Diagnosis of Kaposi’s sarcoma

Alvian Arifin Saiboo\(^1\), Dwi Murtiastutik\(^2\), Etty Hary Kusumastuti\(^3\), Putri Halla Shavira\(^1\)

Abstract

Kaposi’s sarcoma has a picture reminiscent of several skin conditions, so further testing is needed to show the diagnosis of Kaposi’s sarcoma. Lymphatic endothelium cells infected with KSHV or human herpesvirus 8 form the basis of Kaposi’s sarcoma (KS), a multicentric tumor (HHV-8). These macules and plaques might be purple, reddish-blue or dark brown-black in color. KS is distinguished by this look. Inflamed, ulcerated nodular lesions are common. They are neither unpleasant or uncomfortable, and the overlying skin or underlying tissues seldom die as a result of them. The gold standard examination in establishing the diagnosis of KS is histopathology. Several techniques that can be used for histopathological tissue retrieval are punch biopsy, shave biopsy, excision biopsy and incision biopsy. Immunohistochemical examination can also be performed to rule out the differential diagnosis. Immunohistochemical examination that we can do is with LANA-1, CD 34, CD 31, D2-40. Diagnosis of Kaposi’s sarcoma is difficult to diagnose only from a clinical picture, so similar diagnoses, i.e. histopathological and immunohistochemical examinations, are required.

Keywords: Kaposi’s sarcoma, immunohistochemical, human herpesvirus-8, biopsy.


Introduction

As the name suggests, Moritz Kaposi was the first to identify Kaposi’s sarcoma in 1872. Within two years of Moritz’s discovery of multifocal pigmented sarcomas in young men, all of them perished from the cancer. Moritz found KS, which he referred to as classic KS or sporadic KS. When infected with KSHV or HHV-8, lymphatic endothelial cells get infected with KS, which is a multicenter tumor of lymphatic endothelial cells. Classic or sporadic form, first described by Kaposi, is now divided into four main clinical subtypes: epidemic in HIV-infected individuals, subtype in patients receiving immunosuppressive medication, and iatrogenic form in transplant recipients. The endemic form may be seen in sub-Saharan Africa. This literature review aims to assist clinicians in establishing the diagnosis of Kaposi’s sarcoma.\(^1,2\)

Kaposi’s Sarcoma

Hungarian dermatologist Moritz Kaposi identified KS as an extremely uncommon kind of angioproliferative malignancy that affects blood vessels and lymphatic systems. In addition to the skin, oral mucosa, nose, throat, and visceral lymph nodes, KS may spread to other parts of the body, including as the intestines.\(^3\) In 1996, viruses associated with the examined KS samples were discovered. Kaposi’s sarcoma-associated herpes virus (KSHV), now known as human herpes virus-8 (HHV-8), has been identified as a cause of KS-associated infection in populations in Eastern Europe, Africa and the United States. KSHV causes infection cell endothelium. which play a role in the pathogenesis of KS. Virus-encoded G proteins induce VEGF production, promote endothelial growth, and cytokines produced by inflammatory cells recruited at the site of infection also create a local proliferative environment.\(^2\)

Immunohistochemical studies have shown endothelial properties in KS, but it remains controversial whether this endothelial phenotype is vascular, lymphatic, or perhaps a combination of both. In addition, most of the cells that make up the substance of KS plaques or nodules are spindle cells that are morphologically different from normal endothelial cells and express the pan-endothelial marker CD31. These spindle cells also express markers of vascular differentiation (CD34) and lymphatic differentiation (VEGFR-366.86, podoplanin87, and LYVE-188).\(^4\)

To confirm a diagnosis of KS, histopathological samples are collected from the patient’s body. Even while histological confirmation of a KS diagnosis is still the gold standard, it might be difficult to make an accurate diagnosis if the pathologist isn’t familiar with the whole range of
KS-related histopathology. Conventional hematoxylin and eosin (H&E) staining is generally the sole method for determining the pathological characteristics of KS that are present in all instances.\textsuperscript{5,6}

**Clinical Picture**
Purple, reddish-blue, or dark brown-black patches, plaques, and nodules occur on the skin as a sign of KS. Toxins and blood may readily leak from nodular lesions. Typically, neither the top skin nor the lower tissues are necrotic in these lesions, nor are they unpleasant or irritating (Figure 1). Sizes range from microscopic to several centimeters, and lesions may persist for months or years or develop quickly in a matter of weeks before spreading. Involvement in practically all visceral organs has been seen, including glands, lymph, liver, pancreas, heart, testis, bone marrow, bones, and skeletal muscle. There are three primary areas of non-skin disease: the mouth (oral, glossal, and palatine mucosa), the digestive system, and the respiratory system.\textsuperscript{6}

The use of a skin biopsy in the diagnosis of skin disorders is highly recommended. Punch, shave, excision, and incision are the most frequent methods of biopsy. As with any tool, there are benefits and drawbacks to each approach. Shock excision may be used for minor inflammatory lesions (less than 4 mm). Select the broadest, most discolored, or thickest portion of the lesion when dealing with big inflammatory lesions. Biopsies of annular plaques should be performed near the lesion’s upper margin. To avoid nonspecific observations in ulcers or ulcerated lesions, include some normal tissue next to the affected area as well. Incisional biopsy of the ulcer junction and surrounding normal tissue is the best procedure.\textsuperscript{8,9}

**Punch Biopsy**
Pathologists favor punch biopsy for inflammatory skin illnesses because it enables them to evaluate all skin layers from the epidermis down to subcuticular adipose tissue. Typically, a 4 mm diameter punch is sufficient for histological evaluation in most punch biopsies (Figure 2). In order to provide an accurate diagnosis, smaller punch biopsies should only be used in aesthetically sensitive regions, such as the upper lip.\textsuperscript{8,9}

When the region is numb, the skin is stretched in a perpendicular direction to the resting surface. Using this technique, a circular flaw in the skin is transformed into an oval. The thumb and middle finger stabilize and provide pressure to the punch while the index finger supports and rotates the punch. It is pressed into the skin in a circular manner until the point where it feels like there is no resistance. This is because the punch enters the semisolid subcutaneous tissue at a lower level than the skin. It’s up to you whether you want to stitch the wound or let it heal naturally. Good vascularization, such as on the face, genitals or mucous membranes, speeds healing and reduces scarring.\textsuperscript{8,9}

To avoid extreme pain and suffering while conducting a biopsy on places where the skin is thin and close to bone, such as the forehead, shins, the back of the nose, or the scalp, avoid touching the periosteum.

---

**Figure 1.** Extremities of patients with classical KS. Dorsum pedis (a: papules and plaques), lateral pedis (b: papules), knee (c: papules), elbow (d: papules and nodules), dorsum manus (papules, plaques), and distal pedis (f: papules, plaques). plaster, nodule).

**Figure 2.** Punch biopsy.\textsuperscript{9}
Excision and Incision Biopsy

For suspected melanoma, deep subcutaneous or dermal tumors, and deep inflammatory processes, excisional biopsy is indicated. It takes more time and expertise to do than other biopsy methods, but the dermatopathologist is able to collect more tissue and conduct research if necessary. A little portion of skin is removed using a knife, and the incision is stitched up, much like a regular excision. The border from normal skin should be 2 millimeters wide for pigmented lesions. In order to have an accurate histological diagnosis, the incision should go all the way to the subcutaneous fat.8,9

Deeper inflammation (such as panniculitis), ulcers, porokeratosis, cutaneous lymphoma, and mild vascular vasculitis are all good candidates for an incisional biopsy. This kind of biopsy may also be used in cases when shave biopsy leaves a scar on a location that is aesthetically sensitive, or if a punch biopsy does not offer enough tissue for a complete diagnosis. There are some similarities between this approach and excisional biopsy, however the sample must encompass a 1-millimeter patch of neighboring normal skin at one end of the ellipse rather than a whole lesion. In order to capture adipose tissue samples, the ellipse must be smaller than the excision, but must reach deep into the subcutaneous tissue.8,9

Shaving biopsy

Individual lesions that are prominent or where pathology is restricted to the epidermis should be sampled using a shave biopsy. Basal cell and squamous carcinomas of the skin may both be successfully biopsied with a shaver (SCC). Diagnosis and aesthetics go hand in hand when it comes to the optimal depth for a shave biopsy. Diagnosis will be impossible if the tissue is too thin. Slow healing and scarring might occur if the wound is too deep. As a general rule, it is sufficient to get a sample of the superficial dermis. Adjustable grip blades make shaving biopsies easier to execute. A scalpel knife or size 15 scissors may also be used in the absence of a scalpel blade. Begin by cutting at a 45-degree angle to the lesion's edge, then continue cutting at right angles. To eliminate a lesion, flatten the blade to a 0 degree angle and continue swiping it from side to side. Pressure, 20 percent aluminum chloride in alcohol ("Driclor"), aluminum sulphate in aqueous solution ("Stingose"), or electrocautery may all be used to establish hemostasis. Electrocautery following aluminum chloride in alcohol is combustible, so exercise caution.8,9

There are no stitches needed to close the wound. A cotton-tipped applicator may be used to apply the aluminum chloride solution many times with the same pressure. As a consequence of the curettage technique, a sample that may be used for histological analysis is left fragmented. The lesion should be sampled with a normal shave biopsy prior to curettage if curettage is performed to treat the lesion.8,9

Histological Overview

The histological appearance of KS does not differ significantly between different clinical subtypes, but varies depending on the stage of the injury. Classical SC (sometimes in other variants) skin lesions go through three stages: spots, plaques, and nodules.8,10

a. The patch stage is characterized by superficial skin growth of small angular vessels lined with invisible endothelial cells representing lymphatic vessels. These smooth but "rare" vessels tend to separate the collagen bundles and are accompanied by a small number of corner cells that represent sparse infiltration of lymphocytes and plasma cells and endothelial markings. Pink, red, or purple spots on the skin of the macula are usually located in the distal part of the lower extremities. Microscopic examination reveals dilated, uneven, and twisted blood vessels lined with endothelial cells and diffuse chronic inflammatory cells, sometimes containing hemosiderin. These lesions are difficult to distinguish from granular tissue (Figure 3).8,10

b. In the more advanced plaque stage, the blood vessels can reach deep into the skin and cover the subcutaneous area. Spinal endothelial cell populations also form between small, branched vessels. Later, the lesion spreads proximally and becomes an enlarged, enlarged, purple plaque composed of skin vessels, surrounded by lined, fleshy cells (Figure 4). Other common symptoms include extravasation of erythrocytes, hemosiderin-containing macrophages, and other mononuclear cells. The plaque phase is most common in HIV-positive patients (75% of HIV-positive patients).8,11

c. In the nodal phase, skin collagen is replaced by endothelial cells at these angles. Pleomorphism and many mitotic patterns are absent. The spindle cells form intersecting vesicles that are separated by a special space in the form of a slit containing erythrocytes. The resulting sit-like vascular space is a very characteristic feature of KS.
After all, node damage is a sure sign of cancer. These lesions are composed of tubular cells and usually multiply in the skin and subcutaneous tissue, with a slit-shaped cavity arranged between them. Spinal cord cells represent endothelial cells and smooth muscle cells and usually contain round and pink spheres in the cytoplasm that are degenerate red blood cells within the phagolysosome. Bleeding and accumulation of hemosiderin are more pronounced, mitosis is more common. This nodal stage is often accompanied by involvement of lymph nodes and visceral organs, especially in the African and AIDS-related versions. 

The nodal phase is the most common phase of KS. 

Immunohistochemical Analysis

Immunohistochemistry (IHK) is a laboratory test used to detect specific antigens (i.e., proteins) in tissues and cells based on antigen-antibody recognition; Attempts to use specificity to bind antibodies to antigens at the light microscopic level. The IHK method is often used to diagnose various diseases. Dermatopathology plays an important role in diagnosing various skin diseases. However, in many cases it is not possible to distinguish between overlapping clinical and histological features. 

Immunohistochemistry is a commonly used tool in the diagnosis of soft tissue cancer. IHK is a valuable resource if accurate histological examination and differential diagnosis are ineffective and differential diagnosis remains. Once a differential diagnosis has been made, IHK, cyto genetic or molecular diagnostic tests (especially in situ hybridization) are used for the final diagnosis. There are several records that can be checked in KS, such as:

- **LANA-1**
  It was initially found by Moore and his colleagues as a nuclear antigen in effusion lymphoma cells as a delay-related nuclear antigen (LANA-1) or latent nuclear antigen (LNA, LNA-1). Patients with KS have antibodies that react with this protein. Using Western blot analysis, it was shown to be the most immunocompromised of the KSHV proteins, with a molecular weight of 222–234 kDa and a less rapid transition than expected. An crucial function is assumed to be played by LANA in regulating viral and cellular gene expression. KSHV antibodies may be detected using this antigen as an antigen in blood testing. 

- **CD 34**
  It’s encoded by the CD34 gene in humans, mice, rats, and many other species. CD34 is a transmembrane phosphoglycoprotein protein Cell surface antigens (CD34) are identified using a set of procedures. Hematopoietic stem cell CD34 was discovered by Civin et al. in Tindle and serves as a glycoprotein on the cell surface and as a factor in cell adhesion. Hematopoietic stem cells may also connect directly to extracellular matrix cells or stromal cells by this mechanism. The selection and enrichment of hematopoietic stem cells is an essential part of clinical bone marrow transplantation. CD34 expression is seen in almost all hematopoietic cells because of this long-standing clinical and historical association. In other words, it may be found in a wide range of cell types. It is a single-line sialomucine protein family member that has features that are both hematopoietic and vascular connective tissue related. 

- **CD 31**
  There is a high prevalence of CD31 in a variety of cell types such as endothelial, platelet-derived growth factor (PDGF), macrophage, and Kupffer cell types as well as T and B cells, NK cells, megakaryocytes, and osteoclasts (to name a few). Hemangioendothelioma, epithelioid sarcoma, various vascular malignancies, histiocytic cancer, and plasmacytoma are all known to express CD31. Cancer and Kaposi’s sarcoma are very uncommon forms of sarcoma. 

- **D2-40**
  D2-40 is a new monoclonal antibody against 40,000 O-bound sialoglycoproteins that reacts with epitopes resistant to lymphatic endothelial attachment. In normal tissue, D2-40 indicates lymphatic endothelium but does not stain blood vessels, including arteries and capillaries, as determined by the PAL-E response to vascular endothelial markers. Because D2-40 identifies three of the seven angiosarcomas, this subsection is at least partially differentiated along the lymphatic endothelial line and is classified as lymphangiosarcoma. 

Clinical Diagnosis

KS usually presents as purple, red-blue, brown-black spots, plaques, and / or nodules and may present with symptoms such as bleeding, ulcers, verrucous, and hyperkeratosis. Lymphedema may precede macular degeneration. Dermoscopy helps to raise the suspicion of KS by showing the classic colors of vascular cancer (purple, yellow-green, blue and red), especially if the nodules are tight. Other dermoscopic features such as polychromatic color, spots on the collar, white streaks, white lumps, and serpentine veins may confirm the diagnosis of KS, especially in nodular lesions. The lower extremities are areas of the skin that prefer the classic KS. Skin lesions can last for months or even years without progress or growth. Injuries to internal organs such as skin and mucous membranes, gastrointestinal tract, bones and liver may also occur. Classical CS is slower than epidemic KS and is more advanced, widespread, and life-threatening after organ transplantation. 

Histological Diagnosis

Histology is the gold standard for the diagnosis of SC. Spotted KS is characterized by increased vascularity that is curved, thin-walled, and covered with thin skin endothelial cells. Inflammatory lymphocytes are rare and skin plasma cells infiltrate. The KS plaque phase is characterized by a more or less dilated, concave vascular space covered with normal or slightly abnormal endothelial cells. In addition, there may be oval cells or angular cells between the collagen fibers of the skin. The nodular phase of KS is characterized by abnormally rotating cells that form large agglomerates and form fuscicular vessels throughout the skin. Erythrocytes and lateral cells are visible between erythrocytes and side cells, and inflammatory cell infiltrates are composed of plasma cells, lymphocytes, and...
dendritic cells. Decreased KS shows only fibrous tissue with hemosiderin pigment accumulation and no tuberculosis cells. In advanced KS, such as anaplastic KS, abnormal spindles may be present that mimic other sarcomas, in which case immunohistochemical analysis may be used. diagnostic auxiliary diagnostics.

CONCLUSION

KS is a multicellular neoplasm of the lymph node infected with the herpes virus (KSHV) or human herpesvirus-8 (HHV-8) associated with Kaposi’s sarcoma. Histology is the gold standard for diagnosing KS and immunohistology may be needed in the future to help make the diagnosis.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

There is no conflict of interest.

AUTHOR’S CONTRIBUTION

Author AAS conceived the study, data collection, drafted, and revised the manuscript. Author DM and EHK contributed in revised the manuscript. Author PHS contributed in data collection.

REFERENCES