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REVIEW

Human Herpesvirus-8/Kaposi Sarcoma Herpesvirus in Solid Organ Transplantation: A Narrative Review of Neoplastic Manifestations

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Abstract

Purpose of Review This comprehensive narrative review aims to provide an in-depth analysis of Human herpesvirus-8/Kaposi Sarcoma-associated herpesvirus (HHV-8/KSHV) and Kaposi sarcoma herpesvirus-associated diseases (KADs), with a special focus on malignancies in the setting of transplantation, by addressing the major issues related to clinical presentations, epidemiology, pathological features, diagnosis, treatment, and outcome.

Recent Findings HHV-8/KSHV is an oncogenic virus belonging to the family of the γ-herpesvirus responsible for a wide range of KADs such as Kaposi's Sarcoma (KS), multicentric Castleman disease (MCD), primary effusion lymphoma (PEL), diffuse large B cell lymphoma not otherwise specified (DLBCL-NOS), and KSHV inflammatory cytokine syndrome (KICS). In solid organ transplant (SOT) recipients, the incidence of HHV-8/KSHV-related malignancies are becoming more frequent because of prolonged life expectancy, and related aging and immunosenescence. HHV-8/KSHV infection in SOT is a rare but serious complication associated with significant morbidity and mortality. Enhanced clinical awareness of the diverse manifestations of KADs is critical for early diagnosis and improved outcomes. Multidisciplinary management is essential, given the complexity of these cases.

Summary Future research should focus on establishing standardized protocols for screening, diagnosis, and treatment to improve clinical outcomes. Targeted donors and recipients serological screening strategies, combined with vigilant post-transplant monitoring have the potential to enhance patient care.

Keywords Human herpes virus 8/kaposi's sarcoma-associated herpesvirus · Kaposi sarcoma · Primary effusion lymphoma · Diffuse large B-cell lymphoma · Multicentric castleman disease · Kaposi sarcoma inflammatory cytokine syndrome · Solid organ transplantation

Abbreviations

CDC	Center for disease control
CNI	Calcineurin inhibitor
DLBCL-NOS	Diffuse large B cell lymphoma not otherwise specified
CRP	C-reactive protein
GI	Gastrointestinal
HHV-8/KSHV	Human herpes virus 8/kaposi's sarcoma-associated herpesvirus
HAART	Highly active antiretroviral therapy
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem-cell transplant
HTx	Heart transplant
KAD	HHV-8/KSHV-associated disease
KICS	Kaposi's sarcoma-associated herpesvirus inflammatory cytokine syndrome
KS	Kaposi Sarcoma
KTx	Kidney transplant
LANA	Latency-associated nuclear antigen
LTx	Lung transplant
MCD	Multicentric castleman disease

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MSM	Men who have sex with men
mTOR	Mammalian target of rapamycin
OLTx	Liver transplant
PEL	Primary effusion lymphoma
PET/CT	Positron emission tomography/computed tomography
PT	Post-transplant
PLWH	People living with HIV
SOT	Solid organ transplant
UCD	Unicentric castleman disease

Introduction

Human herpesvirus-8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), is an oncogenic virus belonging to the family of the γ-herpesvirus. In contrast to its asymptomatic/paucisymptomatic course in immunocompetent individuals, HHV-8/KSHV may cause severe primary infections or reactivate under immunosuppression in solid organ transplant (SOT) recipients, leading to the development of KSHV-associated diseases (KADs) such as Kaposi's Sarcoma (KS), multicentric Castleman disease (MCD), primary effusion lymphoma (PEL), diffuse large B cell lymphoma not otherwise specified (DLBCL-NOS), and KSHV inflammatory cytokine syndrome (KICS) [1]. The majority of current evidence on HHV-8/KSHV is derived from studies conducted in HIV-infected patients. However, with the increasing life expectancy of SOT recipients, malignancies are becoming more prevalent due to aging and immunosenescence. Recently the Center for Disease Control and Prevention (CDC) released a note reporting, during 2021– 2025, an increase in the number of reports of suspected donor-derived HHV-8/KSHV infections resulting in KS, KICS, or other KADs in SOT recipients [2]. Therefore, a more thorough characterization of KAD in this at-risk population is essential.

The purpose of this review is to improve our understanding of HHV-8/KSHV and KADs with a special focus on malignancies in the setting of transplantation, including clinical presentations, epidemiology, pathological features, diagnosis, treatment, and outcome.

Epidemiology and Life Cycle of HHV-8/KSHV

HHV-8/KSHV seroprevalence varies by geographic origin and risk group, with higher rates in sub-Saharan Africa and the Mediterranean areas, particularly among people living with HIV (PLWH) and men who have sex with men (MSM) [3, 4]. In the SOT setting, seroprevalence ranges from 4% to 10%, with lower rates in donors as compared to recipients. In HIV-positive recipients, seroprevalence can reach 40% [5–8].

HHV-8/KSHV persists in the host through a biphasic life cycle, alternating between latent infection (primarily in B cells, endothelial cells, and monocytes) and lytic replication. The proteins expressed during the latent phase promote cell survival, proliferation, and immune evasion, thus inhibiting apoptosis and modulating cell cycle checkpoints. In contrast, the expression of lytic genes modulates tumor microenvironment, promoting angiogenesis, inflammation, and paracrine signaling that support tumor growth [9–11]. It is mainly transmitted via saliva and through sexual contact in endemic areas, particularly among MSM, and intravenous drug use in non-endemic regions [12]. In the SOT setting, HHV-8/KSHV malignancies may develop either due to reactivation of a latent infection in seropositive recipients or to a primary donor-derived infection, acquired through transplantation. Notably, HHV-8/KSHV cells may be harbored in the allograft and transmit the virus to the recipient, or, rather, KS tumors themselves may directly originate from donor-derived HHV-8/KSHV cells, seeded with the graft and then proliferating in the immunosuppressed recipient [13].

HHV-8/KSHV Associated Diseases

HHV-8/KSHV is associated with a broad spectrum of neoplastic disorders: the most common malignancy is KS, while less frequent tumors include PEL, DLBCL-NOS, and MCD. HHV-8/KSHV is also implicated in inflammatory diseases like KICS [11, 14]. These entities have been recognized in the recently published classifications of lymphoid neoplasms [15, 16].

Kaposi Sarcoma

The most prevalent neoplasia linked to HHV-8/KSHV is KS, which can affect the skin, mucosal membranes, lymph nodes, and internal organs including the allografts. There are five recognized epidemiologic forms: classic KS, mainly affecting elderly men in the Mediterranean areas, with a typically mild and cutaneous presentation; endemic KS, prevalent in sub-Saharan Africa, more aggressive with lymph node and visceral involvement; epidemic KS, seen in PLWH and usually disseminated and severe; iatrogenic or post-transplant (PT)-KS, occurring in immunosuppressed patients such as SOT recipients [17, 18]; and a recently identified form in HIV-negative MSM without known immunodeficiency, which tends to follow a slow and mild course. Immunosuppression is a key factor in most KS types [19]. In transplant settings, factors such as the type of transplanted organ, the

level and duration of immunosuppression, and both donor and recipient serostatus impact the development and course of KS.

Epidemiology and Risk Factors for KS

The global distribution of KS reflects the prevalence of HHV-8/KSHV and occurs more frequently in men. Recently Fu et al. described the global burden of KS by using data from 185 countries [20]. The authors found an age-standardized incidence rate and an age-standardized mortality rate of 0.39 and 0.18 per 100,000 people, respectively.

While the incidence of epidemic KS has significantly declined due to the widespread use of highly active antiretroviral therapy (HAART), PT-KS has shown an increase, driven by the expanding and aging population of transplant recipients [17]. In the SOT setting, the risk of developing KS is nearly 400 times higher than in the general population [21]. Approximately 8.8 to 12.5 instances of KS per 100,000 person-years are reported in the US, among SOT patients, with the majority of cases occurring within the first two years after-transplant [21]. An Italian multicenter study reported a higher rate (2.3 per 1,000 per year), likely due to greater HHV-8/KSHV prevalence in Southern Europe [22].

A recent systematic review by Saowapa et al. analyzed the prevalence of KS among kidney transplant (KTx) recipients [23]. The authors found that KS developed in 1.5% of KTx recipients with higher incidence among African and Middle Eastern recipients (1.7%). Tapering of immunosuppression resulted in complete remission in almost 50% of cases.

lung transplant (LTx) recipients have a higher risk of KS [24–26]. Other risk factors are male sex, advanced age, and origin from endemic areas as outlined by the Italian multicenter study by Piselli and colleagues, in which 73 KS cases were reported among [18] more than 4,000 SOT patients. In a study conducted by our group in 2025, among 155 seropositive recipients, only three cases of KS were observed with a median time from transplant of 383 days, while in seronegative recipients (49 with mismatch and 5 with primary non-donor-derived infections) two KS with KICS cases occurred earlier, at 132 and 232 days [5], respectively.

Dollard and colleagues [24]described six cases of donor-derived HHV-8 infection, four LTx, one liver (OLTx) and one KTx recipients, resulting in disseminated KS, at a median time of eight months from transplants, four of whom died from KS or its complications.

Durand et al. described [7], in 45 HIV-positive OLTx recipients, three cases of donor-derived KS: one with localized disease, one with liver and lungs involvement, and one with nodal KS and concomitant HHV-8/KSHV-associated DLBCL. In the recent study by Nambiar [6]et al., conducted among HIV-infected KTx, three cases of cutaneous KS and one case of allograft KS were reported.

Clinical Characteristics

KS typically presents as painless purple or violaceous lesions, macules, papules, or nodules. Occasionally, these lesions ulcerate or infiltrate deeper tissues. KS may be also associated with lymphedema, resulting from lymph nodes involvement and lymphatic obstruction. KS can affect any skin area, including surgical scars (Koebner phenomenon), and mucosa [27]. In the SOT setting, disseminated KS is common with lymph nodes, visceral organs and allograft involvement; visceral KS [24] without skin lesions has also been described. Cases of PT-KS with unusual localizations of disease have been reported, including KS of the graft with nodules and portal vein thrombosis or bladder wall thickening, and tonsillar KS [28–30].

Disseminated KS requires high suspicion, especially in SOT recipients with graft dysfunction or respiratory/gastrointestinal (GI) symptoms, like cough, hemoptysis, bleeding, or weight loss.

A concomitant KAD, such as MCD or KICS, or a hemophagocytic lymphohistiocytosis (HLH) should be suspected in the case of elevated HHV-8/KSHV DNAemia, and either C-reactive protein (CRP) or ferritin levels, systemic symptoms, and/or cytopenia. Patients with KS who have unexplained effusions should be evaluated for PEL [31].

Diagnosis

Diagnosis of localized KS is clinical but should be confirmed histologically. In disseminated KS, CT scans, endoscopy, and bronchoscopy assist in diagnosis and staging. GI lesions should be biopsied for confirmation, while lung biopsy carries bleeding risks [31]. Positron emission tomography/computed tomography (PET/CT) may be useful to localize disease and guide biopsies [32]. Histological examination reveals the presence of spindle cells that are invariably positive for the latency-associated nuclear antigen (LANA) of HHV-8/KSHV. HHV-8/KSHV DNA is also detected in lesions. Currently, there is no specific staging system for either endemic or iatrogenic KS [31]. According to Bettuzzi et al., three clinical scenarios, localized non-aggressive, locally aggressive, and widespread disease, should guide the management of PT-KS [31].

Treatment and Prevention

The main strategy for treating PT-KS is immunosuppression modulation, while indication for chemotherapy depends on the extent of the disease. It is advised to switch

from calcineurin inhibitors (CNI) to mammalian target of rapamycin (mTOR) inhibitors, due to their anti-proliferative properties [13, 33] and the associated recovery of T-cell responses against HHV-8/KSHV [34]. Treatment options for localized cutaneous KS include imiquimod, intralesional chemotherapy, radiotherapy, cryotherapy, and surgery. Based on patient characteristics and the severity of the disease, chemotherapy with pegylated liposomal doxorubicin is recommended for severe or progressing cases, with paclitaxel is to be considered as a second-line treatment [31].

Immunotherapy and alternative treatments are being explored to reduce chemotherapy toxicity in KS, such as pomalidomide, an immunomodulator that enhances T and NK cell functions and pembrolizumab, a PD-1 inhibitor that showed partial responses, with manageable safety, in trials for epidemic and classic/endemic KS, although it has not yet been approved for this specific indication

The management of PT-KS is challenging, due to the lack of established standards and depends on expert judgment, since a customized strategy is crucial. Selected cases of KS in SOT are described in Table 1.

Primary Effusion Lymphoma

Clinical Characteristics

PEL is an uncommon, aggressive subtype of non–Hodgkin lymphoma (NHL) that typically occurs in elderly individuals from HHV-8/KSHV endemic regions, with an epidemiology similar to KS [11]. In PLWH, it represents around 2%–4%

Table 1 Selected cases of Kaposi sarcoma in SOT recipients

Author (Journal, Year)	No. of KS cases/ SOT patients included	Type of transplant	Country	Time from Tx	Localization	Treatment	Outcome
Stallone G., *N Engl J Med*, 2005 [65]	**6 / 15**	**Kidney**	Italy	0,3 year	Cutaneous	Discontinuation of CSA, switch to sirolimus	Complete remission in all 6 cases
Dollard S.C. et al., *Am J Transplant*, 2018 [66]	**1/ 2**	**Liver**, **Kidney**	US	0,8 year	Visceral	Switch to sirolimus	Complete resolution
Nair V. et al., Transpl *Infect Dis*, 2019 [30]	**1 / NA**	**Kidney**	US	0,7 year	Visceral	Switch to mTOR, Doxo	Complete resolution
Howard J.H. et al., *Transpl Infect Dis*, 2020 [29]	**1 / NA**	**Kidney**	US	1,4 year	Lymph nodes (tonsils)	IS reduction, switch to sirolimus	Resolution
Dollard S.C. et al., *Am J Transplant*, 2021[24]	**6 / 22**	**4 Lung** **1 Kidney** **1 Liver**	US	Median 0,8 year	Visceral and Lymph nodes	IS reduction, CHT, Switch to sirolimus	4/6 died due to KS complication
Lee J.J. et al., *Korean J Transplant*, 2023 [67]	**1 / NA**	**Kidney**	Korea	~10 weeks	Visceral	Allograft	Graftectomy
Nambiar P. et al., *Clin Infect Dis*, 2025 [6]	**4 / 257**	**Kidney**	US	1 year	Skin/Allograft	Tacrolimus, MMF, Pred	All recovered
Fu W. et al., *Transpl Infect Dis*, 2018 [68]	**1 / NA**	**Liver**	US	0,4 year	Multiple nodules	IS reduction, Doxo	Complete resolution
Ocwieja K.E. et al., *Pediatr Transplant*, 2019 [28]	**1 / NA**	**Liver**	US	0,3 year	Visceral + lymph nodes	Switch to sirolimus + paclitaxel	Remission
Durand C.M. et al., *Am J Transplant*, 2022 [7]	**3 / 45**	**Liver**	US	1 year	Cutaneous + visceral	Switch to sirolimus	1/3 fatal outcome
Kates A. et al., *J Infect Dis*, 2024 [14]	**1 / NA**	**Liver**	US	0,4 year	Disseminated	Switch to sirolimus + CHT	Death
Denaro N. et al., J Clin Med. 2025 [69]	**1 / NA**	**Lung**	Italy	10 years	Cutaneous + visceral	Doxo + Paclitaxel	Complete response
Mularoni A. et al. *Am J Transplant*, 2025 [5]	**5 / 1963**	**2 Lung** **2 Heart** **1 Liver**	Italy	Median 1 year	Cutaneous and visceral	IS reduction, switch to mTOR, CHT, Rituximab	2 Heart died, 1 liver and 2 lung complete response
Bonazzetti et al., *Clin Microbiol Infect* 2025 [8]	**12 / NA**	**Multiorgan**	Italy	Median 1 year	Cutaneous and visceral	IS reduction, Switch mTOR, CHT	90-day mortality 19%

CHT chermoteraphy, *CSA* cyclosporine A, *Doxo* liposomal doxorubicin, *KS* kaposi sarcoma, *IS* immunosuppression, *MMF*, mycophenolate mofetil, *mTOR* mammalian target of rapamycin, *Pred* prednisone, *SOT* solid organ transplantation, *Tx* transplant

of HIV-associated NHLs [35]. Neoplastic cells are typically HHV-8/KSHV positive and often co-infected with Epstein-Barr virus (EBV), suggesting viral interplay. PEL usually presents as malignant effusions in body cavities without solid masses, although rare extracavitary solid tumors have been reported [11]. Only a limited number of PEL cases have been documented in the SOT setting, and just one case after hematopoietic stem cell transplantation (HSCT) [36]. Recently, Zanelli and colleagues performed a systematic review describing 13 PT-PEL cases: six in KTx, three in heart (HTx), two in OLTx and in bowel transplant recipients, and one in a HSCT recipient. All patients were male, with a mean age at disease onset of 54.9 years, while the average onset was 8 years PT. Importantly, KS was concurrently present in 4 out of the 13 cases, with KS preceding PEL in three cases. All the reported cases died, despite therapy, highlighting the uniformly fatal course of PEL, at a median time of six months from diagnosis, with a mortality rate of 100% [36].

HHV-8/KSHV serostatus was reported in 6 of 13 cases: two patients were seropositive and 2 seronegative, prior to transplant. In one case pre-transplant serology was unavailable but seropositivity was detected at PEL diagnosis. One patient seroconverted PT [36].

A possible explanation for the lower number of cases in HSCT recipients could be related to the intensive pre-transplant regimens, which may eradicate latent HHV-8/KSHV reservoirs, contrary to what observed in standard immunosuppressive protocols used in SOT. Another suggested hypothesis is that immune reconstitution, following bone marrow transplant, may offer protection against viral reactivation. Table 2 provides a detailed overview of cases in SOT [37].

Testa et al. reported a case of PEL in a 55-year-old OLTx recipient, atypically presenting with refractory ascites and sclerosing peritonitis. The diagnosis was made post-mortem: autopsy revealed HHV-8/KSHV–associated PEL, manifesting as solid tumor infiltration and extensive peritoneal fibrosis [38]. Zanelli et al. also described the case of a rare extranodal solid tumor variant of PEL in an HIV-negative small bowel transplant recipient who died within one month, despite therapy. Histopathology revealed plasmablastic lymphoma cells positive for HHV-8/KSHV LANA-1 and plasma cell markers, but negative for CD20 [39].

These cases highlight the importance of recognizing atypical clinical presentations in this patient population and maintaining a high index of suspicion to favor a prompt and accurate diagnosis and initiate treatment.

Diagnosis

The diagnosis of PEL is particularly challenging due to its heterogeneous clinical presentation and the absence of a detectable tumor mass. Detection of HHV-8/KSHV in the neoplastic cells is an essential diagnostic hallmark of PEL.

The diagnosis is typically based on the identification of malignant lymphoid cells within body-cavity effusions. Cytological evaluation reveals pleomorphic tumor cells with immunoblastic, plasmablastic, or anaplastic morphology, along with characteristic null-cell phenotype [40]. The immunophenotype of PEL cells characteristically express CD45 and other activation or plasma cell-associated markers (CD30, CD38, CD138, MUM1/IRF4) [11, 14].

Treatment

No standardized treatment exists, but chemoimmunotherapy regimens such as EPOCH, which includes etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin are commonly employed [41–43]. Rituximab may beneficial by reducing cytokine-mediated inflammation and targeting HHV-8/KSHV-infected B cells.

The rarity of PEL and the compromised health of affected patients limit large-scale clinical trials, resulting in the lack of robust evidence for an optimal therapy [11, 14].

Emerging treatments focus on targeting tumor immunophenotypes or viral pathogenesis [41], including either intracavitary cidofovir or monoclonal antibodies against CD30 (e.g., brentuximab) or CD38 (e.g., daratumumab) particularly in relapsed cases [44].

Diffuse Large B-cell lymphoma, not otherwise Specified

Clinical characteristics

HHV-8/KSHV–associated large B-cell lymphoma, not otherwise specified (HHV-8/KSHV-DLBCL-NOS) is a distinct lymphoma subtype that often develops in patients with HHV-8/KSHV–associated MCD [11, 14, 45].

In contrast to PEL, HHV-8/KSHV-DLBCL-NOS more commonly involves nodal or splenic sites. Histologically, it is composed of EBV-negative large plasmablastic cells expressing LANA, vIL-6, IRF4, and cytoplasmic IgMλ [41].

The clinical presentation of HHV-8/KSHV-DLBCL-NOS is variable [41]. Signs and symptoms often overlap with those of MCD and PEL, being associated with cytokine storm and HHV-8/KSHV DNAemia. KS may also be concurrently present [11, 14].

To date, only two cases of HHV-8/KSHV-positive DLBCL subtypes occurring in SOT recipients have been documented in the literature [46, 47]. In both cases, KS was also present and diagnosed prior to the development of DLBCL.

Table 2 Reported cases of PEL, DLBCL, and MCD in SOT recipients

Author (Journal, Year)	No. of cases/ SOT patients included	Type of transplant	Country	Time from Tx	Localization	Concomitant KAD	Treatment	Outcome
	PEL							
Boulanger et al. *Am J Transplant 2008* [70]	**2 / NA**	**Kidney**	France	3–4.5 years	Ascites, pleural and pericardial effusions	Yes, KS	CHT; m-TORi	Deaths at 8 m and 8 days PD
Melo et al. *Am J Transplant 2008* [71]	**1 / NA**	**Kidney**	Brazil	11 years	Pleural effusion	no	IS reduction; m-TORi; CHT	Death 4 mo PD
Shi et al. *Cytopathology 2012* [72]	**1 / NA**	**Kidney**	China	10 years	Pleural effusions and ascites	no	CHOP	Death 4 mo PD
Kalogeraki et al. *Diagn Cytopathol 2015* [73]	**1 / NA**	**Kidney**	Greece	NA	Ascites	no	CHOP	Death 7 mo PD
Cain et al. *Histopathology 2018* [74]	**1 / NA**	**Kidney**	UK	2 years	Intravascular (multiorgan)	Yes, KS	Tacrolimus	Death 2 weeks after
Régnier-Rosencher et al. *Int J Stroke. 2010* [75]	**2 / NA**	**Kidney**	France	NA	Pleural effusion	Yes, KS	CHT; IS reduction	death within 1 year
Testa et al. *Transplant Proc 2010* [38]	**1 / NA**	**Liver**	Italy	1 year	Ascites, peritoneal fibrosis	no	NA	Death (diagnosed post-mortem)
Christenson et al. *Am J Transplant 2015* [76]	**1 / NA**	**Liver**	US	10 years	Lymphomatous effusion	no	IS switch CNI to m-TORi, Doxo	Death 7 mo PD
Kugasia et al. *Transpl Infect Dis 2019* [77]	**1 / NA**	**Heart**	US	0,5 year	Pleural effusion	No	CHOP; IS switch CNI to m-TORi	death 14 mo PD
Jones et al. *N Engl J Med 1998* [78]	**1 / NA**	**Heart**	US	8 years	Pleural effusion	Yes, ks	CHT; IS reduction	Death due to MOF 6 mo PD
Dotti et al. *Leukemia 1999* [79]	**1 / 2**	**Heart**	Italy	3,6 years	Pleural effusion	No	CSA reduction; AZA	Death within 1 mo
Zanelli et al. *Br J Haematol 2021* [39]	**1 / NA**	**Small bowel**	Italy	NA	Extranodal solid tumor	No	CHT; IS reduction	Death within 1 mo
	DLBCL							
Kapelushnik et al. *Br. J.J of Haematol 2001* [46]	**1 / NA**	**Kidney**	Istrael	0,9 year	generalized LN	Yes, KS	L-DAU + IFN-α	Remission at 22 mo
Sathy et al. *Am J transplant 2008* [47]	**1 / 2**	**Lung**	US	0,7 year	Multiorgan involvement	Yes, KS	IS, doxo, rituximab	Death due to sepsis and MOF
	MCD							
Mandel et al. *Br. J.J of Radiol 1993* [80]	**1 / NA**	**Kidney**	Australia	4 years	Pulmonary, cutaneous, visceral	Yes, KS	IS	Death due to MOF (17 mo PD)
Cagirgan et al. *Nephron 1997* [81]	**1 /NA**	**Kidney**	Turkey	2 years	Generalized LAP, splenomegaly	no	Reduced IS, increased Pred	Death from septic shock
Theate et al. *Clin transplant 2003* [82]	**1 / NA**	**Kidney**	Belgium	16 years	Cervical LAP	Yes, PTLD	IS reduction	Complete resolution, (12 mo PD)
Al Otaibi et al. *transplant Proc 2007* [83]	**1 / NA**	**Kidney**	Kuwait	7 years	Mediastinal LAP	no	Nefrectomy	NA
Gaitonde et al. *Histopathology 2007* [84]	**1 / NA**	**Liver**	US	0,6 year	Axillary LAP	Yes, KS	Tacrolimus	Death from MOF
Bonatti et al. *Pediatr Transplantation 2012* [85]	**1 / NA**	**Liver**	US	1 year	Generalized LAP, splenomegaly	no	Reduced IS; switch to sirolimus + MMF	Complete resolution
Pietrosi et al. *Am J transplant 2011* [86]	**1 / 215**	**Liver**	Italy	0,3 year	LAP, ascites	no	CDV; tacrolimus	Death from MOF (50 days PD)
Lim et al. *Am J transplant* 2011 [87]	**1 / NA**	**Liver**	China	4 years	Generalized LAP	no	CHOP, VGCV, IS reduction	Complete resolution (3 years)

Table 2 (continued)

Author (Journal, Year)	No. of cases/ SOT patients included	Type of transplant	Country	Time from Tx	Localization	Concomitant KAD	Treatment	Outcome
	PEL							
Vijgen et al. *transplantetion 2016* [88]	**1 / NA**	**Liver**	Switzerland	1 year	NA	no	MP, rituximab, IS	Death from MOF (32 days PD)
Jha LK et al. *Case rep Hepatol 2018* [89]	**1 / NA**	**Liver**	US	0,8 year	systemic symptoms	no	Tacrolimus, Pred, VGCV; rituximab	Complete resolution
Patel et al. *Heart & Lung 2014*(90)	**1 / NA**	**Heart**	US	1,5 years	Generalized LAP	Yes, KS	Tacrolimus, MMF, Pred, reduced IS	death 25 days PD

AZA azathioprine, *CDV* cidofovir, *CHT* chermoteraphy, *CSA* cyclosporine A, *DAU + IFN-α* liposomal daunorubicin and alpha-interferon, *LAP* linfadenopathy, *KS* kaposi sarcoma, *IS* immunosuppression, *MMF* mycophenolate mofetil, *MOF* multiple organ failure, *MP* methylprednisolone, *m-TOR* mammalian target of rapamycin, *NA* not applicable, *PD* post-diagnosis, *Pred* prednisone, *PTLD* post-transplant lymphoproliferative disorder, *SOT* solid organ transplantation, *VGCV* valganciclovir

Kapelushnik et al. reported a 17-year-old male with HHV-8/KSHV mismatch who developed HHV-8/KSHV-associated DLBCL and KS nine months after KTx, presenting with splenomegaly and lymphadenopathy. The patient was treated with liposomal daunorubicin and alpha-interferon and achieved remission at 22 months [46].

Sathy et al. described a 45-year-old male who developed DLBCL and KS seven months post LTx; despite treatment, he died from suspected sepsis and multiorgan failure, with post-mortem revealing widespread KS and plasmacytoid B-cell lymphoma [47].

Diagnosis

Diagnosis of HHV-8/KSHV-DLBCL requires confirmation of HHV-8/KSHV infection in neoplastic cells, typically through immunohistochemistry or molecular methods, along with the exclusion of other HHV-8/KSHV-associated lymphoproliferative disorders [48]. At histological examination, neoplastic cells efface the architecture of involved tissues, lymph nodes, spleen, bone marrow, or peripheral blood- and morphologically resemble plasmablasts or immunoblasts. This lymphoma subtype is aggressive and generally carries a poor prognosis, although younger age may be associated with improved outcomes [11, 14].

Treatment

Treatment is difficult due to its rarity, complex diagnosis, and poor response to chemotherapy [45]. Current guidelines recommend curative anthracycline-based regimens, including EPOCH [11, 14, 41].

Multicentric Castleman Disease

Clinical Characteristics

Castleman disease, first described in 1956, includes lymphoproliferative disorders with unicentric (UCD) and multicentric Castleman (MCD) forms. While UCD is localized and shows a more indolent course, MCD is usually characterized by a disseminated and aggressive course and can be either idiopathic or HHV-8/KSHV-associated [41]. MCD mainly affects PLWH and co-occurrence with KS is common [11, 49]. In the SOT setting, MCD can be considered a rare disease (< 1%) [14, 41].

MCD is a polyclonal B cell lymphoproliferative disorder characterized by widespread lymphadenopathy and inflammatory features, with episodic flares of systemic symptoms and aberrant host immune responses with elevated inflammatory markers and high HHV-8/KSHV DNAemia that can lead to organ damage and, eventually, death. Typical clinical manifestations include fever, fatigue, night sweats, weight loss, peripheral edema, cytopenia, skin rashes, and involvement of respiratory and gastrointestinal systems, organomegaly, and lymphadenopathy. Generalized lymphadenopathy is commonly present and typically associated with pathognomonic histological features, which enable differentiation between MCD and KICS. Recent therapeutic advancements, including the use of rituximab and antiretroviral therapy in HIV-positive patients, have markedly improved a prognosis, that was previously associated with high mortality [11, 14, 50]. In HIV-negative patients, treatment with rituximab is associated with higher progression rate than in HIV-positive patients [51]. However, in the SOT

setting, MCD tends to follow a more severe course, with acute presentations and frequently associated with other KADs, with a significant risk of relapse and mortality [1, 13].

In the context of transplantation, the incidence of MCD remains poorly defined, with limited reported cases. A systematic review by Jinwen Lin et al. identified ten cases: six KTx, three OLTx, and one HTx recipient. All patients were male, averaging 45 years at onset, with a mean symptoms' onset of 4 years, after transplant. Other KADs were reported in four cases with concomitant KS and in one case with HHV-8/KSHV-associated lymphoproliferative disorder. Clinical presentations varied from subclinical disease to generalized lymphadenopathy, splenomegaly, and systemic symptoms [52]. In this case series, patients with systemic and aggressive clinical presentation, treated solely with IS reduction of steroids had fatal outcome while milder disease presentation and treatment with rituximab, antivirals and/or chemotherapy was generally associated with better survival.

Diagnosis

Definitive diagnosis of MCD requires histopathological confirmation, via excisional lymph node biopsy. The histologic features MCD are the presence of HHV-8/KSHV infected IgMλ restricted polyclonal plasmablasts within the mantle zone of B-cell follicles, with immunohistochemical staining positive for LANA [11, 49, 53].

From a clinical perspective, MCD should be suspected in the presence of suggestive signs and symptoms, based on the diagnostic criteria for active MCD, established by Gérard et al. that requires the presence of fever, elevated CRP, and at least three of the following symptoms: lymphadenopathy, splenomegaly, effusions, respiratory and neurological symptoms, jaundice and anemia. However, as these criteria were developed for MCD in the setting of HIV infection, their relevance and applicability to SOT recipients remains to be evaluated [54]. For instance, a common characteristic of this disease, not included in the above-mentioned criteria, is the presence of elevated HHV-8/KSHV viral load in plasma and in body-cavity effusions. In SOT recipients, the clinical similarities between this disease and KICS necessitate a careful differential diagnosis. Being KICS increasingly reported in this setting, histopathological analysis of lymphadenopathy, when present, is crucial.

Treatment

Generally, treatment of MCD is individualized by disease severity, immune status and comorbidities. Rituximab, a CD20-targeting monoclonal antibody, is first-line therapy, effectively reducing symptoms and viral load. In a study conducted by Bower and colleagues, among 21 HIV-positive patients with MCD treated with rituximab, 67% had partial response, 29% stable disease, and 95% two-year survival, with no severe adverse events [49, 53, 55, 56]. However, 36% of those with KS experienced progression. Similarly, Gerard et al. reported 92% one-year survival in 24 MCD patients treated with rituximab, with 77% maintaining remission [54]. Yet, adverse effects including infections (80%), infusion reactions (38%), and neutropenia (13%) were common, and 67% of patients with KS had a disease progression. These findings highlight the risk of KS exacerbation following rituximab described in HIV infected patients. Relevant to this, combination therapy with liposomal doxorubicin may be used in cases with concomitant MCD and KS [1]. Therapy with monoclonal antibody targeting IL-6, although indicated in idiopathic MCD, may be considered a rescue therapy for HHV-8-associated MCD. Immunosuppression is often managed by switching from CNI to mTOR inhibitors for their antiproliferative effects. Antivirals may be considered in high HHV-8/KSHV DNAemia, though evidence is limited [57].

PT-MCD remains a rare but potentially fatal complication, particularly in immunosuppressed individuals. Timely diagnosis and treatment are critical to improving patient outcomes.

KICS

Clinical Characteristics

Among immunocompromised hosts, HHV-8/KSHV is also associated with aggressive inflammatory conditions named KICS, a potentially life-threatening KAD, characterized by hyperinflammatory host responses, organ damage, also including, rarely, bone marrow failure [13, 41]. In SOT recipients, while HHV-8/KSHV related malignancies other than KS are very rare, KICS and other inflammatory conditions have been increasingly recognized.

KICS can be defined as a severe systemic inflammatory disorder that occurs in the context of HHV-8/KSHV infection, most commonly SOT recipients with donor- and non-donor-derived primary infection. Clinically, KICS is characterized by high level of HHV-8/KSHV DNAemia, elevated CRP levels, and a combination of inflammatory symptoms. KICS is rapidly progressive and can be fatal without prompt recognition and treatment [58].

KICS shows several similarities to MCD, possibly sharing common aberrant systemic inflammation that causes similar clinical manifestations. However, while lymphadenopathy can be present in both entities, in MCD histological examination of lymph node is diagnostic and characterized by the presence of a hypocellular germinal center with polyclonal

Table 3 Diagnostic criteria for KICS

Domain	Criterion / Feature	Description
1. Clinical Manifestation	a. symptoms	Persistent fever, fatigue, edema, weight loss, respiratory, neurologic, or gastrointestinal symptoms
1. Clinical Manifestation	b. laboratory abnormalities	cytopenias (anemia, thrombocytopenia), hypoalbuminemia, hyponatriemia
1. Clinical Manifestation	c. radiographic abnormalities	lymphadenopathy, splenomegaly, hepatomegaly
2. Evidence of systemic inflammation	elevated C-reactive protein ≥ 3 g/dL	
3. Virologic	Elevated HHV-8/KSHV DNAemia in plasma (≥ 1000 copies/mL) or peripheral blood mononuclear cells (≥ 100 copies/10^6 cells)	
4. Exclusion of MCD	No evidence of HHV-8/KSHV-associated MCD	Biopsy if lymphadenopathies are present

Diagnosis of KICS established if present at least 2 clinical manifestations from at least 2 categories (1a, b, and c), together with each of the criteria in 2, 3, and 4

IgMλ plasmablastic cells involved in the cytokine production. Zhou et al. have identified IgMλ plasmablasts with similar immunophenotypes in the body-cavity effusions of patients with KICS and MCD, suggesting a potential role for these cells in the pathogenesis of KICS [59].

In SOT recipients, KICS was first described, formally, in a kidney-liver transplant recipient following donor-derived infection who was successfully treated with modification of immunosuppressive therapy, antivirals, and rituximab therapy [33].

Diagnosis

The diagnosis of KICS relies on the criteria elaborated by Polizzotto and colleagues. Based on this working case, evidence of high level HHV-8/KSHV DNAemia and elevated CRP are required for the diagnosis of KICS along whit at least two signs/symptoms drawn from two categories. The three categories are: (1) symptoms, which include fever, fatigue, and respiratory, neurological, or gastrointestinal symptoms, (2) laboratory abnormalities, as cytopenia, hypoalbuminemia, or hyponatremia, and (3) radiographic findings including hepatosplenomegaly, body-cavity effusions, or lymphadenopathy. If lymphadenopathies or polyserositis are present, MCD or PEL should be ruled out through histological examination (Table 3).

The applicability of KICS criteria to the SOT population remains uncertain, as these criteria were originally proposed based on a small cohort of HIV-infected patients and prior to the current understanding of KICS. Further studies are needed to evaluate the inclusion of novel and more specific criteria of KCIS including supportive biomarkers as elevated levels of IL-6, IL-10, immune exhaustion markers such as PD-1 and LAG-3 [5, 58, 60].

Treatment

The cornerstone of treatment is the tapering of immunosuppression, ideally by switching from CNI to mTOR inhibitors. This strategy should be implemented in patients with KICS but also, as early as possible, in recipients with mismatch, at first evidence of transmission, witnessed by the detection of HHV-8/KSHV DNAemia. This approach could avoid progression towards KICS and unfavorable outcome. Antiviral therapy with foscarnet, ganciclovir or cidofovir may also be added in patients with symptoms or high-level DNAemia. In patients with KICS, four cycles of rituximab should be administered. Rituximab has shown to improve survival in transplant recipients with KICS. In a cohort of 1856 SOT recipients, we described the occurrence of KICS as a result of a primary infection in 11 cases, associated with KS only in 2 of them. Mortality rates in SOT recipients treated (7 cases) and untreated (4 cases) with rituximab were 14% and 75%, respectively. In our view, rituximab therapy should be initiated as soon as the patient meets the diagnostic criteria for KICS. Accordingly, in the setting of rising DNAemia, clinicians should remain vigilant to enable early recognition of KICS and prompt initiation of appropriate treatment.

Recognition that additional KADs can be concurrently present in patients with KICS, or may develop subsequently, is clinically important. In cases of concurrent KS, systemic chemotherapy should be considered [1, 5, 33, 61]. During the course of KICS with ongoing appropriate therapy, a worsening of the patient's clinical condition, manifested by relapse of fever, absence of improvement in laboratory or imaging findings, and/or rising viral load and ferritin levels, should raise suspicion for secondary HLH. In such cases, an individualized and tailored management approach is recommended, including consideration of adjunctive therapy with dexamethasone and/or etoposide on a case-by-case basis [62, 63].

Regarding prevention, there is insufficient evidence to support a pre-emptive strategy based on the introduction of antivirals in case of HHV-8/KSHV DNAemia above a defined threshold before symptoms development. Current prevention strategies rely on identification of at-risk recipients through serological screening and HHV-8/KSHV DNA monitoring, with immunosuppression reduction/switch to mTOR inhibitors in case of positive DNAemia.

Germinotropic Lymphoproliferative Disorder

Germinotropic lymphoproliferative disorder (GLPD) is a rare entity described in 2002 and recognized by recent classifications [11, 15, 16]. Only few cases have been described in the literature, normally including adult men, who are mostly HIV-negative, and generally showing an indolent course. Either a "wait or watch approach" or systemic chemotherapy may be required, depending on the clinical course [64]. No cases have so far been described in the SOT setting.

Conclusion and Future Perspectives

HHV-8/KSHV infection in SOT is a rare but serious complication associated with significant morbidity and mortality, particularly in high-risk patients. Enhanced clinical awareness of the diverse manifestations of KADs is critical for early diagnosis and improved outcomes. Multidisciplinary management is essential, given the complexity of these cases. Future therapeutic perspectives may include investigating the efficacy of new antivirals against HHV-8/KSHV in patients with high DNAemia, as well as identifying targets for virus-specific cytotoxic T-lymphocyte (CTL) therapy, with the rationale of target HHV-8/KSHV infected cells and induce the reconstitution or supply specific T cell response in the immunocompromised host as for EBV.

The mechanisms governing HHV-8/KSHV infection in transplant recipients, particularly those explaining the heterogeneity of clinical manifestations and outcomes according to the type of transplanted organ, remain poorly defined. Future studies should focus on host-, virus-, and immune-related determinants of disease risk and progression. Important host factors include transplant type, intensity and type of immunosuppression, use of lymphodepleting agents, recent rejection, and concomitant infections contributing to the net state of immunosuppression. Virus-related factors, such as miRNA expression patterns associated with neoplastic versus inflammatory phenotypes, and immune-related factors, including virus-specific T-cell responses and baseline serological status, also warrant further investigation.

Current evidence is limited by cases heterogeneity and small cohorts, underscoring the urgent need for robust, systematic studies. Future research should prioritize standardized protocols for screening, diagnosis, and treatment. Serological screening of donors and recipients, along with vigilant PT monitoring, may improve outcomes but its inclusion in pre-transplant protocols should be guided by regional seroprevalence. Collaborative multicenter efforts studies are essential to develop evidence-based guidelines for prevention and management of HHV-8/KSHV complications in transplant populations.

CHT, chermoteraphy; CSA, cyclosporine A; Doxo, liposomal doxorubicin; KS, Kaposi Sarcoma; IS, immunosuppression; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; Pred, prednisone; SOT, solid organ transplantation; Tx, transplant;

AZA, azathioprine; CDV, cidofovir; CHT, chermoteraphy; CSA, cyclosporine A; DAU + IFN-α, Liposomal daunorubicin and alpha-interferon; LAP, linfadenopathy; KS, Kaposi sarcoma; IS immunosuppression; MMF, mycophenolate mofetil; MOF, multiple organ failure; MP, methylprednisolone; m-TOR,, mammalian target of rapamycin; NA, not applicable; PD, post-diagnosis Pred, prednisone; PTLD, Post-transplant lymphoproliferative disorder; SOT, solid organ transplantation; VGCV, valganciclovir;

Key References

- Mularoni A, Cona A, Bulati M, et al (2025) Serologic screening and molecular surveillance of Kaposi sarcoma herpesvirus/human herpesvirus-8 infections for early recognition and effective treatment of Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome in solid organ transplant recipients. Am J Transplant 25:1070–1085.
  - ○This study highlights the value of integrating serologic screening and molecular monitoring of HHV-8 in solid organ transplant recipients to enable early detection and timely treatment of HHV-8/KSHV-associated diseases, especially KICS. It provides important clinical evidence supporting proactive surveillance strategies to improve outcomes in this high-risk population.
- Nambiar PH, Liang T, Labo N, et al (2025) Kaposi Sarcoma–Associated Herpesvirus Risk and Disease in Kidney Donors and Transplant Recipients With Human Immunodeficiency Virus in the United States. Clin Infect Dis. https://doi.org/10.1093/cid/ciaf229.
  - ○The authors investigate the risk and clinical impact of HHV-8/KSHV infection in kidney donors and transplant recipients with HIV in the U.S., offering valuable insights into donor-derived transmission, disease burden, and post-transplant complications.
- Cesarman E, Chadburn A, Rubinstein PG (2022) KSHV/HHV8-mediated hematologic diseases. Blood 139:1013–1025.

○Cesarman et al. provide a comprehensive overview of the hematologic disorders caused by KSHV/HHV8, detailing their pathogenesis, clinical features, and therapeutic approaches. This authoritative review is essential for understanding the complex spectrum of HHV-8/KSHV-associated lymphoproliferative diseases.

- Patel R, Lurain K, Yarchoan R, Ramaswami R (2023) Clinical management of Kaposi sarcoma herpesvirus-associated diseases: an update on disease manifestations and treatment strategies. Expert Rev Anti Infect Ther. https://doi.org/10.1080/14787210.2023.2247161.

○The authors offer an up-to-date review of the clinical manifestations and evolving treatment strategies for KADs. This article is valuable for clinicians seeking current guidance on managing the diverse presentations of HHV-8/KSHV-related conditions, including Kaposi sarcoma and associated lymphoproliferative disorders.

- Zhou T, Yuan CM, Lurain K, et al (2023). A novel approach for characterization of KSHV-associated multicentric Castleman disease from effusions. Br J Haematol 200:462–475.

○Zhou and colleagues, using multiparameter flow cytometry, studied the cellular populations in the body-cavity effusions of patients with MCD and KICS and observed the presence lambda-restricted plasmablasts, responsible for cytokine production, in some of these patients. Their work advances understanding of MCD and KICS pathology.

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Declarations

Competing Interests The authors declare no competing interests.

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