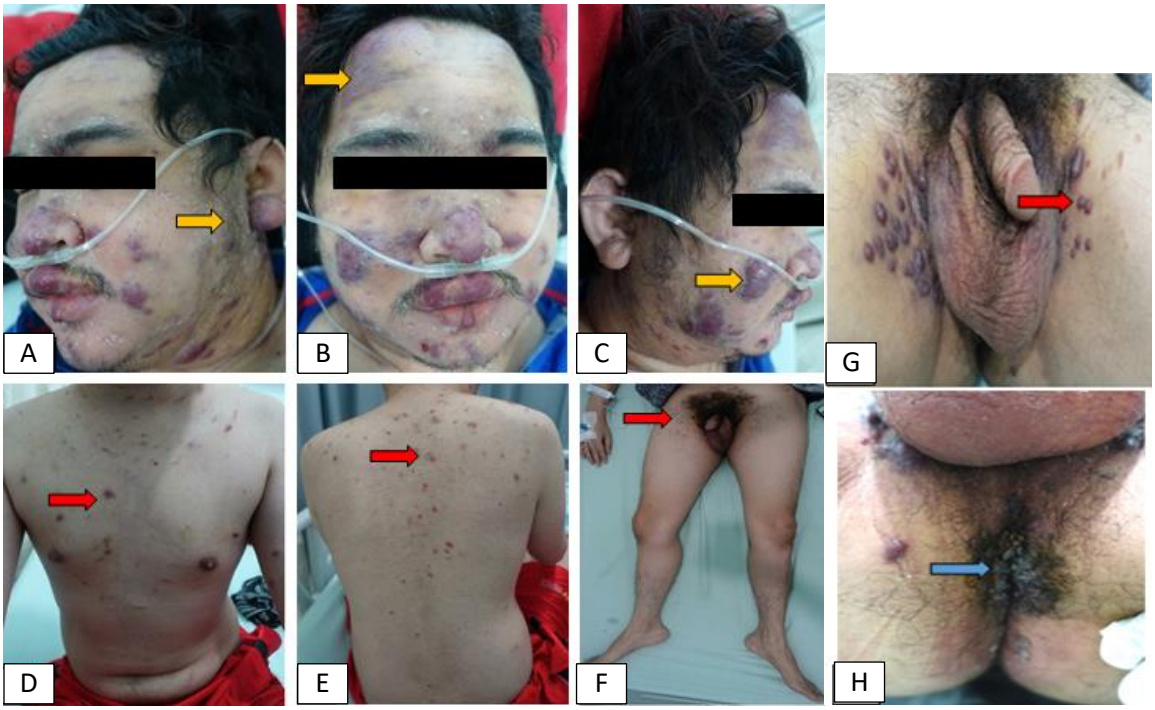

Figure 1 (A-C) In the facial region, multiple discrete, partially confluent patches, papules and erythematous nodules are seen with well-defined borders with angioedema (yellow arrows). (D-G) In the anterior and posterior trunk regions, the inguinal region shows patches, papules and multiple erythematous nodules with well-defined borders (red arrows). (H) In the perineal region, multiple papules are seen with some brownish verrucous surfaces with erosions (blue arrows).

examinations (acetowhite test, histopathology and PCR).[8] This case report aims to increase knowledge about the diagnosis and management of KS and CA in patients with HIV infection so as to reduce disease morbidity and mortality.

Case Report

A 23-year-old male patient was consulted by the Internal Medicine Department to the Dermatovenereology Department of Dr. Moewardi General Regional Hospital (RSDM) Surakarta with the main complaint of lumps appearing in several areas of the body. Based on autoanamnesis, the patient also complained of nausea and vomiting and pain in the epigastrium. In addition, the patient also complained of shortness of breath since 2 days. The patient was diagnosed 4 months ago as HI positive and was routinely checked in to the VCT polyclinic and received triple antiretroviral (ARV) drugs for adults which was then replaced with tenoflam and then again with neviral and duviral. History of anal fistula surgery (+) 6 months ago. Two months ago the patient starte developing multiple, asymptomatic, small purplish red lumps on the face, body and groin.

On physical examination, the general condition of the patient appeared to be moderately ill, with adequate nutritional status. Vital signs within normal limits, namely BP 110/70 mmHg, HR 84x/minute, RR 24x/minute, temperature 36.8^{o}C and pain scale 2. Dermatovenereological status in the facial region et superior extremity region et truncus anterior et posterior et inguinal showing papules and nodules multiple discrete erythema, partially confluent, well circumscribed with angioedema. In the perineal region, multiple discrete papules were seen with

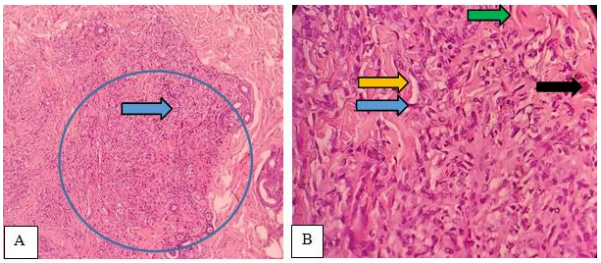

Figure 2 Histopathological appearance of the right upper arm with HE staining (A) In the dermis layer, spindle cells were seen (blue circle and blue arrow) (40x magnification). (B) Spindle cells (blue arrows) with blood vessels forming a slit-like vascular space (yellow arrows), relatively monomorphous cells with sufficient cytoplasm, nuclei with fine chromatin (green arrows), bleeding areas and hemosiderin (black arrows) are found. (100x magnification).

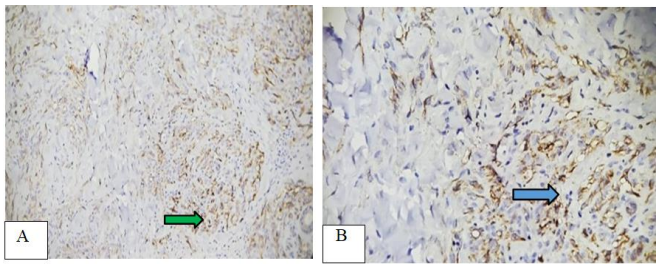

Figure 3 Immunohistochemistry (A) Positive CD-31 staining of some cells (green arrows) (40x magnification) (B) Immunohistochemistry of CD-31 in the dermis showing vascular clefts lined with brown endothelial cells (blue circles and arrows) (magnification 100x).

a verrucous surface and erosions in several parts. There was no enlarged lymph nodes and organ enlargement **(Figure 1)**. From the anamnesis and physical examination, a differential diagnosis of Kaposi's sarcoma, multiple pyogenic granulomas and angiosarcomas was made. Genital and perineal lesions were diagnosed as condyloma acuminata.

Blood laboratory results showed decreased hemoglobin levels by 9.5 g/dl (12.0–15.6 g/dl), erythrocytes 3.37 million/uL (4.10-10 million/uL) and albumin 2.8 g/dl (3.8–5.1 g/dl). Increase in SGOT 12 U/L (<4.5 U/L) and SGPT 18 U/L (<4.5 U/L). Anti-HCV and non-reactive HBsAg. Examination of CD4 levels on October 12, 2020 showed a decrease in absolute CD4 7 cells/uL (404–1,612 cells/uL), CD4 percentage 2.2% (33-58%), a decrease in absolute CD8 167 cells/uL (220-1129 cells/uL), CD8 percentage of 4.9% (13-39%) and a decrease in CD4-CD8 ratio of 0.04 (0.69-2.83) which indicates the possibility of complications and worsening of infection. The results of the Treponema Pallidum Hemagglutination Assay (TPHA) examination were non-reactive. The acetowhite test in this case was positive for a verrucous papule lesion that turned white. The results of histopathological examination of the skin tissue of the right arm, the dermis layer showed a focus of spindle cells with blood vessels forming a slit-like vascular space, relatively monomorphous cells with sufficient cytoplasm, a nucleus with fine chromatin, bleeding areas and hemosiderin **(Figure 2)**. The results of the immunohistochemical examination of the right upper arm lesion with CD31 staining showed a vascular cleft lined with brown endothelial cells suitable for the histopathological picture of KS **(Figure 3)**. Histopathological picture taken from the skin tissue of the perineal area in the epidermal layer showed epidermal hyperplasia composed of polypoid, acanthosis and dominant koilocytosis. In the dermis layer, plasma cells and eosinophils are visible. The histopathological appearance of the perineal area corresponds to that of condyloma acuminata.

A final diagnosis of KS in HIV with condyloma acuminate was made. The management of the Internal Medicine Department is injection of vitamin C 1 gram per 24 hours and injection of omeprazole 40 mg per 24 hours intravenously, azithromycin tablets 500 mg every 24 hours, paracetamol tablets 500 mg every 8 hours, zinc tablets 10 mg every 12 hours, as well as a plan for chemotherapy and antiretroviral therapy. The plan of skin management in this patient was the weekly application of 80% trichloroacetic acid (TCA) on verrucous papules in the perineal area

and gentamicin ointment twice a day on eroded lesions. On day 21 the patient died due to HIV.

Discussion

Kaposi's sarcoma is an angioproliferative cancer originating from endothelial cells that line lymph nodes or blood vessels, often occurring in immunocompromised patients such as HIV or organ transplant patients.[9] KS patients with HIV have an increased risk of morbidity and mortality. The incidence of KS worldwide is 1 in 100,000 in the general population, whereas in HIV-infected persons it is approximately 1 in 20 and 1 in 3 HIV-infected homosexual men who have not received ARVs.[9] Incidence is 2-3 times higher in men and six times higher in men who has sex with men (MSM). Incidence of HIV-associated KS occurs at age 20-54 years.[10] Pathogenesis of KS is related to HHV-8 infection, immunosuppression or changes in immune function associated with chronic infection and autoimmunity or malnutrition. Human herpesvirus 8 (HHV-8) or Kaposi's sarcoma herpesvirus (KSHV) is one of the most oncogenic viruses associated with KS etiology, especially in classic and endemic KS.[10] There are four variants of KS, namely classic KS, which occurs in men aged 50-70 years, epidemic KS, associated with HIV infection, iatrogenic KS, which occurs in patients undergoing immunosuppressive drug therapy, and endemic KS, which occurs in sub-Saharan Africa, which is associated with lymphadenopathy.[11] Our patient was a 23-year-old bisexual HIV positive suffering from epidemic form of KS.

HIV infection plays a major role in the pathogenesis of KS by causing severe immunosuppression and destroying CD4+ cells. The risk factor associated with KS is having a CD4+ count below 200 cells/mL.[3] The patient in this case was HIV positive with a decreased CD4+ (7 cells/mL), which led to the development of KS. Clinical manifestations of KS on skin lesions appear in the form of macules, plaques, papules, nodules and multiple tumors that are pink, reddish purple or black in color. The color does not go away with pressure (compression test) and lesions are not painful. The initial skin lesions are usually asymptomatic, pigmented, small macules or papules that vary in color from pale pink to bright purple. Lesions mainly appear on the skin and mucosal surfaces.[2] Lesions in KS can metastasize to visceral organs such as the lungs and gastrointestinal tract. Lung lesions produce dyspnea, dry cough and sometimes cough with blood with or without life-threatening fever. Gastrointestinal lesions are usually asymptomatic but may cause bleeding and obstruction, usually confirmed by endoscopy. Visceral lesions with KS are rare (only 15% of 469 patients have visceral lesions after AIDS-associated KS is diagnosed).[12] AIDS-associated Kaposi's sarcoma usually presents with oral lesions on the roof of the mouth and gums, often causing dysphagia and secondary infection.[2] In these patients skin lesions in the form of papules and multiple confluent erythematous nodules with well-defined borders on the face, body and lower limbs according to the KS.

There are two stages of HIV-associated KS, namely T0 which indicates the tumor is located in the skin and lymphatics with minimal involvement of the oral mucosa and T1 indicates KS with edema and ulceration, nodular oral KS or KS involving visceral organs. In this case the patient had papules, plaques and multiple purplish nodules on the face, chest, back, hands and groin area. This shows the appearance of KS with various stages (patches, plaques and tumors) on the face, back, upper extremities and thighs that occur simultaneously in one individual. The patient pattern is very similar to the clinical manifestations of KS in HIV

patients.[10] Shortness of breath could be due to spread of lesion to the lungs.

The differential diagnosis in this case was multiple pyogenic granuloma and angiosarcoma. Pyogenic granuloma (PG) is the most common vascular tumor, can arise spontaneously or after trauma, usually occurs in children and young adults, especially in pregnant women.[13,14] In this patient, skin abnormalities in the form of papules, erythematous nodules with a size of 5-10 mm, located in the facial region (lips and eyelids), chest, back, upper arms and groin can lead to multiple pyogenic granulomas. The compression test performed on the patient was palpable with a hard surface that did not bleed easily and there was no partial discoloration of the surface, based on histopathological examination with HE staining, there was no evidence of stalked globular tumor, so the diagnosis of multiple pyogenic granulomas in this patient could be ruled out. Another differential diagnosis in this patient is angiosarcoma (AS). Angiosarcoma is a rare and very aggressive malignant tumor originating from lymphatic or vascular endothelial cells, it can occur in any location of the body, where skin lesions are the most common (about 60% of cases).[15] The patient in this case presented with abdominal discomfort, nausea, vomiting and shortness of breath. Physical examination of the skin lesions revealed red nodules but did not bleed easily. Histopathological examination with HE showed spindle cells with blood vessels that formed slit-like vascular spaces, relatively monomorphic cells with sufficient cytoplasm and nuclei with fine chromatin. Histopathological examination of the nucleus with fine chromatin can rule out the diagnosis of AS, because the AS contains a nucleus with coarse chromatin.

The proliferation of spindle cells (cells with an elongated cytoplasm and nucleus) on histopathological examination is the hallmark of KS. Kaposi's sarcoma originates from lymphatic endothelial cells, spindle cell immunohistochemistry using antibodies against vascular endothelial markers such as CD-31 indicating the vascular nature of the lesion and lymphatic endothelial markers in spindle cells.[2] Immunohistochemistry containing KSHV DNA by nucleic acid amplification technique or polymerase chain reaction (PCR) is the gold standard for diagnosing KS, but PCR for KHSV DNA is currently only available in a few highly specialized clinical molecular pathology laboratories.[2] In our patient, a biopsy was taken from the right upper arm. Hematoxylin eosin (HE) histopathological biopsy results showed that in the dermis layer, spindle cells were found with blood vessels that formed slit-like vascular spaces, relatively monomorphic cells with sufficient cytoplasm, nuclei with fine chromatin and areas of bleeding and hemosiderin. We confirmed the cause of the tumor from endothelial cells by performing immunohistochemical examination of CD-31 staining for a definitive diagnosis of KS, which gave a positive result. Based on the anamnesis, clinical manifestations and histopathological examination, the patient was diagnosed with KS.

Condyloma acuminata is the most common sexually transmitted disease caused by HPV. The emergence of developing lesions on the skin and mucous membranes after infection with certain types of human papilloma virus (HPV), such as types 6 and 11. Factors that play a role in the recurrence of condyloma acuminata include age, predilection, medication history, HIV infection and perianal sexual behavior.[15]

The differential diagnosis in this case is CA and condyloma lata. Condyloma lata is a form of secondary syphilis. The lesions are white or gray papules on warm and moist areas of the body with a smoother surface and more rounded shape

than CA.[16] In this patient, the skin disorder was in the form of skin-colored papules and there was no history of syphilis. So that the diagnosis of condyloma lata can be ruled out.

The diagnosis of CA is established clinically by anamnesis, where the patient complains of more and more skin-colored nodules that are not painful, a history of sexual intercourse with more than 1 partner without protection and physical examination reveals multiple papules that are well-defined and shaped like a chicken's comb or can also form a "cauliflower" pattern. Examination by giving 3-5% acetic acid will result in a white discoloration of the lesion (acetowhite test).[15] Histopathological examination of CA showed that the epidermis appeared hyperplastic, polypoid, acanthosis and dominant koilocytosis.[17] Based on the history of this patient, complaints of lumps with brownish rough surface near the anus and the patient is bisexual with multiple partners and has a history of having unprotected sex. Physical examination revealed multiple verruca papules in the perianal region and a positive result on 5% acetic acid examination. On histopathological examination with HE staining, the epidermis layer was composed of polypoid, epidermal hyperplasia, acanthosis, dominant coikilocytosis and the dermis layer showed plasma cell powder and eosinophils. So this patient was diagnosed with CA.

Until now there has been no therapy that has successfully cured KS. Management of skin lesions in KS include local excision, liquid nitrogen, laser, topical alitretinoin gel and vincristine injection. Systemic therapy is given to KS with extensive skin lesions (>25 lesions), visceral organ lesions, extensive edema and rapid progression. The recommended regimens for systemic therapy of KS are liposomal anthracyclines and taxanes. The key to HIV-related KS therapy is optimal control of HIV infection with antiretroviral (ARV) therapy. The prognosis for KS patients is poor based on the AIDS Clinical Trial Group (ACTG) staging system with a mean survival rate of 15-24 months.[18] The cause of death for KS patients is not always the KS itself but other complications related to HIV-AIDS. The patient in this case had received treatment for ARV but was discontinued due to suspicion of drug allergy caused by ARV. Treatment for KS and CA has not been given because the patient died due to respiratory failure, possibly due to KS metastases to the lungs.

Conclusion

HIV patients with low CD4 cells are susceptible to KS and CA due to their immunocompromised condition. The diagnosis of KS is based on typical findings on biopsy results with HE staining, namely the presence of spindle cells with blood vessels that form slit-like vascular spaces, relatively monomorphic cells with sufficient cytoplasm and nuclei with fine chromatin, and positive CD-31 findings on histochemical examination. The diagnosis of CA was established from the results of a biopsy with HE staining, which showed polypoid, acanthosis and koilocytosis dominant in the epidermal layer. Histopathological and immune-histochemical biopsy results support the diagnosis of KS and CA. The key to HIV-related KS therapy is optimal control of HIV infection with antiretroviral (ARV) therapy. The patient received gentamicin ointment therapy for erosional lesions, but had not had time to receive therapy for KS and CA because of respiratory failure and died. The prognosis for these patients according to the AIDS Clinical Trial Group (ACTG) staging system is poor.

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