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Tissue Biomarkers in Kaposi Sarcoma

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Abstract

Kaposi sarcoma is a vascular neoplasm arising from blood and lymphatic endothelial cells and is etiologically associated with Kaposi sarcoma–associated herpesvirus (KSHV/HHV-8). It is common in HIV-infected people, although it can also arise in non-HIV-infected patients. Histopathological examination remains the diagnostic gold standard; however, the morphological features of Kaposi sarcoma often overlap with those of other vascular tumors, creating diagnostic challenges. Tissue biomarkers play a crucial role in diagnosing Kaposi sarcoma. It can reveal the endothelial origin, the association with HHV-8 and the malignant origin of Kaposi sarcoma. This review summarizes several tissue biomarkers that were expressed in Kaposi sarcoma that can serve as diagnostic markers and molecular markers for Kaposi sarcoma.

LANA-1 (Latency-Associated Nuclear Antigen-1) is a protein that is characteristically expressed in Kaposi sarcoma. It was expressed in HHV-8 infected spindle cells of Kaposi sarcoma tissue. CD31 and CD34 biomarkers can confirm the vascular nature of spindle cells. D2-40 or podoplanin confirmed the lymphatic endothelial differentiation and supports the lymphatic phenotype of Kaposi sarcoma. Finally, Ki-67 biomarker is expressed in proliferating cells that can support the malignant behavior of Kaposi sarcoma. These biomarkers can confirm the diagnosis and support the molecular nature of Kaposi sarcoma.

Keywords: Cancer; HIV; Kaposi sarcoma; HHV-8; LANA-1

1. Introduction

Kaposi sarcoma is a cancer that arises from the cells that line blood and lymph vessels, generating malignant lesions or tumours on the skin and other organs such as the mouth, lymph nodes, gastrointestinal tract, and lungs (1,2). These lesions usually manifest as painless, purple, red, or brown spots or lumps, which may be either flat or elevated (3). Kaposi sarcoma results from an infection with human herpesvirus 8 (HHV-8) and is more prevalent among individuals with compromised immune systems, like those affected by HIV/AIDS (4,5). It has several forms including classic, AIDS-associated, endemic (African), iatrogenic (due to immunosuppression like organ transplantation), and non-epidemic types (6,7). Treatments vary from surgical removal and radiation therapy to antiretroviral therapy in AIDS-associated cases (7).

The microscopic features of Kaposi sarcoma have characteristic elements but can mimic other lesions, making diagnosis sometimes challenging. Kaposi sarcoma typically shows spindle cell proliferation with irregular, slit-like vascular spaces containing red blood cells (8). These spindle cells are elongated tumor cells that form a complex vascular network.

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Kaposi sarcoma can be microscopically confused with other vascular lesions such as arteriovenous malformations, pyogenic granuloma, microvenular hemangioma, and tufted hemangioma due to overlapping features (9–12). Careful attention to the spindle cell pattern, vascular channel formation, and HHV-8 immunostaining helps in distinguishing Kaposi sarcoma from these mimics.

2. Review content

Tissue biomarkers are critical for diagnosing Kaposi sarcoma. These are several tissue biomarkers that expressed in Kaposi sarcoma tissue:

2.1. LANA-1 (Latency-Associated Nuclear Antigen-1)

Latency-Associated Nuclear Antigen-1 (LANA-1) is expressed by Kaposi sarcoma-associated herpesvirus (KSHV/HHV-8). It is presented during the latent phase of infection and localizes in the host cell nucleus. This protein important in maintaining the continuity of the viral genome through the tethering mechanism of Kaposi sarcoma-associated herpesvirus DNA episomes to the host cell chromosome, thus allowing stable replication of viral episomes during cell division without entering the lytic phase (13–15). Furthermore, LANA-1 is recognized for its interactions with different cellular proteins, including transcription factors and cell cycle regulators, which aid in the modulation of viral and host gene expression that promotes the survival and growth of infected cells (16). LANA-1's function in blocking apoptosis and evading immune responses has been extensively documented, as this protein can adjust cellular signaling pathways to avert programmed cell death and diminish the host immune system's ability to detect infected cells (16,17). The reliable and distinct nuclear expression of LANA-1 serves as a significant diagnostic marker, particularly through immunohistochemical analysis in Kaposi sarcoma, primary effusion lymphoma, and KSHV-associated Castleman's disease (18,19). Consequently, LANA-1 is essential for sustaining latent infection and KSHV pathogenesis, and it also holds considerable diagnostic importance in both clinical applications and research related to KSHV-associated diseases.

2.2. CD31

CD31, also known as platelet endothelial cell adhesion molecule-1 (PECAM-1), is a glycoprotein that spans the membrane, predominantly found on vascular endothelial cells, and is essential for angiogenesis, cell adhesion, and the migration of leukocytes. In Kaposi sarcoma (KS), a vascular neoplasm associated with Kaposi sarcoma-associated herpesvirus (KSHV/HHV-8) infection, CD31 expression is significantly increased and reflects the endothelial origin of spindle cells, the main histopathological feature of KS (20,21). Immunohistochemical examination shows strong and diffuse CD31 staining in KS tumor cells, making this biomarker widely used to confirm vascular differentiation and help distinguish KS from other non-vascular spindle neoplasms (22,23). In addition to its diagnostic value, CD31 expression is also associated with the pathological angiogenesis process underlying KS progression, where activation of endothelial signaling pathways contributes to cell proliferation, new blood vessel formation, and increased vascular permeability (24). Therefore, CD31 not only serves as a sensitive immunohistochemical marker for the identification of Kaposi sarcoma tissues, but also reflects a key biological mechanism in the pathogenesis and progression of KSHV-related vascular tumors.

2.3. CD34

CD34 is a glycoprotein that spans the membrane, found on hematopoietic progenitor cells and vascular endothelial cells, and is involved in cell adhesion and the formation of blood vessels. In Kaposi sarcoma (KS), a vascular tumor closely linked to Kaposi sarcoma-associated herpesvirus (KSHV/HHV-8) infection, CD34 is prominently and diffusely expressed immunohistochemically in spindle cells and atypical vascular structures typical of KS lesions (25,26). This consistent CD34 expression reflects endothelial differentiation of the tumor cells and supports the concept that KS originates from endothelial cells or endothelial precursors transformed by KSHV infection (27). Diagnostically, CD34 staining is very useful in confirming the vascular nature of the lesion and helps distinguish KS from non-vascular spindle tumors and from reactive fibroblastic lesions, although its interpretation still needs to be combined with other markers such as CD31 and LANA-1 to increase diagnostic specificity (28) . In addition, high CD34 expression is also associated with the pathological angiogenesis process that plays a role in the progression of SK, where endothelial cell proliferation and new blood vessel formation are the main mechanisms of lesion development (26,29) . Thus, CD34 is an important tissue biomarker in the histopathological evaluation of Kaposi sarcoma, both as a marker of vascular differentiation and as a reflection of the angiogenic activity of KSHV-associated tumors.

2.4. D2-40

D2-40 is a monoclonal antibody that recognizes podoplanin, a transmembrane glycoprotein expressed primarily on lymphatic endothelial cells and plays a role in lymphangiogenesis. In Kaposi sarcoma (KS), a vascular neoplasm closely associated with Kaposi sarcoma-associated herpesvirus (KSHV/HHV-8) infection, D2-40 expression indicates positive immunohistochemical staining in tumor spindle cells and lymphatic-like vascular structures, reflecting lymphatic endothelial differentiation of neoplastic cells (30). These findings support the hypothesis that KS has a lymphatic phenotype or originates from endothelial cells with lymphatic characteristics that undergo transformation due to KSHV infection. (31) Diagnostically, D2-40 has important value in identifying the lymphatic component in KS lesions and helps differentiate them from other vascular tumors that predominantly show blood endothelial differentiation, although its use needs to be combined with other endothelial markers such as CD31 and CD34 and the KSHV-specific marker, namely LANA-1, to improve diagnostic accuracy (32,33). In addition, podoplanin expression detected by D2-40 is also associated with the process of lymphangiogenesis and local invasion, which contribute to the progression and clinical characteristics of SK lesions (34,35). Thus, D2-40 is a relevant tissue biomarker in the histopathological evaluation of Kaposi sarcoma, both for diagnostic purposes and to understand the biological aspects and differentiation of tumor cells related to KSHV infection.

2.5. Ki-67

Ki-67 is a nuclear protein expressed during the active phases of the cell cycle (G1, S, G2, and M) and is widely used as a marker of cell proliferation in various neoplasms. In Kaposi sarcoma (KS), a vascular tumor associated with Kaposi sarcoma-associated herpesvirus (KSHV/HHV-8) infection, the Ki-67 proliferation index is generally higher than in benign vascular lesions, such as hemangioma or reactive vascular proliferations, and therefore can be used as a supporting tool in histopathological evaluation (36,37). Increased Ki-67 expression reflects increased spindle cell proliferative activity in KS and correlates with the biological aggressiveness and progression of the lesion (38). However, Ki-67 expression is nonspecific as it can also be found in various other malignant vascular neoplasms as well as in certain reactive conditions with high proliferative activity (39). Therefore, Ki-67 cannot be used as a single diagnostic marker to establish the diagnosis of SK, but must be interpreted together with histopathological features and other immunohistochemical panels, especially endothelial markers such as CD31 and CD34 and the KSHV-specific marker, namely LANA-1 (37,40). Thus, Ki-67 has a role as an additional parameter that helps differentiate SK from benign vascular tumors and assess the level of tumor cell proliferation, but does not have diagnostic specificity when used alone.

3. Tissue Biomarkers that can serves as diagnostic markers in Kaposi Sarcoma

Immunohistochemical approaches to Kaposi sarcoma (KS) require a combination of several biomarkers to achieve an accurate diagnosis, given the complex and heterogeneous nature of the tumor. LANA-1 is the most specific marker because it indicates latent infection by Kaposi sarcoma-associated herpesvirus (KSHV/HHV-8) and serves as the primary etiopathogenetic basis for KS (41–44). However, LANA-1 does not provide information on vascular differentiation or tumor proliferative activity, requiring combination with other markers. CD31 and CD34 are used to confirm the endothelial origin of KS spindle cells, with CD31 reflecting blood endothelial differentiation and CD34 marking endothelial cells and vascular precursors involved in pathological angiogenesis (45–47). Meanwhile, D2-40, a podoplanin marker, provides additional information on lymphatic endothelial differentiation, supporting the concept that KS has a lymphatic or mixed blood-lymphatic phenotype due to KSHV-induced cellular reprogramming (48,49). In this context, Ki-67 serves as a proliferation marker that provides an overview of tumor biological activity. A higher Ki-67 index in KS compared to benign vascular lesions reflects increased spindle cell proliferation and correlates with lesion progression (38,45). However, because Ki-67 is nonspecific and can also be elevated in other vascular neoplasms and reactive conditions, its use is not diagnostic in itself. (38,50). Therefore, interpretation of Ki-67 should be done in an integrative manner along with LANA-1 as a specific marker of KSHV etiologic, CD31 and CD34 as markers of vascular differentiation, and D2-40 as a marker of lymphatic differentiation. This combination of biomarker panels allows a more comprehensive assessment of the etiology, cell differentiation, and proliferative activity of KS, thereby improving diagnostic accuracy and understanding of tumor biology compared to the use of a single marker (41,50,51).

4. Conclusion

Although histopathology remains the gold standard for diagnosing Kaposi sarcoma, tissue biomarkers are essential in identifying Kaposi sarcoma (KS). Immunohistochemical staining for the latent nuclear antigen (LANA-1) of human herpesvirus 8 (HHV-8) serves as the key biomarker for diagnosing KS, as it identifies the virus responsible for the tumor. Other endothelial markers used to support diagnosis include CD31, CD34, and D2-40, which help differentiate KS from

other vascular or spindle cell tumors. Additionally, markers such as Ki-67 can provide information on cell proliferation but are less specific for diagnosis. PCR-based methods detecting HHV-8 DNA in tissue can also aid diagnosis, especially in small or ambiguous biopsy samples. Thus, the combination of histopathology and specific biomarkers like LANA-1 significantly improves accurate identification of Kaposi sarcoma.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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