DOI: https://doi.org/10.54393/pjhs.v5i07.1864

PAKISTAN JOURNAL OF HEALTH SCIENCES
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 7 (July 2024)

Original Article

Determining the Stage of Kaposi Sarcoma Through Histopathological Analysis: Identifying The Most Effective Finding

Muhammad Anique[1*], Humera Akhlaq[2], Sarah Azhar[3], Amna Jahan[4], Jehangir Kazi[5] and Qandeel Abbas Somroo[6]

[1]Department of Pathology, Bhitai Dental and Medical College, Mirpurkhas, Pakistan
[2]Department of Oral Pathology, Sindh Institute of Oral Health Sciences, Karachi, Pakistan
[3]Department of Pathology, Baqai Medical University, Karachi, Pakistan
[4]Department of Pathology, Institute of Medical Sciences, Lahore, Pakistan
[5]Department of Pathology, Sulaiman Roshan Medical College, Tando Adam, Pakistan
[6]Department of Pathology, Indus Medical College, Tando Muhammad Khan, Pakistan

ARTICLE INFO

Keywords:
Kaposi Sarcoma, Spindle Cell Proliferation, Histopathological Analysis, Inflammatory Infiltrate

How to Cite:
Anique, M., Akhlaq, H., Azhar, S., Jahan, A., Kazi, J., & Soomro, Q. A. (2024). Determining the Stage of Kaposi Sarcoma Through Histopathological Analysis: Identifying The Most Effective Finding: Effective Histopathological Findings for Staging Kaposi Sarcoma. Pakistan Journal of Health Sciences, 5(07). https://doi.org/10.54393/pjhs.v5i07.1864

***Corresponding Author:**
Muhammad Anique
Department of Pathology, Bhitai Dental and Medical College, Mirpurkhas, Pakistan
aniquemuhammad@icloud.com

Received Date: 11th June, 2024
Acceptance Date: 28th July, 2024
Published Date: 31st July, 2024

ABSTRACT

Kaposi Sarcoma (KS) is a complex disease presenting as vascular tumors affecting the skin, mucous membranes, lymph nodes, and internal organs. It shows variable clinical presentations and forms. **Objective:** To identify the most effective histopathological indicators for staging Kaposi Sarcoma. **Methods:** This cross-sectional study was conducted at Bithai Medical and Dental Center, Mirpur Khas, from December 2022 to December 2023. A total of 119 biopsy specimens were analyzed for spindle cell density, arrangement, atypia, vascular space formation (size and morphology), inflammatory cells (lymphocytes, plasma cells), hemosiderin extent and distribution, and mitotic activity. Data analysis was performed using SPSS version 24.0. **Results:** The study included 38 males (31.93%) and 81 females (68.07%). The nodular stage was most prevalent (72 cases, 60.5%), followed by the patchy stage (29 cases, 24.37%) and plaque stage (18 cases, 15.12%). Significant histopathological findings included spindle cell proliferation in 62 cases (52.11%), vascular space formation in 39 cases (32.77%), inflammatory infiltrate in 31 cases (26.05%), hemosiderin deposits in 43 cases (36.13%), and mitotic activity in 35 cases (29.41%). **Conclusions:** Spindle cell proliferation and vascular space formation are the most reliable indicators for staging KS. Inflammatory infiltrate composition, hemosiderin deposits, and mitotic activity showed less consistency across different specimens.

INTRODUCTION

Kaposi Sarcoma (KS) is an angio-proliferative disorder associated with human herpesvirus 8 (HHV-8). Initially described by Moritz Kaposi in 1872, it was once considered an uncommon malignancy primarily affecting elderly men of Mediterranean or Eastern European descent [1]. However, the epidemiological landscape of KS has dramatically changed, especially with the advent of the HIV/AIDS pandemic. Among people with HIV (PWH), KS rates are elevated 521-fold compared to the general population [2]. From 2000 to 2015, KS incidence declined from 109 per 100,000 person-years to 47 per 100,000 person-years, with an annual percentage change of –6%. Rates decreased across all demographic and HIV transmission groups, with 1,904 PWH (0.20%) diagnosed with KS by the end of 2015. In the general population, the incidence of classic KS is approximately 1 case per 10 million inhabitants per year. The prevalence of Kaposi sarcoma herpesvirus is higher among Black individuals, people living with HIV, and those with a history of syphilis [3]. KS presents in four main epidemiological forms. Classic KS typically occurs in older men of Mediterranean, Eastern European, or Middle Eastern descent, progressing

DOI: https://doi.org/10.54393/pjhs.v5i07.1864

slowly and primarily affecting the lower extremities [4]. Endemic KS is found in sub-Saharan Africa, affecting children and adults independent of HIV infection and can be more aggressive than the classic form. Iatrogenic KS is associated with immunosuppressive therapy, particularly in organ transplant recipients, with potential regression upon reducing immunosuppression [5]. AIDS-related KS is highly aggressive and common in individuals with HIV infection, being one of the AIDS-defining illnesses, though its incidence has decreased with widespread antiretroviral therapy (ART) [6].

HHV-8 infection plays a crucial role in KS pathogenesis. Hemangioendothelioma cells infected by HHV-8 proliferate due to various viral oncogenes such as the viral G-protein coupled receptor (vGPCR) and latency-associated nuclear antigen (LANA) [7]. These genes contribute to cell survival and division, while HHV-8 infection increases the production of pro-inflammatory cytokines like interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), leading to angiogenesis and tumor growth. The virus's ability to evade immune monitoring facilitates chronic infections and cancer growth in immunosuppressed individuals. KS manifests in different forms and stages, with presentations ranging from purple patches, plaques, and nodules to more severe symptoms affecting the oral cavity, gastrointestinal tract, and internal organs, causing significant morbidity and necessitating systemic treatment [8]. Diagnosis of KS primarily relies on histopathological biopsy samples, supported by clinical findings and imaging studies. Characteristic histopathological findings include spindle cell proliferation, slit-like vascular spaces, inflammatory infiltrates, and hemosiderin deposits. Immunohistochemical staining for HHV-8 latent nuclear antigen-1 (LNA-1) confirms the virus's presence [9]. Imaging studies such as CT or PET scans assess the extent and visceral involvement. In AIDS-related KS, HIV tests and CD4+ T cell counts provide insight into immune compromise. Treatment varies by stage, involvement, and patient status, ranging from surgical excision and radiation therapy for localized lesions to systemic treatments like liposomal anthracyclines and antiretroviral therapy for more extensive disease. Immunotherapy agents like interferon-alpha have been used, particularly for classic KS [10]. Despite advances in understanding KS histopathology, gaps remain, notably the lack of universally accepted criteria for histopathological staging [11]. Most studies rely on qualitative descriptions of histopathological features, and quantitative methods for assessing spindle cell density, vascular space formation, and mitotic activity are underutilized [12]. Such approaches could offer more objective and reproducible criteria for staging KS [13]. Moreover, limited research correlates histopathological findings with clinical outcomes, such as therapy response and survival rates.

The primary objective of this study was to identify the most effective histopathological findings for accurately determining the stage of Kaposi Sarcoma (KS). By systematically analyzing the histopathological features associated with the patch, plaque, and nodular stages of KS, this study aims to characterize key histopathological features and evaluate diagnostic accuracy. This research seeks to identify the most indicative and consistent markers for staging KS, thereby providing a robust basis for clinical diagnosis and treatment planning.

METHODS

This cross-sectional study was conducted at Bithai Medical and Dental Center, Mirpur Khas, from December 2022 to December 2023, after receiving approval from the Ethics Review Committee, Bithai Medical and Dental Center, Mirpur Khas (Reference Number: BDMC/R&D/ERC/2022-01). Patient demographics, clinical history, and preoperative diagnostic results were documented along with other pertinent clinical data. Specific inclusion and exclusion criteria were designed. Sample size was calculated through open EPI software. Biopsy samples from patients diagnosed with Kaposi Sarcoma, confirmed through histopathology, were included in this study. Inadequate or poor-quality biopsy samples and samples from patients with concurrent malignancies or conditions that might confound histopathological analysis were excluded. Informed consent was obtained from all patients/participants. Patient registration numbers, dates, and unique identifying numbers were appropriately labeled on each specimen container. Hematoxylin and eosin (H&E) staining was used to assess general tissue morphology, while immunohistochemical (IHC) staining for HHV-8 latent nuclear antigen-1 (LNA-1) confirmed the presence of HHV-8 infection. A comprehensive macroscopic analysis of the biopsy samples was performed, noting dimensions, weight, color, and any obvious anomalies. The specimen's orientation and specific areas of interest identified during physical inspection were documented and sampled. The fixed tissue was processed through clearing, paraffin embedding, and dehydration. A microtome was used to cut thin sections, typically 4-5 micrometers in size, which were then mounted on glass slides. Hematoxylin and eosin (H and E) staining was carried out routinely for light microscopic examination at different magnifications. The biopsy tissue's cellularity, architecture, and cytological characteristics were assessed by a resident histopathologic and two consultant histopathologists. Each specimen was thoroughly examined for the density, arrangement, and atypia of spindle cells, the vascular space formation by assessing the presence, size, and morphology of vascular spaces. The type and density of

DOI: https://doi.org/10.54393/pjhs.v5i07.1864

inflammatory cells (lymphocytes, plasma cells, etc.), extent and distribution of hemosiderin, and mitotic activity were also documented to assess the staging and identification of the most effective findings. Data analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 24. For quantitative variables, the calculations included mean and standard deviation; for qualitative variables, frequencies and percentages were calculated. A p-value of less than or equal to 0.05 was considered significant.

RESULTS

The study involved a total of 119 patients distributed across various age groups. In the youngest cohort, ages 11-20, there was 1 patient (0.84%), who was female. The 21-30 age group had 23 patients (19.32%), with a male-to-female ratio of 8 to 15. The largest group was the 31-40 age bracket, encompassing 43 patients (36.13%), comprising 13 males and 30 females. In the 41-50 age range, there were 26 patients (21.85%), with 8 males and 18 females. The 51-60 group included 19 patients (15.97%), split into 6 males and 13 females. Lastly, the 61-70 age group had 7 patients (5.89%), with 3 males and 4 females. Overall, the patient population consisted of 38 males (31.93%) and 81 females (68.07%), illustrating a higher prevalence of the condition in females across all age groups (Table 1).

Table 1: Age and Gender Distribution of Kaposi Sarcoma in The Study Sample

Age Groups (Years)	Number of Patients	Males	Females
11-20	01 (0.84%)	00	01
21-30	23 (19.32%)	08	15
31-40	43(36.13%)	13	30
41-50	26(21.85%)	08	18
51-60	19 (15.97%)	06	13
61-70	07 (5.89%)	03	04
Total	119	38 (31.93%)	81 (68.07%)

The study analyzed 119 cases of Kaposi Sarcoma, distributed across different pathological stages and genders. The nodular stage was the most prevalent, accounting for 72 cases (60.5%). Among these, 22 were males and 50 were females. The patchy stage was observed in 29 cases (24.37%), with a gender distribution of 9 males and 20 females. The plaque stage comprised the remaining 18 cases (15.12%), including 7 males and 11 females. This data highlights that females are more frequently affected across all stages of Kaposi Sarcoma, with the nodular stage being the most common form observed in the patient cohort. Total cases were 119 in which males were 38 and females were 81 (Table 2).

Table 2: Stages of Kaposi Sarcoma

Variables	Total Cases N (%)	Male (n)	Female (n)
Pathological Staging			
Nodular stage	72 (60.5%)	22	50
Patchy stage	29 (24.37%)	9	20
Plaque stage	18 (15.12%)	7	11

The histopathological analysis of 119 Kaposi Sarcoma cases revealed significant findings in various parameters. Spindle cell proliferation was observed in 62 cases (52.11%), with a p-value of 0.04, indicating statistical significance. Vascular space formation was present in 39 cases (32.77%), with a p-value of 0.02. Inflammatory infiltrate was found in 31 cases (26.05%), also with a p-value of 0.02. Hemosiderin deposits were identified in 43 cases (36.13%), showing a highly significant p-value of less than 0.01. Lastly, mitotic activity was noted in 35 cases (29.41%), with a p-value of 0.04. These findings underscore the importance of these histopathological features in the assessment and staging of Kaposi Sarcoma, with each parameter contributing significantly to the diagnosis (Table 3).

Table 3: Histopathological Findings of Kaposi Sarcoma

Histopathological Findings	Results N (%)	P-Value
Spindle Cell Proliferation	62 (52.11%)	0.04
Vascular space formation	39 (32.77%)	0.02
Inflammatory Infiltrate	31 (26.05%)	0.02
Hemosiderin Deposits	43 (36.13%)	<0.01
Mitotic Activity	35 (29.41%)	0.04

In figure 1, the histopathological features of Kaposi Sarcoma are depicted as follows: A) Perivascular infiltrate primarily consisting of plasma cells, B) Spindled cells with slit-like vascular channels containing hemosiderin, C) Vascular spaces lined by lesional cells, and D) Spindled cells.

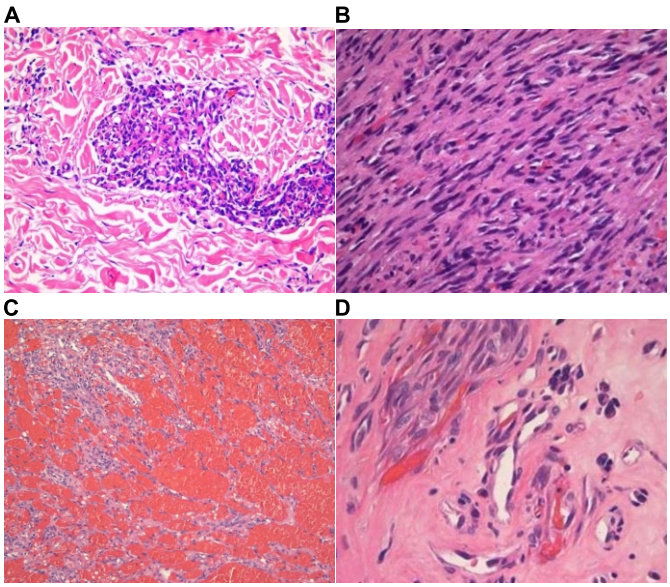

Figure 1: A: Perivascular Infiltrate Comprised Mainly Of Plasma Cells, **B:** Spindled Cells, With Slit-Like Vascular Channels Containing Hemosiderin, **C:** Vascular Spaces Lined By Lesional Cells, **D:** Spindled Cells

DOI: https://doi.org/10.54393/pjhs.v5i07.1864

DISCUSSION

Kaposi Sarcoma (KS) is a multifaceted disease primarily associated with Human Herpesvirus 8 (HHV-8), also known as Kaposi Sarcoma-associated herpesvirus (KSHV). It manifests as vascular tumors affecting the skin, mucous membranes, lymph nodes, and internal organs. KS presents in various forms, including classic, endemic, iatrogenic, and AIDS-related variants [14]. This study has shown that the most common stage of KS observed is the nodular stage, found in 60.5% of cases, followed by the patch and plaque stages, found in 24.3% and 15.12% of cases, respectively. These findings align with previous research by Gervas R et al., who reported the nodular stage in 74.5% of cases, followed by patchy (19.4%) and plaque (6.1%) stages, albeit in a different sequence [15]. The histopathological analysis provided crucial insights into diagnosing and classifying KS. Spindle cell proliferation was observed in 62 cases (52.11%), with a statistically significant p-value of 0.04. Spindle cells are a hallmark of KS, representing the transformed endothelial cells that proliferate in response to HHV-8 infection. The presence of spindle cells is essential for diagnosing KS, as these cells form the bulk of the tumor mass in advanced stages. Vascular space formation was noted in 39 cases (32.77%), with a p-value of 0.03. These spaces, formed by endothelial cells, appear as slit-like structures in plaque and nodular stages of KS [4]. Inflammatory infiltrates were observed in 31 cases (26.05%), with a p-value of 0.02. These infiltrates, composed of lymphocytes, plasma cells, and macrophages, play a role in the progression of KS lesions, especially in the early stages [16]. Hemosiderin deposits were identified in 43 cases (36.13%), indicative of chronic bleeding and erythrocyte extravasation, frequently coinciding with extensive vascular proliferation and hemorrhage in the plaque and nodular phases. Mitotic activity was observed in 35 cases (29.41%), with a p-value of 0.04. Higher mitotic rates suggest increased proliferation, characteristic of more advanced and aggressive disease stages [17]. These findings have significant implications for clinical practice and research. Establishing a unified histological staging system for KS could reduce diagnostic variability and ensure uniformity across medical settings [18]. Identifying critical histological markers of disease progression allows for better prognostication and tailored interventions based on disease severity [19]. These results can enhance the education and training of pathologists, improving their ability to identify and stage KS accurately. Incorporating these findings into medical school curricula and continuing medical education programs can enhance diagnostic accuracy and consistency. Additionally, the study's insights can inform health policies, particularly in regions with high KS prevalence, such as areas heavily affected by HIV/AIDS. By understanding the most indicative histopathological features, healthcare providers can implement more effective management strategies for KS [20]. The cross-sectional nature of the study does not capture the dynamic changes during KS progression. Longitudinal studies tracking histopathological features over time would provide a more comprehensive understanding of disease evolution.

CONCLUSIONS

The histopathological examination revealed that spindle cell proliferation and vascular space formation are the most consistent and reliable indicators for staging KS. These features demonstrate progressive changes from the patch stage to the nodular stage, reflecting the increasing aggressiveness and complexity of the disease. Additionally, inflammatory infiltrate composition, hemosiderin deposits, and mitotic activity were found to provide supplementary information for KS staging, albeit with less consistency.

Authors Contribution

Conceptualization: MA
Methodology: MA, QAS
Formal analysis: MA, JK
Writing, review and editing: MA, HA, SA, AJ, JK, QAS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Roy P, Parisapogu A, Agrawal H. Pneumonia or Kaposi Sarcoma: Beneath the Dyspnea with Non-compliance of HIV. Cureus. 2022 Oct; 14(10). doi: 10.7759/cureus.30152.

[2] Peprah S, Engels EA, Horner MJ, Monterosso A, Hall HI, Johnson AS *et al.* Kaposi sarcoma incidence, burden, and prevalence in United States people with HIV, 2000-2015. Cancer Epidemiology, Biomarkers & Prevention. 2021 Sep; 30(9): 1627-33. doi: 10.1158/1055-9965.EPI-21-0008.

[3] Vestergaard SV, Birn H, Jensen SK, Sørensen HT, Nitsch D, Christiansen CF. Twenty-four-Year Trends in Incidence and Mortality of Nephrotic Syndrome: A Population-Based Cohort Study. Epidemiology. 2023 May; 34(3): 411-20. doi: 10.1097/EDE.0000000000001576.

[4] Esser S, Schöfer H, Hoffmann C, Claßen J, Kreuter A, Leiter U *et al.* S1 Guidelines for the Kaposi Sarcoma. JDDG: Journal der Deutschen Dermatologischen

DOI: https://doi.org/10.54393/pjhs.v5i07.1864

Gesellschaft. 2022 Jun; 20(6): 892-904. doi: 10.1111/ddg.14788.

[5] Ohmoto A and Fuji S. Clinical features and treatment strategies for post-transplant and iatrogenic immunodeficiency-associated lymphoproliferative disorders. Blood Reviews. 2021 Sep; 49: 100807. doi: 10.1016/j.blre.2021.100807.

[6] Kivai JM, Guantai AN, Mwanda WO, Maitho TE. Pattern of distribution of AIDS-related Kaposi's sarcoma lesions in HIV patients in a referral hospital in Kenya. African Journal of Pharmacology and Therapeutics. 2020 Jan; 9(1).

[7] Uppal T, Sarkar R, Dhelaria R, Verma SC. Role of pattern recognition receptors in KSHV infection. Cancers. 2018 Mar; 10(3): 85. doi: 10.3390/cancers10030085.

[8] Srkalovic G, Nijim S, Srkalovic MB, Fajgenbaum D. Increase in Vascular Endothelial Growth Factor (VEGF) Expression and the Pathogenesis of iMCD-TAFRO. Biomedicines. 2024 Jun; 12(6): 1328. doi: 10.3390/biomedicines12061328.

[9] Maciolek KA, Abel EJ, Jarrard DF, Downs TM. Kaposi's sarcoma of the Penis and Scrotum. Rare Genitourinary Tumors. 2016 Jun: 323-60. doi: 10.1007/978-3-319-30046-7_22.

[10] Le Hingrat Q, Sereti I, Landay AL, Pandrea I, Apetrei C. The hitchhiker guide to CD4+ T-cell depletion in lentiviral infection. a critical review of the dynamics of the CD4+ T cells in SIV and HIV infection. Frontiers in Immunology. 2021 Jul; 12: 695674. doi: 10.3389/fimmu.2021.695674.

[11] Unger M and Kather JN. A systematic analysis of deep learning in genomics and histopathology for precision oncology. BioMed Central Medical Genomics. 2024 Feb; 17(1): 48. doi: 10.1186/s12920-024-01796-9.

[12] Silini AR, Di Pietro R, Lang-Olip I, Alviano F, Banerjee A, Basile M *et al.* Perinatal derivatives: where do we stand? A roadmap of the human placenta and consensus for tissue and cell nomenclature. Frontiers in Bioengineering and Biotechnology. 2020 Dec; 8: 610544. doi: 10.3389/fbioe.2020.610544.

[13] Igrec J and Fuchsjäger MH. Imaging of bone sarcomas and soft-tissue sarcomas. InRöFo-Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren 2021 Oct; 193(10): 1171-1182. doi: 10.1055/a-1401-0215.

[14] Lopes AD, Marinho PD, Medeiros LD, de Paula VS. Human gammaherpesvirus 8 oncogenes associated with Kaposi's sarcoma. International Journal of Molecular Sciences. 2022 Jun; 23(13): 7203. doi: 10.3390/ijms23137203.

[15] Gervas R and Mgaya E. Histopathological patterns and topographical distribution of Kaposi Sarcoma at Muhimbili National Hospital, Tanzania. African Health Sciences. 2021 Dec; 21(4): 1733-8. doi: 10.4314/ahs.v21i4.29.

[16] Motlhale M, Sitas F, Bradshaw D, Chen WC, Singini MG, de Villiers CB *et al*. Epidemiology of Kaposi's sarcoma in sub-Saharan Africa. Cancer Epidemiology. 2022 Jun; 78: 102167. doi: 10.1016/j.canep.2022.102167.

[17] Jary A, Veyri M, Gothland A, Leducq V, Calvez V, Marcelin AG. Kaposi's sarcoma-associated herpesvirus, the etiological agent of all epidemiological forms of Kaposi's sarcoma. Cancers. 2021 Dec; 13(24): 6208. doi: 10.3390/cancers13246208.

[18] Ethel C, Blossom D, Krown SE, Martin J, Bower M, Whitby D. Kaposi sarcoma (Primer). Nature Reviews: Disease Primers. 2019; 5(1). doi: 10.1038/s41572-019-0060-9.

[19] Lamb CA, Saifuddin A, Powell N, Rieder F. The future of precision medicine to predict outcomes and control tissue remodeling in inflammatory bowel disease. Gastroenterology. 2022 Apr; 162(5): 1525-42. doi: 10.1053/j.gastro.2021.09.077.

[20] Ibrahim Khalil A, Franceschi S, de Martel C, Bray F, Clifford GM. Burden of Kaposi sarcoma according to HIV status: A systematic review and global analysis. International Journal of Cancer. 2022 Jun; 150(12): 1948-57. doi: 10.1002/ijc.33951.