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Kaposi sarcoma herpesvirus (KSHV) inflammatory cytokine syndrome (KICS): a case study

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Abstract

Background Kaposi sarcoma herpesvirus-inflammatory cytokine syndrome (KICS) is a rare, life-threatening condition associated with Kaposi sarcoma and systemic immune dysregulation induced by Human Herpesvirus 8 (HHV-8). With a mortality rate approaching 60%[1] (Goncalves, Ziegelbauer, Uldrick, Yarchoan in Curr Opin HIV AIDS 12(1):47–56, 2017), KICS poses significant diagnostic and therapeutic challenges. This report examines a case of KICS in a patient with well-controlled HIV, emphasising the clinical complexities, treatment strategies, and the need for heightened awareness.

Case presentation A 59-year-old British male with a controlled HIV infection on Bictegravir/Emtricitabine/Tenofovir alafenamide presented with fever, malaise, lymphadenopathy, splenomegaly, and a purplish plantar plaque. Laboratory findings included anaemia, thrombocytopenia, hypoalbuminemia, hyponatremia, elevated inflammatory markers, and a high HHV-8 level. Diagnosis of HHV-8 positive lymph nodes and Kaposi sarcoma on the plantar aspect was confirmed. The patient was treated with Foscarnet, steroid, Rituximab, Tocilizumab, intravenous immunoglobulin (IVIG), and Paclitaxel, reducing viral load and improving cell count. This case highlights the complexities of managing Kaposi sarcoma within the realm of immune complex syndrome.

Conclusions Our case report underscores the critical need for heightened awareness and recognition of KICS, given its rarity and unique clinical characteristics. By elucidating the complex interrelationships between Kaposi sarcoma, inflammatory cytokines, and immune dysregulation, we aim to contribute to the existing knowledge base and facilitate improved diagnosis, management, and therapeutic interventions for this challenging syndrome. Further research is warranted to explore novel treatment modalities and unravel the underlying mechanisms driving KICS.

Keywords Kaposi sarcoma herpesvirus (KSHV), Human herpesvirus 8 (HHV-8), Kaposi sarcoma herpesvirus-inflammatory cytokine syndrome (KICS), Human immunodeficiency virus (HIV)

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Introduction

Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), is a double-stranded DNA virus belonging to the Herpesviridae family. Genome sequence analysis showed that the virus was unique and a member of the subfamily Gammaherpesvirinae. It is the etiological agent behind Kaposi sarcoma (KS), a multicentric vascular tumour that predominantly affects immunocompromised individuals, such as those with human immunodeficiency virus (HIV) infection. While KS is the most recognised clinical manifestation of HHV-8 infection, there are several other associated conditions, including multicentric Castleman disease (MCD), primary effusion lymphoma (PEL), and KSHV-inflammatory cytokine syndrome (KICS).

KICS is a complex condition characterised by the sustained elevation of proinflammatory cytokines, such as interleukin-6 (IL-6), IL-10, tumour necrosis factor-alpha (TNF-α), and interferon-alpha (IFN-α). This syndrome manifests with systemic symptoms like fever, weight loss, and cytopenia, often posing diagnostic challenges due to overlapping features with other conditions such as immune reconstitution inflammatory syndrome (IRIS) [2], TAROF syndrome [3], parvovirus B19 infection, disseminated lymphoma, and septic shock [4]. The precise pathogenesis of KICS remains incompletely understood, although it is thought to involve aberrant immune responses to HHV-8 infection, resulting in excessive production of inflammatory cytokines, particularly IL-6. The dysregulated release of these mediators can lead to diverse clinical presentations, ranging from constitutional symptoms to severe complications like multiorgan failure [5, 6].

KS comprises five distinct variants, each characterised by unique clinical courses and affected populations [7]. Epidemic or acquired immunodeficiency syndrome (AIDS)-related KS is associated with HIV infection and remains a critical AIDS-defining condition. Classic KS predominantly affects elderly men of Eastern European or Mediterranean descent, presenting as indolent lesions. Endemic KS is observed in African countries, impacting younger adults and children. Iatrogenic KS occurs in immunosuppressed individuals, such as organ transplant recipients, reflecting the role of immune dysregulation in its pathogenesis. Most recently, a novel variant termed nonepidemic KS has been identified, with a predilection for HIV-negative men who have sex with men (MSM) [8]. These distinctions highlight the diverse manifestations of KS and underscore the importance of tailored approaches to diagnosis and management.

Given the few reported cases and limited awareness among healthcare providers, KICS remains a diagnostic and therapeutic challenge. Currently, there is no standardised management for KICS, but treatment typically involves immunosuppressive therapy to modulate the heightened immune response alongside antiretroviral therapy for HIV-positive patients. Prompt recognition and treatment of this syndrome are crucial in preventing disease progression and enhancing patient outcomes.

In this report, we present a case of KICS in a patient with HIV infection, highlighting the importance of considering this syndrome in the differential diagnosis of patients with unexplained inflammatory manifestations, particularly in the setting of HHV-8 infection. A better understanding of the pathophysiology and management of KICS is essential for optimising patient care and outcomes in this unique clinical entity.

Case presentation

In January 2024, a 59-year-old British male businessman presented with a two-week history of fever and malaise following a recent trip to Rio de Janeiro, Brazil. He reported no outdoor activities that could have exposed him to animals or insects. Upon admission to Queen Mary Hospital, he exhibited no symptoms affecting the respiratory, neurological, or urinary systems.

The patient was diagnosed with HIV in March 2009, presenting a CD4 count of 585 cells/uL, and a viral load of 2,200 copies/mL. He has consistently taken Bictegravir/Emtricitabine/Tenofovir alafenamide since September 2021. A former smoker, the patient does not engage in regular alcohol or drug use and has not utilised over-the-counter or traditional Chinese medications. Physical examination identified a vaguely palpable left axillary lymph node and a left groin lymph node, splenomegaly extending 6 cm below the left costal margin, and a painless purplish plaque on the plantar aspect of the right foot, which the patient reported noticing since April 2023 (Fig. 1). The oral mucosal surface and conjunctiva were uninvolved. Onychomycosis was observed on bilateral toes.

The initial comprehensive evaluation, as detailed in Table 1, revealed a range of haematological abnormalities, including anaemia, thrombocytopenia, hypoalbuminemia, and hyponatremia, consistent with systemic inflammation. Elevated levels of inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin, were prominently observed. A peripheral blood smear analysis displayed characteristic findings of a leucoerythroblastic blood picture, hypochromic microcytic red cells with anisopoikilocytosis, and sporadic atypical lymphocytes without any evidence of platelet clumps or blasts. The patient's HIV RNA level was undetectable (< 20 copies/ml), and the CD4 count registered at 191 cells/μL (CD4%: 16.1% (Reference interval: 23.1–46.1%) upon admission (Fig. 2). A meticulous microbiological assessment, documented in Table 2, was performed. Notably, the HHV-8 real-time PCR detected

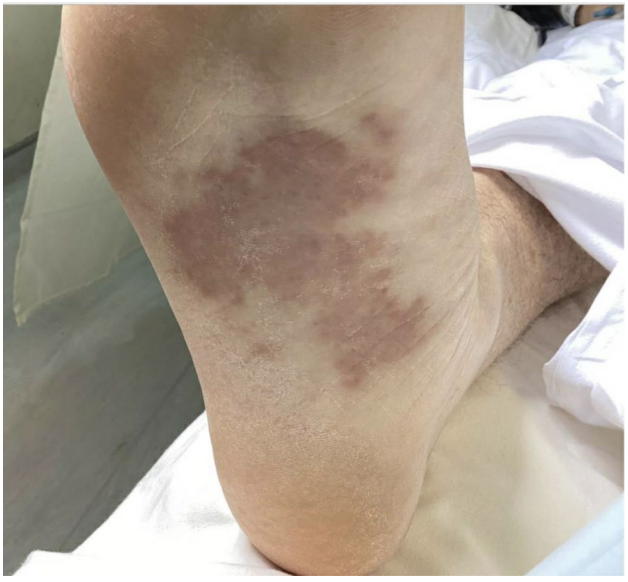

Fig. 1 Right plantar rash of the patient

Table 1 Laboratory Data

Investigations	Result (reference range)
Haemoglobin	4.2 g/dL (13.3–17.1)
White blood cells	6.38×10^9/L (3.89–9.93)
Platelet	59×10^9/L (167–396)
Sodium	129 mmol/L (135–145)
Potassium	4.5 mmol/L (3.5–5.5)
Creatinine	130 µmol/L (67–109)
eGFR (CKD-EPI)	51 (> 90)
Albumin	28 g/L (39–50)
Globulin	40 g/L (24–37)
Total bilirubin	12 umol/L (4–23)
Alkaline Phosphatase	47 U/L (42–110)
Alanine Aminotransferase	6 U/L (8–58)
Aspartate Aminotransferase	10 U/L (15–38)
CRP	16.96 mg/dL (< 0.5)
ESR	> 140 mm/h (< 7)
Ferritin	2562 pmol/L (67–899)
Lactate Dehydrogenase (LDH)	360 U/L (118–221)
Fasting triglyceride	2.0 mmol/L (< 1.7)
Haptoglobin	1.92 g/L (0.30–2.00)
Fibrinogen	5.79 g/L (1.71–3.38)
Autoimmune markers including ANA, Anti-dsDNA, ANCA and Anti-ENA	Atypical ANCA positive

2.91×10^5 copies/mL. The cytokine profile demonstrated significantly elevated IL-10 and IL-18, suggesting a severe underlying inflammatory process (Fig. 9). Radiographic imaging with chest X-ray and abdominal X-ray yielded unremarkable results. Positron emission tomography-computed tomography (PET-CT) imaging revealed diffuse mild hypermetabolic lymphadenopathy with SUV ranges from 1.9 to 2.8 in the neck, thorax, abdomen, pelvis, and groins, accompanied by splenomegaly, raising concerns for potential lymphoma (Figs. 3 and 4). However, a trucut biopsy of the left groin lymph node with SUV 2.4 unveiled a lymphoproliferative lesion comprising plasma cells and small lymphocytes, lacking definitive features of lymphoma, MCD or Kaposi sarcoma. Immunostaining identified scattered HHV-8 positive cell aggregates. The bone marrow biopsy displayed trilineage hyperplasia, plasmacytosis, histiocytosis, and iron block without evidence of underlying leukaemia, lymphoma or hemophagocytic lymphohistiocytosis (HLH). Concurrently, the trephine biopsy indicated reactive marrow changes reflective of the inflammatory milieu. A skin biopsy of the right plantar lesion confirmed Kaposi sarcoma. The dermis exhibited focal infiltration by numerous irregulars and ecstatic vascular channels, some containing entrapped native blood vessels. These channels were lined by cells with mildly enlarged, hyperchromatic, and hobnail nuclei. Immunohistochemistry revealed that the lining cells were positive for vascular markers (CD34 and ERG) and displayed nuclear positivity for HHV-8 (Figs. 5, 6 and 7).

While awaiting the orthopaedic team's plantar biopsy results, the patient experienced a persistent high fever. Concurrently, the patient exhibited progressive pancytopenia, with haemoglobin levels falling below 5 g/dL and platelet counts dropping below 10×10^9/L despite daily transfusions. This transfusion-resistant pancytopenia is thought to be multifactorial, potentially arising from KICS and sequestration of blood cells due to massive splenomegaly. The patient also displayed coagulopathy, with an international normalised ratio (INR) elevated up to 1.7 and CRP levels exceeding 200 mg/dL. The HHV-8 viral load at KICS diagnosis was 2.91×10^5 copies/mL.

Consequently, the medical team initiated antiviral foscarnet to suppress HHV-8 replication. However, a subsequent increase in creatinine levels led to the discontinuation of foscarnet after one week. With a strong suspicion of KICS, the patient was administered four weekly doses of Rituximab and a single dose of Tocilizumab to deplete B cells and inhibit IL-6 production, respectively. These interventions aimed to reduce the elevated levels of proinflammatory cytokines and chemokines resulting from HHV-8 lytic replication. Following a gradual tapering schedule, dexamethasone, recognised for its anti-inflammatory properties in suppressing inflammatory mediators, was also administered throughout the treatment. During Rituximab therapy, the patient developed increased purplish lesions on the right plantar area and the bilateral dorsal sides of the feet. Considering the potential for Rituximab use without concurrent chemotherapy to provoke a flare of Kaposi sarcoma, the oncology team promptly initiated weekly Paclitaxel following confirmation of Kaposi sarcoma through plantar biopsy.

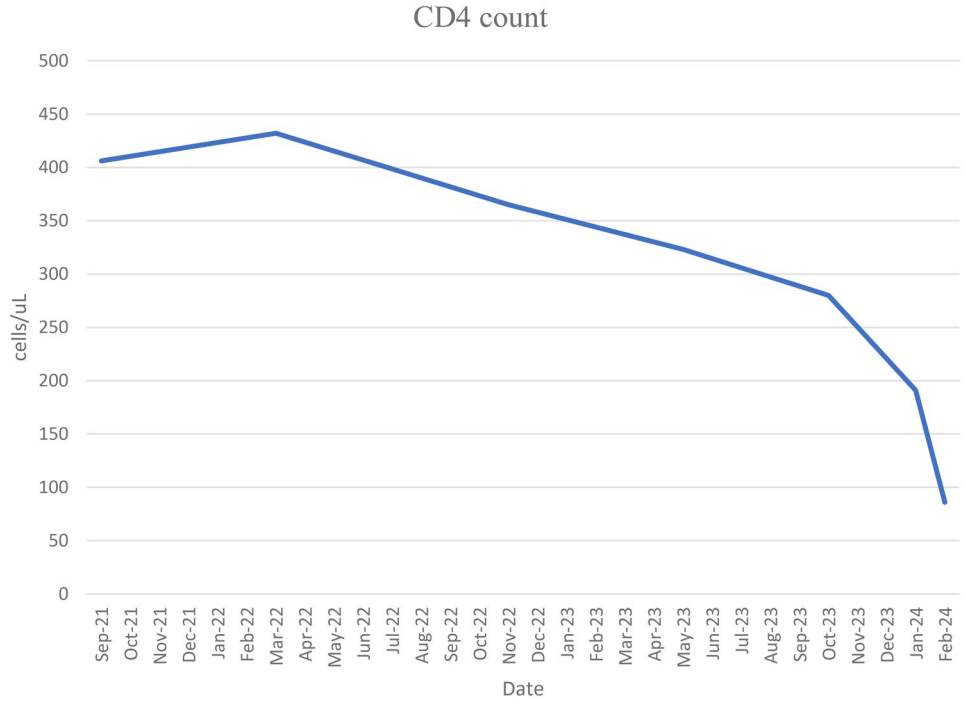

Fig. 2 CD4 count trend of the patient

Table 2 Microbiology Investigations

Nasopharyngeal swab for respiratory virus PCR	Enterovirus/ rhinovirus RNA detected
Tuberculosis (TB) workup including sputum, stool, early morning urine and bone marrow aspirate for TB culture and TB PCR	Negative
Cytomegalovirus Antigen pp65	Not detected
Cryptococcal antigen	Negative
Aspergillus antigen	Negative
Epstein Barr Virus DNA PCR	< 100 IU/mL
Blood culture	No growth
Midstream urine culture	No growth
Penicillium marneffei Antibody	< 1 in 40
Interferon Gamma Release Assay (IGRA)	Negative
Melioidosis Antibody IgM	Positive
Parvovirus B19 IgM and PCR	Negative
Dimorphic fungal serology (Histoplasma & Blastomyces Antibody)	Negative
Brucella, *Leptospira*, *Typhoid*, *Rickettsia*, *Coccidioides*, *Toxoplasma* serology	Negative
Dengue virus serology	Negative
Zika virus PCR	Negative
Malaria blood smear	Negative
Venereal disease research laboratory test (VDRL)	Negative

After the treatment regimen, the patient exhibited a resolution of fever, and the formerly detected massive splenomegaly was no longer palpable. A regression of bilateral foot lesions was also observed. Upon completing the fifth weekly cycle of Paclitaxel, the patient's CD4 count rose from a nadir of 86 cells/μL to the most recent measurement of 263 cells/μL. A decreasing trend in HHV-8 PCR viral levels was observed (Fig. 8). Moreover, there was a significant reduction in inflammatory markers, including CRP, IL-10, and IL-18 (Fig. 9). Platelet levels normalised, and the necessity for transfusions ceased two weeks before discharge. The patient will continue chemotherapy in an outpatient setting.

Discussion

KICS presents a unique challenge due to its hyperinflammatory state triggered by KSHV lytic activation, manifesting with symptoms like fever, anasarca, cytopenia, and hepatosplenomegaly, resembling conditions such as MCD and HLH. There is also a case suggesting that KICS can lead to septic shock [4, 9]. While KICS is often linked to untreated HIV patients with high viral loads and low CD4 counts, our case highlights its occurrence in individuals effectively managing their HIV [10].

Intricate molecular mechanisms characterise the pathogenesis of KSHV. The KSHV genome demonstrates a propensity for manipulating cellular genes to enhance viral survival and drive pathogenesis through interactions with host cellular machinery and the immune system. Noteworthy instances include viral homologs of interferon regulatory factors, such as ORF K9/vIRF-1 and ORF K11.5/vIRF-2, and viral IL-6 (vIL-6), which mimics human IL-6 (hIL-6) and is capable of directly activating gp130 signalling independently of other receptor

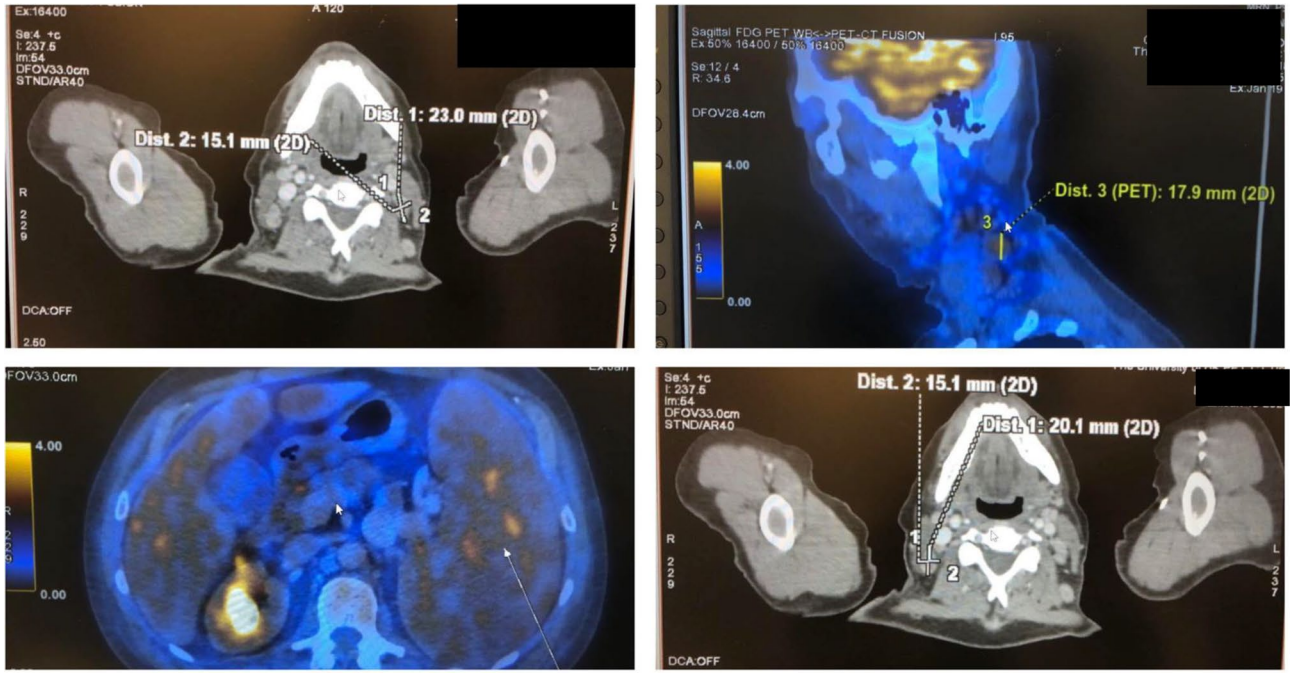

Fig. 3 PET-CT findings of the patient

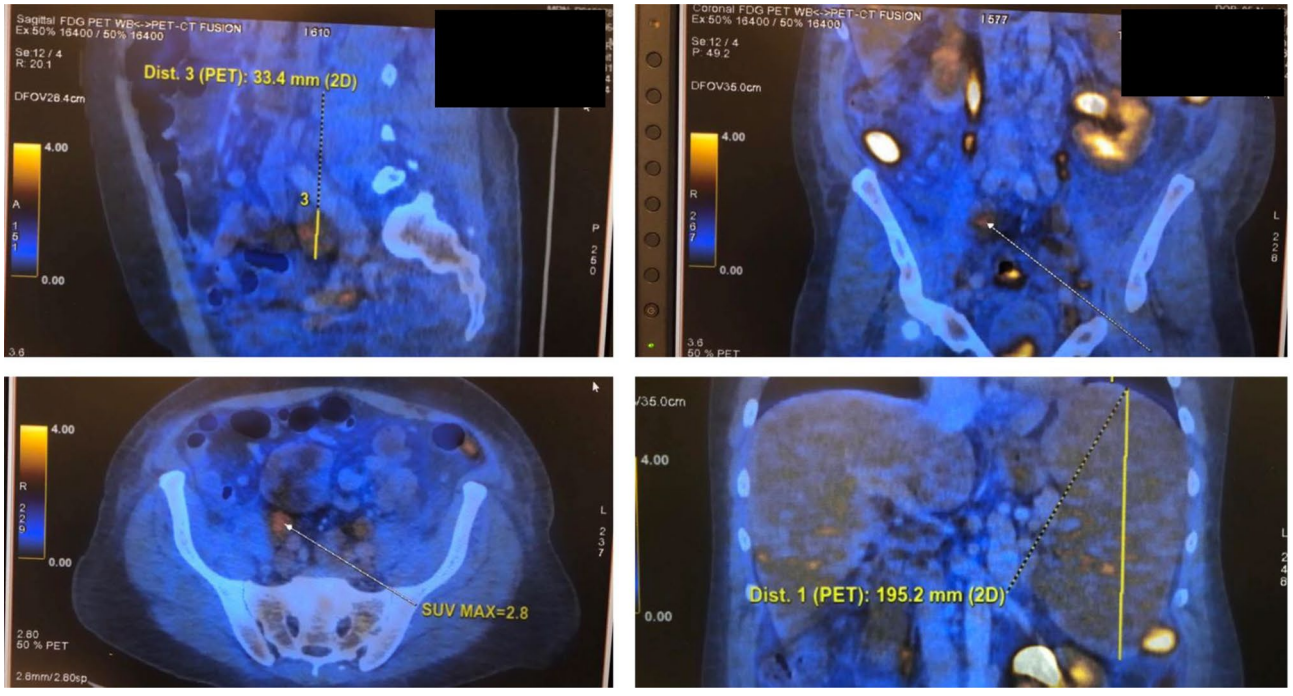

Fig. 4 PET-CT findings of the patient

subunits. These mechanisms contribute to the inflammatory manifestations of KICS [11–13].

While viral IL-6 is traditionally associated with lytic gene expression, it is intriguing that its expression may occur independently of full lytic activation in specific contexts. Moreover, these viral proteins have been shown to interact with host proteins in ways that support viral survival and may induce the expression of other anti-inflammatory cytokines, such as IL-10[6], potentially contributing to immune dysregulation. These interactions shed light on the complex interplay between KSHV and host cellular processes, contributing to the hyperinflammatory state observed in conditions like KICS [12].

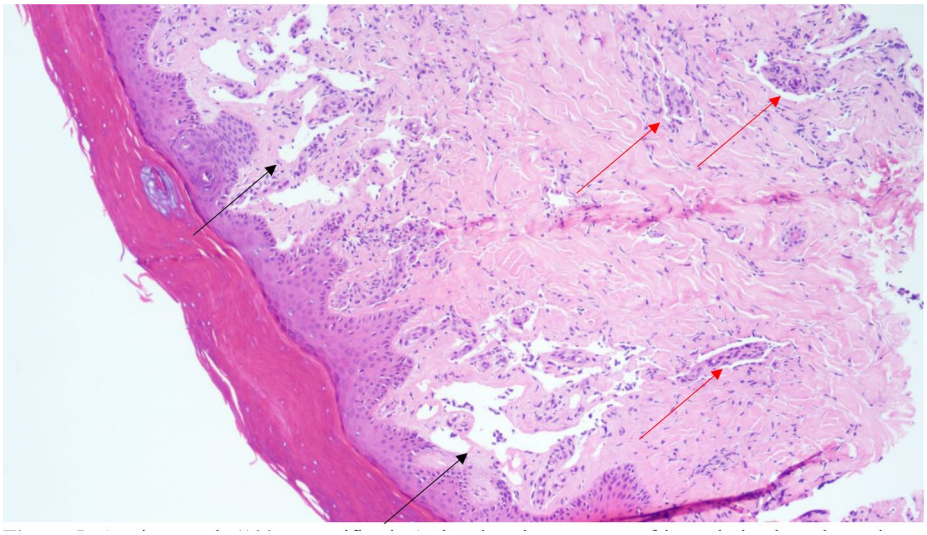

Fig. 5 A micrograph (100x magnification) showing the presence of irregularly shaped ectatic vascular channels which dissect into dermal collagen (black arrow). Within some of these neoplastic vascular channels are entrapped native vessels (red arrow), a histologic feature known as promontory sign and is classic to Kaposi sarcoma

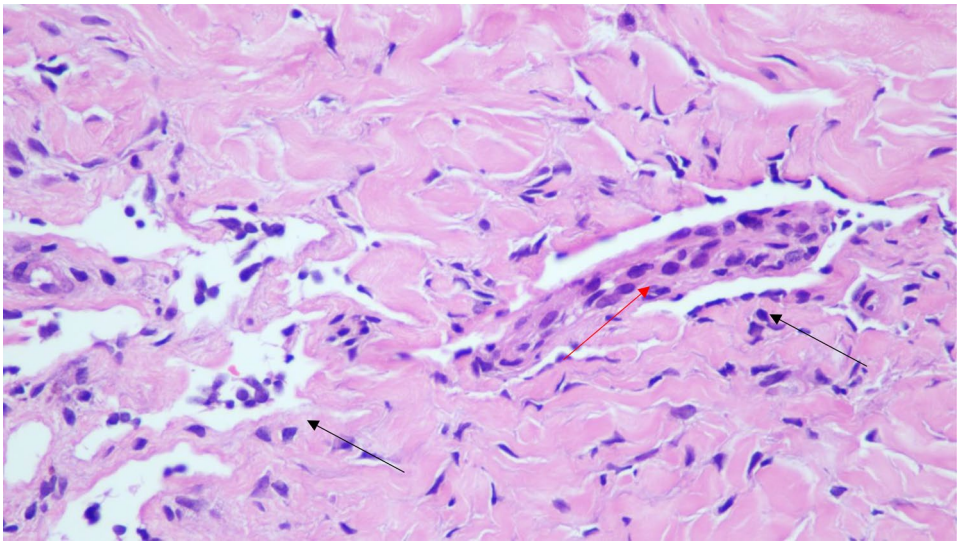

Fig. 6 A higher power (200x magnification) of these abnormal vascular channels (black arrow) and the promontory sign (red arrow)

Infectious and non-infectious causes were systematically evaluated and excluded using clinical, laboratory, and imaging studies to establish the final diagnosis of KICS. Mycobacterial infections, including disseminated tuberculosis (TB) and nontuberculous mycobacteria, were ruled out based on negative cultures, the absence of granulomatous inflammation on lymph node biopsy, and no radiological evidence of miliary TB or cavitary lesions. Viral infections, such as parvovirus B19 and herpesvirus-associated HLH, were excluded by negative PCR testing. Visceral leishmaniasis, considered due to the patient's travel history, systemic symptoms, and splenomegaly, was excluded based on the absence of characteristic intracellular amastigotes on bone marrow biopsy. Endemic mycoses, including cryptococcosis, histoplasmosis, blastomycosis, talaromycosis, and coccidioidomycosis, were excluded through negative fungal cultures, antigen tests, and biopsy findings. Non-infectious causes, such as lymphoma, were excluded based on the absence of clonal B-cell populations on immunohistochemistry, no lymph node architectural disruption or clonal proliferation on biopsy, and PET-CT findings consistent with diffuse, low-grade reactive SUV uptake rather than focal, high-grade neoplastic patterns. Autoimmune diseases, such as systemic lupus erythematosus, were excluded through negative autoimmune markers, normal complement levels, and lack of clinical features such as malar rash, arthritis, or serositis.

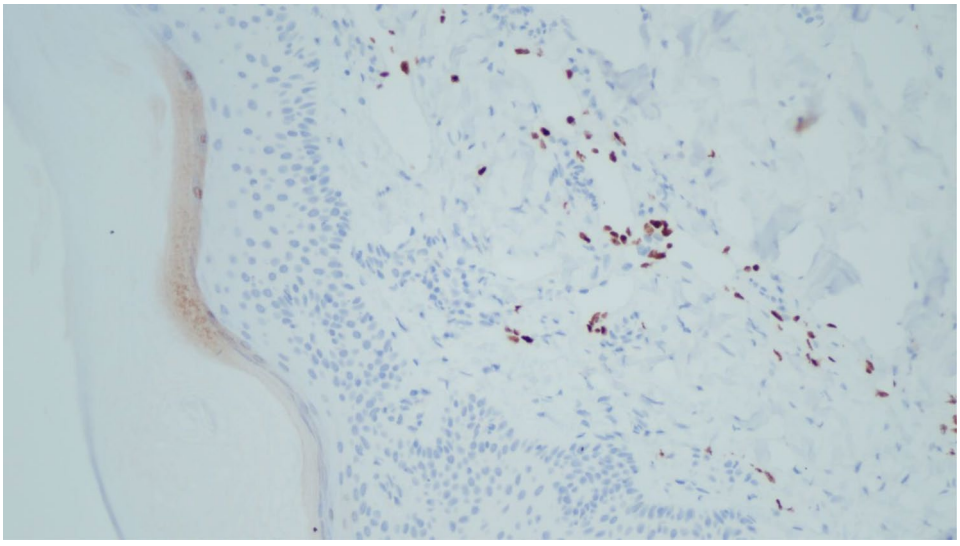

Fig. 7 HHV-8 immunostain highlights the endothelial cells lining the neoplastic vascular channels

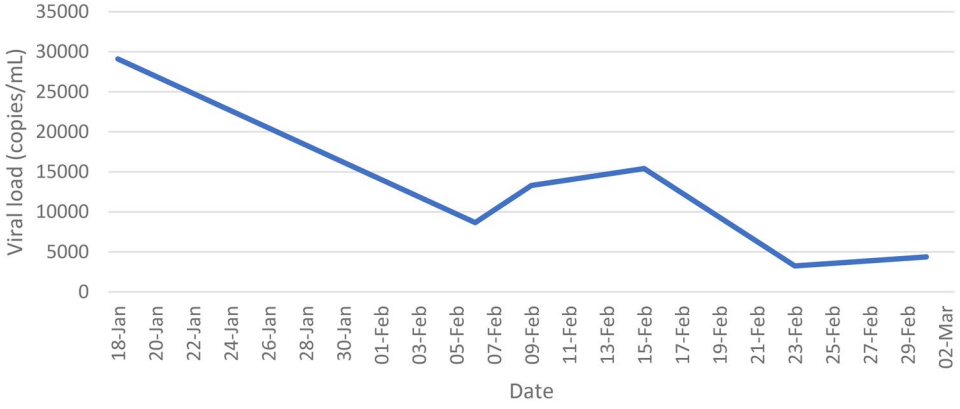

Fig. 8 HHV-8 qPCR monitoring

	Before treatment	After treatment (after cycle 2 of Paclitaxel)	Reference range
Interleukin 10 (pg/mL)	>10000	34.30	<8.8
Interleukin 18 (pg/mL)	3252	811.08	<43.3

Fig. 9 Cytokine profile (IL-10 & IL 18) before and after treatment

This case meets the diagnostic criteria for KICS as defined by the Working Case Definition for KICS [5], which requires at least two distinct categories of symptoms, laboratory aberrations or radiological findings, corroborated by evidence of systemic inflammation, elevated KSHV viral load in plasma (≥ 1000 copies/mL), and the absence of characteristic MCD features such as regressed germinal centres or mantle zone hyperplasia upon biopsy assessment.

It is essential to acknowledge that KICS is not confined to HIV patients alone. Other categories of immunocompromised hosts, such as transplant recipients, are also at risk [14, 15]. KICS can occur as the sole clinical manifestation of HHV-8 infection or reactivation, as observed in solid organ transplant recipients following primary infection [14]. Furthermore, KICS can sometimes be further complicated by HLH during its clinical course, which may justify the use of dexamethasone in specific cases, even though corticosteroids are not universally required for KICS management [16].

From a therapeutic standpoint, established guidelines for KICS management remain limited. Remarkably, our approach in this case entailed a therapeutic strategy combining antiviral medications, i.e. Foscarnet, to curtail the viral load alongside anti-inflammatory agents, specifically corticosteroids, aimed at quelling the hyperinflammatory

response. Rituximab-based therapy has long been a cornerstone in managing HHV-8-associated MCD [17]. Observations and retrospective studies suggest its use in KICS, owing to its potential to disrupt the cytokine cascade by targeting HHV-8-infected CD20 + B cells, thus reducing the viral reservoir and limiting viral proliferation [15, 18, 19]. A combination therapy of rituximab, foscarnet, and everolimus has successfully treated post-transplant KICS [20]. However, rituximab therapy is associated with notable risks, including potential exacerbation of cutaneous KS, infusion-related reactions, and increased susceptibility to infections due to immunosuppression. As a result, conventional KS treatments, such as liposomal doxorubicin or paclitaxel, are often employed in these cases.

The effectiveness of monoclonal antibodies in KICS treatment remains under investigation. Tocilizumab, which targets the gp80 subunit of the IL-6 receptor, has shown promise in limited case reports due to the pivotal role of IL-6 in KICS pathogenesis [14]. However, it is essential to note that HHV-8 vIL-6 can activate signalling independently via the gp130 receptor subunit [21, 22]. This underscores the need for further research and clinical trials before tocilizumab can be routinely considered for KICS management.

Our management approach involved monitoring inflammatory markers, evaluating improvements in cytopenia and hypoalbuminemia, and using quantitative HHV-8 plasma PCR to confirm the diagnosis and assess treatment response [10]. Comprehensive management also requires vigilance for organ dysfunction and an evaluation of Kaposi sarcoma involvement through imaging and tissue biopsy. This holistic approach remains essential for addressing the complexities of KICS.

Conclusion

KICS is a rare but severe condition requiring vigilant recognition in patients with HHV-8 infection. It predominantly affects immunocompromised hosts, including HIV-infected individuals. This case highlights the importance of combining antiviral, immunomodulatory, and chemotherapeutic agents to address the multifaceted pathophysiology of KICS. Treatment with rituximab, tocilizumab, and steroids shows promise in KICS management, but further research is needed to establish standardised treatment protocols.

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Author contributions
MHC, CSL and PYT wrote the main manuscript text. SWL and EYLA prepared the figures. MCC, TSHC, DPLL, KYY, FNIH and TYT reviewed the manuscript.

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Data availability
Availability of data and materials: Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Informed consent was obtained from the patient.

Consent for publication
Written informed consent for their personal or clinical details, along with any identifying images to be published in this study, was obtained from the patient.

Competing interests
The authors declare no competing interests.

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