Journal of Infection 90 (2025) 106366

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Review

Clinical management of human herpesvirus-8-related illnesses in solid organ transplant recipients

Alessia Dalla Pria [a,b,*], Ines Ushiro-Lumb [c], Mark Bower [a,b]

[a] Department of Oncology and National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London, UK
[b] Centre for Immunology and Vaccinology, Department of Infectious Diseases, Imperial College, London, UK
[c] Organ and Tissue Donation and Transplantation, NHS Blood and Transplant (NHSBT), London, UK

ARTICLE INFO

Article history:
Accepted 23 November 2024
Available online 2 January 2025

Keywords:
Solid organ transplant
Graft-related infection
Primary infection
Post-transplant Kaposi Sarcoma
KSHV
HHV8

SUMMARY

In solid organ transplant recipients (SOTRs), the oncogenic virus human herpesvirus-8 (HHV-8) also named Kaposi sarcoma herpesvirus (KSHV) causes four clinical diseases: Kaposi Sarcoma, Primary Effusion Lymphoma, Multicentric Castleman Disease (MCD), and KSHV inflammatory cytokine syndrome (KICS). This review outlines these clinical scenarios and discusses their management. Although HHV8-related disease in SOTR was first described more than three decades ago, there is a lack of data on treatment so much of the guidance is based on evidence in other immunodeficient patients, particularly people living with HIV. Whilst reduction of immunosuppression and switch from calcineurin inhibitors to mTOR inhibitors may be sufficient in early-stage post-transplant KS, systemic chemotherapy is necessary for advanced-stage KS and in KSHV-related lymphomas. For MCD and KICS, which usually follow primary HHV-8 infection, rituximab-based immunochemotherapy regimens are the cornerstone of treatment for these potentially lethal diseases. Although HHV-8 infection in SOTR is well recognized, it remains under-reported and greater awareness of the different clinical presentations of HHV-8 in this context is fundamental to improve outcomes.

Introduction

Infection is a leading cause of increased morbidity and mortality in solid organ transplant recipients (SOTRs), and the long-term risk of malignancy is also significantly higher in this population. Herpesviruses are well-known opportunistic pathogens in this setting and Epstein Barr virus (EBV), an oncogenic gamma herpesvirus, is linked to post-transplant lymphoproliferative disease (PTLD). The closely related oncogenic virus Human Herpesvirus type 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), is causally associated with several manifestations in immune-suppressed individuals. In SOTRs, this may follow primary infection (from an HHV-8 seropositive donor to a seronegative recipient) or from viral reactivation in a previously infected recipient following iatrogenic immunosuppression to prevent graft rejection. Graft-related primary HHV-8 infection in SOTR has long been recognized but is infrequently reported, possibly due to diagnostic limitations and low case ascertainment. All forms of HHV-8-associated disease have been described following graft-related primary HHV-8 infection. They are often associated with high HHV-8 load in blood and poor outcomes. The increasing awareness and testing in the UK has led to the recognition of graft-related primary infection, along with the challenging clinical management of these rare diseases. Although HHV-8-related disease in SOT were first described in 1991, relatively few publications have addressed optimal clinical management, so much of the advice is based upon published experience from people living with HIV (PLWH).

HHV-8-related diseases in the post-transplant period

Recognizing primary HHV-8 infection can be particularly demanding in the complex setting of post-solid organ transplantation. The presentation often overlaps with other, much more common clinical entities so awareness and a low threshold for investigation are required. In our experience, primary HHV-8 infection in SOTR is usually followed by the production of specific antibodies and detectable viral deoxyribonucleic acid (DNA) in blood within weeks of transplantation. This is characteristic of herpesviruses, with

* Corresponding author at: Department of Oncology and National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London, UK.
E-mail addresses: a.dalla-pria17@imperial.ac.uk (A. Dalla Pria), Ines.Ushiro-Lumb@nhsbt.nhs.uk (I. Ushiro-Lumb), m.bower@imperial.ac.uk (M. Bower).

https://doi.org/10.1016/j.jinf.2024.106366

establishment of long-life infection and when disease ensues, symptoms usually become apparent within the first 6 months after infection. Early diagnosis of disease should allow treatment, based on the experience in PLWH and the slowly growing experience in SOTR. This article outlines the evidence, aiming to inform the management of post-transplant HHV-8 disease. (See Table 1 for a summary).

Post-transplant Kaposi Sarcoma (PT-KS)

Kaposi Sarcoma (KS), the most common HHV-8-related disease in SOTR, is reported to be 200-fold more frequent in this group than in the general population.[1] A recent meta-analysis of 15 studies (including 323 subjects) reported that 1.5% kidney transplant recipients develop PT-KS, with higher rates in Africa and the Middle East than in Western Europe.[2] This geographic variation in PT-KS incidence mirrors the population seroprevalence of HHV-8 which varies from around 40% in South Africa, to 10% in Middle East and 2–4% in Northern Europe.[3] PT-KS that develops shortly after SOT, usually within the first 6 months, is believed to represent primary HHV-8 infection and often has a more aggressive natural history with rapidly progressive disease and visceral involvement. In contrast, late presentation of PT-KS several years after transplantation is believed to relate to reactivation of latent pre-existing HHV-8 infection and frequently follows a more benign course.

The management of PT-KS is mainly based on case reports and expert opinion.[4,5] Three strategies are used: (i) reduction of immunosuppression, (ii) conversion from calcineurin inhibitors (CNI), such as tacrolimus and cyclosporin, to mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus (iii) systemic chemotherapy. A systematic review published in 2024, including six retrospective case series reporting on a total of 68 patients, revealed that reduction or withdrawal of immunosuppression results in remission of PT-KS in 48%.[2] Similar results were published from a multicenter retrospective European cohort study that included 145 SOT recipients diagnosed with KS between 1985 and 2011.[5] The clinical management of PT-KS was reduction of immunosuppression (95%), conversion from calcineurin inhibitors (CNI) to mammalian target of rapamycin (mTOR) inhibitors (28%), and chemotherapy (16%). At 6 months, the reported overall response rate was 83% with 40% complete responses. Systemic chemotherapy is usually reserved for advanced PT-KS with visceral involvement or rapid disease progression. In general, chemotherapy for PT-KS is based on experience in HIV-associated KS, and liposomal anthracyclines are used as first-line therapy and taxanes as second-line.

Post-transplant -Primary Effusion Lymphoma (PT-PEL)

PEL are large B-cell lymphomas that present as serous effusions in the absence of lymph node masses. A histologically related entity that presents with tumor masses, usually at extranodal sites, is called solid or extracavitary PEL (ePEL). PEL is associated with productive HHV-8 infection, and about 80% of cases have demonstrable Epstein-Barr virus (EBV) co-infection.

To our knowledge, just 15 cases of PEL have been described in SOT recipients[6–16] since the first report of fatal post-transplantation PEL in 1998.[17] Hence, clinical guidance is based on expert opinion, retrospective case reports and experience in PLWH. There is little evidence that modification of immunosuppression is beneficial in PT-PEL, even though sirolimus is effective against PEL cell lines *in vitro* where it is primarily cytostatic; indeed PT-PEL has been reported in SOT recipients receiving mTORi.[18] The treatment of PT-PEL with systemic combination chemotherapy regimens is based upon the approach used in HIV-associated PEL.

Table 1
Clinicopathological features of HHV-8 associated diseases in Solid Organ Transplant recipients.

	Kaposi Sarcoma (KS)	Primary Effusion Lymphoma (PEL)	Extra cavitary Primary Effusion Lymphoma (ePEL)	Multicentric Castleman Disease (MCD)	KSHV Inflammatory Cytokine Syndrome (KICS)
Presentation	• Cutaneous or mucosal lesions • Visceral involvement (most frequent sites lungs, gastro-intestinal tract)	• Serous effusions (pleural, pericardial, ascites)	• Extranodal masses or lymphadenopathy	• Generalized lymphadenopathy • Splenomegaly • Constitutional symptoms	• Constitutional symptoms • No lymphadenopathy/ masses
Microscopy	• Vascular proliferation in the dermis with slit-like spaces • Extravasated blood • Inflammatory infiltrate	• Large plasmablasts / immunoblasts in serous effusions usually with prominent nucleoli and abundant basophilic, amphophilic, or vacuolated cytoplasm	• Sheets of large pleomorphic cells with plasmablastic, immunoblastic, or anaplastic morphology effacing architecture	• Abnormal follicles • Plasmablasts predominantly in mantle zones • Interfollicular plasma cell hyperplasia	Not applicable
Phenotype	CD34+	CD30+ CD45+ CD138+ MUM1+ CD20-	CD30+ CD45+ CD138+ MUM1+ CD20-	IgM lambda + CD138- PAX5- CD20+/- CD79a +/-	Not applicable
Clonality	Monoclonal	Monoclonal	Monoclonal	Polyclonal	Not applicable
HHV-8 LANA[a]	+	+	+	+	Not applicable
EBER[b]	-	80%–100% +	80%–100% +	-	Not applicable
Treatment	• Reduction of immunosuppression • Switch to mTOR inhibitor • Liposomal anthracycline chemotherapy	• EPOCH and rituximab if CD20+	• EPOCH and rituximab if CD20+	• Rituximab +/- chemotherapy (etoposide or liposomal anthracycline if concomitant KS)	• Rituximab +/- chemotherapy (etoposide or liposomal anthracycline if concomitant KS)

[a] HHV-8 Latent Nuclear Antigen.
[b] Epstein-Barr virus-encoded small RNAs.

Most PEL do not express CD20, so we recommend dose-adjusted EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin) rather than standard CHOP because of the poor overall survival reported with the latter (40 to 50%). In 6 HIV-negative elderly patients with refractory PEL, intracavitary cidofovir after conventional chemotherapy failure achieved durable remission.[19] In the context of SOT, PT-PEL has been described in liver, kidney and heart transplant recipients. Most patients reported in the literature were treated with heterogeneous approaches such as reduction of iatrogenic immunosuppression, intra-cavitary cidofovir and chemotherapy regimens including Bortezomib. Where follow-up data were available, cytotoxic treatment courses were rarely completed, and overall survival was only 4 months.[20]

Post-transplant HHV-8 associated Multicentric Castleman Disease (PT-MCD)

HHV-8-associated MCD is a polyclonal lymphoproliferation that presents with generalized lymphadenopathy, splenomegaly and profound cytokine-related inflammatory symptoms. In MCD the B lymphocytes present in lymph node mantle zones harbor HHV-8 and express lambda light chains together with IgM heavy chains. HHV-8 associated MCD occurs rarely in SOT recipients; 15 cases have been described in the literature to date, although under reporting is likely.[21–33] Uncontrolled infection with HHV-8, which can occur with significant immunosuppression, results in profound cytokine release from the host along with the secretion by HHV-8 of a viral homologue of interleukin 6 (vIL6), leading to MCD. If MCD is not promptly recognized, it is associated with substantial morbidity and mortality. Signs and symptoms include fever, fatigue, night sweats, lymphadenopathy and hepatosplenomegaly. These features of acute systemic inflammatory illness and multi-organ failure can easily be mistaken for severe sepsis. Given the overlapping presentation with other common processes, diagnosis requires urgent blood tests, including inflammatory makers and HHV-8 DNA measurements in blood, radiological imaging to establish extent of disease and prompt excisional lymph node biopsy seeking features of PT-MCD.

There is limited experience in the treatment of MCD in the context of SOT. Based on substantial experience and favorable outcomes (5 years overall survival 92%) in the treatment of MCD in the HIV population[34] and limited data on successfully treated SOT recipients,[35,32,33] we suggest a rituximab-based approach to treat these patients. Reduction of immunosuppression may be a concomitant strategy, but as immune reconstitution from antiretroviral therapy in HIV patients does not prevent or treat MCD, it cannot be considered an effective treatment on its own. We also support switching from CNI to mTOR inhibitors. This is based on the antiproliferative, and antiangiogenic effects demonstrated in KS[36] and the common etiology of KS and MCD in immunosuppressed patients; furthermore, mTOR activation has been demonstrated in HHV-8 positive MCD. Additional support comes from case reports of the benefits of sirolimus in tocilizumab-refractory idiopathic (HHV-8 negative) MCD.[37,38] Also, successful use of immunosuppression reduction and switch from tacrolimus has been reported in a pediatric case of PT-MCD.[27] This strategy of switching to an mTOR inhibitor has the theoretical extra benefit of reducing the risk of KS progression that is associated with anti-CD20 monoclonal antibody therapy.[39] We would also consider adding etoposide (or liposomal anthracyclines if there is concomitant KS) to rituximab in patients with aggressive disease as is done in the risk-stratified approach in HIV-associated MCD with good outcomes.[40]

Although several anti-herpesvirus agents have demonstrable *in vitro* activity against HHV-8, their clinical utility has not been established. One liver recipient affected by systemic PT-MCD was successfully treated with valganciclovir and cyclosporin,[29] in contrast cidofovir and reduction of immunosuppression was ineffective in another patient.[28] Both ganciclovir and its oral derivative valganciclovir have also been explored in HIV-associated MCD but neither achieved the impressive remission rates documented with rituximab in much larger studies.[41] Although there is a theoretical basis to use antivirals in the setting of active viral replication, particularly in the very early stages of the disease process, we would advise against using antiviral treatment alone for the treatment of this condition. If the patient relapses, we would re-challenge with a rituximab-based therapy because we have demonstrated a 100% response rate in at MCD relapse in HIV patients.[34] The risk of lymphoma in PLWH with HHV-8 positive MCD is extremely high and may affect up to one in five patients[42,43] and in one series was the most frequent cause of death.[44] In many cases the lymphomas were positive for HHV-8 and most frequently were classified as PEL and HHV-8 positive plasmablastic lymphomas; both have a very poor prognoses.

Post transplant KSHV inflammatory cytokine syndrome (PT-KICS)

A relatively new clinical entity, termed KSHV inflammatory cytokine syndrome (KICS), has been recognized in PLWH.[45] Patients with KICS present with severe inflammatory symptoms, with high HHV-8 viral loads and cytokine profiles similar to those seen in MCD, including high levels of both hIL-6 and vIL-6.[11] Symptoms associated with KICS are also similar to those of MCD patients but there is no generalized lymphadenopathy and no histological evidence of MCD.[45] Like MCD, KICS patients have elevated levels of IL-6 and IL-10[45], and may also have other HHV-8-associated tumors.

KHSV Inflammatory Cytokine Syndrome (KICS) shares clinical features with MCD, is linked to the lytic phase of HHV-8 replication and is associated with HHV-8 polyclonal lymphoproliferation (analogous to EBV-PTLD), plasmacytosis, acute bone marrow failure, hemophagocytic syndrome (HPS), pancytopaenia and acute hepatitis.[35] These clinicopathological features of KICS have been described in several SOT recipients.[46–49] Multiple forms of HHV-8 related illnesses such as KS, MCD, KICS and haemophagocytic lymphohistiocytosis (HLH) can present concomitantly.[50] In light of the similarities of the clinical manifestations of HHV-8 associated primary infection in SOT and HIV-associated MCD/KICS and in consideration of two successfully SOT case treated with rituximab[51,52] we would recommend the same approach described for PT-MCD.

This approach comprises of reduction of immunosuppression, anti-CD20 antibody therapy with additional systemic chemotherapy in life-threatening cases, and the use of antiviral agents in the presence of high HHV-8 viraemia, considering reports of successful treatment of primary HHV-8 primary infection with foscarnet.[47] Significant elevation of liver enzymes can be a feature of donor-derived primary HHV-8 infection and it can be particularly severe in liver allograft recipients. Two published cases [28] describe the onset of acute hepatitis accompanied by pleural and peritoneal effusions, no response to antiviral treatment with cidofovir, and progression to multiorgan failure and death. As previously discussed, given the pathogenesis of HHV-8 disease, antivirals should only be considered as one element of the treatment strategy. Delayed use of immunochemotherapy in the context of MCD/KICS in primary HHV-8 infection may lead to a lethal outcome, which cannot be prevented by the sole use of anti-herpesvirus agent.

Tocilizumab, a humanized antibody that targets gp80 (human IL-6 receptor) has demonstrated clinical benefit in idiopathic (HHV-8 negative) MCD. It has been used as a part of a multiagent regimen alongside Rituximab, and in Rituximab refractory cases of MCD and KICS. However, the viral homologue vIL6 bypasses gp80 by binding directly to the gp130 subunit of the IL6 receptor.[53]

Conclusion

Unlike other members of the human herpesvirus family, HHV-8 infection is not ubiquitous and there are endemic regions of high seroprevalence and non-endemic countries. HHV-8-related disease

in SOTR mirrors this geographic distribution and is uncommon in UK, but increased awareness of the various disease presentations is leading to a slow rise in case ascertainment. Although much remains to be learnt about the real impact of HHV-8 in SOTRs, it is important for diagnostic and treatment experiences to be shared, with the aim of improving outcomes for patients who develop symptomatic disease.

Declaration of Competing Interest

The authors have no conflict of interest that could have influenced this manuscript.

References

1. Grulich AE, Vajdic CM. *The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. Semin Oncol* 2015;**42**:247–57. https://doi.org/10.1053/j.seminoncol.2014.12.029
2. Saowapa S, Polpichai N, Siladech P, Wannaphut C, Tanariyakul M, Wattanachayakul P, et al. *Evaluating Kaposi sarcoma in kidney transplant patients: a systematic review and meta-analysis. Cureus* 2024;**16**(1):e52527. https://doi.org/10.7759/cureus.52527. PMID: 38371002; PMCID: PMC10874301.
3. Ablashi DV, Chatlynne LG, Whitman JE, Cesarman E. *Spectrum of Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8, diseases. Clin Microbiol Rev* 2002;**15**:439–64. https://doi.org/10.1128/CMR.15.3.439-464.2002
4. Riva G, Luppi M, Barozzi P, Forghieri F, Potenza L. *How I treat HHV8/KSHV-related diseases in posttransplant patients. Blood* 2012;**120**:4150–9. https://doi.org/10.1182/blood-2012-04-421412
5. Delyon J, Rabate C, Euvrard S, Harwood CA, Proby C, Güleç AT, et al. *Management of Kaposi sarcoma after solid organ transplantation: a European retrospective study. J Am Acad Dermatol* 2019;**81**:448–55.
6. Dotti G, Fiocchi R, Motta T, Facchinetti B, Chiodini B, Borleri GM, et al. *Primary effusion lymphoma after heart transplantation: a new entity associated with human herpesvirus-8. Leukemia* 1999;**13**:664–70. https://doi.org/10.1038/sj.leu.2401390
7. Régnier-Rosencher E, Barrou B, Marcelin AG, Jacobzone-Leveque C, Cadranel J, Leblond V, Francès C. *Primary effusion lymphoma in two kidney transplant recipients. Ann Dermatol Venereol* 2010;**137**:285–9.
8. Shi Y, Hou Y, Hu Q, Su J, Zeng H, Tan Y. *A rare case of HHV-8-positive/HIV-negative/EBV-negative primary effusion lymphoma in a renal transplant recipient. Cytopathology* 2012;**23**:137–9. https://doi.org/10.1111/j.1365-2303.2012.00960.x
9. Shaw RN, Waller EK, Offermann MK. *Induction of human herpesvirus 8 gene expression in a post-transplantation primary effusion lymphoma cell line. Leuk Lymphoma* 2002;**43**:631–4.
10. Christenson ES, Teply B, Agrawal V, Illei P, Gurakar A, Kanakry JA. *Human herpesvirus 8-related primary effusion lymphoma after liver transplantation. Am J Transplant* 2015;**15**:2762–6.
11. Testa A, Baiocchini A, Comandini UV, Falasca L, Nardacci R, Maritti M, et al. *Fatal sclerosing peritonitis associated with primary effusion lymphoma after liver transplantation: a case report. Transplant Proc* 2010;**42**:3849–53.
12. Melo NC, Sales MM, Santana AN, Costalonga EC, Pedreira AB, Ianhez LE. *Pleural primary effusion lymphoma in a renal transplant recipient. Am J Transplant* 2008;**8**:906–7. https://doi.org/10.1111/j.1600-6143.2008.02156.x
13. Kalogeraki A, Haniotis V, Karvelas-Kalogerakis M, Karvela-Kalogeraki I, Psyllaki M, Tamiolakis D. *Primary effusion lymphoma with aberrant T-Cell phenotype in an iatrogenically immunosuppressed renal transplant male: cytologic diagnosis in peritoneal fluid. Diagn Cytopathol* 2015;**43**:144–8.
14. Wang HY, Fuda FS, Chen W, Karandikar NJ. *Notch1 in primary effusion lymphoma: a clinicopathological study. Mod Pathol* 2010;**23**:773–80.
15. Kugasia IR, Kumar A, Epelbaum O. A Rare Case Of Primary Effusion Lymphoma Post Cardiac Transplant With Hiv Negative And Hhv8 Positive Serology; 2017.
16. Man O, Jayakumar R, Haseeb MA, Gupta R, MD; SUNY Downstate MedicalCenter, Brooklyn, NY. 2018 (2018) doi:10.1093/AJCP/AQX121.
17. Jones D, Ballestas ME, Kaye KM, Gulizia JM, Winters GL, Fletcher J, et al. *Primary-effusion lymphoma and Kaposi's sarcoma in a cardiac-transplant recipient. N Engl J Med* 1998;**339**:444–9.
18. Boulanger E, Afonso PV, Yahiaoui Y, Adle-Biassette H, Gabarre J, Agbalika F. *Human herpesvirus-8 (HHV-8)-associated primary effusion lymphoma in two renal transplant recipients receiving rapamycin. Am J Transplant* 2008;**8**:707–10.
19. Moyo TK, Richards KL, Damania B. *Use of cidofovir for the treatment of hiv-negative human herpes virus-8-associated primary effusion Lymphoma. Clin Adv Hematol Oncol* 2010;**8**:372–4.
20. Christenson ES, Teply B, Agrawal V, Illei P, Gurakar A, Kanakry JA. *Human herpesvirus 8-related primary effusion lymphoma after liver transplantation. Am J Transplant* 2015;**15**:2762–6.
21. Mandel C, Silberstein M, Hennessy O. *Fatal pulmonary Kaposi's sarcoma and Castleman's disease in a renal transplant recipient. Br J Radiol* 1993;**66**:264–5.
22. Parravicini C, Corbellino M, Paulli M, Magrini U, Lazzarino M, Moore PS, Chang Y. *Expression of a virus-derived cytokine, KSHV vIL-6, in HIV-seronegative Castleman's disease. Am J Pathol* 1997;**151**:1517–22.
23. Ǧağirgan S, Cirit M, Ok E, Sencan M, Hekimgil M, Unsal A, et al. *Castleman's disease in a renal allograft recipient. Nephron* 1997;**76**:307–9. https://doi.org/10.1159/000190204
24. Theate I, Michaux L, Squifflet JP, Martin A, Raphael M. *Human herpesvirus 8 and Epstein-Barr virus-related monotypic large B-cell lymphoproliferative disorder co-existing with mixed variant of Castleman's disease in a lymph node of a renal transplant recipient. Clin Transplant* 2003;**17**:451–4.
25. Gaitonde S, Vidanovic V, Ni H. *Concomitant and fatal HHV-8+ multicentric Castleman's disease and Kaposi's sarcoma in the same lymph node of an HIV- liver transplant patient. Histopathology* 2007;**50**(7):954–6. https://doi.org/10.1111/j.1365-2559.2007.02702.x
26. Al Otaibi T, Al Sagheir A, Ludwin D, Meyer R. *Post renal transplant Castleman's disease resolved after graft nephrectomy: a case report. Transplant Proc* 2007;**39**:1276–7.
27. B HJR, et al. *Castleman disease in a pediatric liver transplant recipient: a case report and literature review. Pediatr Transplant* 2012;**16**:E229–34.
28. Pietrosi G, Vizzini G, Pipitone L, Di Martino G, Minervini MI, Lo Iacono G, et al. *Primary and reactivated HHV8 infection and disease after liver transplantation: a prospective study. Am J Transplant* 2011;**11**:2715–23.
29. Lim EJ, Crowley P, Mitchell CA, Angus PW. *Post-liver transplantation multicentric castleman disease treated with valganciclovir and weaning of immunosuppression. Am J Transplant* 2011;**11**:169–72.
30. Guglielmo N, Melandro F, Levi Sandri G, Fiacco F, Di Laudo M, Mitterhoffer A, et al. *Concurrent and fatal HHV-8 positive multicentric Castleman's disease and Kaposi's Sarcoma in a HIV negative kidney transplant recipient. Transplant J* 2012;**94**:832.
31. Vijgen S, Wyss C, Meylan P, Bisig B, Letovanec I, Manuel O, et al. *Fatal outcome of multiple clinical presentations of human herpesvirus 8-related disease after solid organ transplantation. Transplantation* 2016;**100**:134–40.
32. Speicher DJ, Sehu MM, Mollee P, Shen L, Johnson NW, Faoagali JL. *Successful treatment of iatrogenic multicentric Castleman's disease arising due to recrudescence of HHV-8 in a liver transplant patient. Am J Transplant* 2014;**14**:1207–13.
33. Jha LK, Ulmer LL, Olivera-Martinez MA, McCashland TM, Fu K, Rochling FA. *Castleman's disease and posttransplant lymphoproliferative disorder after liver transplant: 3-year follow-up. Case Rep Hepatol* 2018;**2018**:1–3.
34. Pria AD, Pinato D, Roe J, Naresh K, Nelson M, Bower M. *Relapse of HHV8-positive multicentric Castleman disease following rituximab-based therapy in HIV-positive patients. Blood* 2017;**129**:2143–7.
35. Riva G, Luppi M, Barozzi P, Forghieri F, Potenza L. *How I treat HHV8/KSHV-related diseases in posttransplant patients. Blood* 2012;**120**:4150–9. https://doi.org/10.1182/blood-2012-04-421412
36. Delyon J, Rabate C, Euvrard S, Harwood CA, Proby C, Güleç AT, et al. *Management of Kaposi sarcoma after solid organ transplantation: a European retrospective study. J Am Acad Dermatol* 2019;**81**:448–55.
37. Liu YT, Gao YH, Zhao H, Zhang MY, Duan MH, Li J, et al. *Sirolimus is effective for refractory/relapsed idiopathic multicentric Castleman disease: a single-center, retrospective study. Ann Hematol* 2024;**103**(10):4223–30. https://doi.org/10.1007/s00277-024-05783-z. Epub 2024 May 1. PMID: 38691144.
38. Bayram E, Pehlivan UA, Fajgenbaum DC, Paydas S. *Refractory idiopathic multicentric Castleman disease responsive to sirolimus therapy. Am J Hematol* 2023;**98**:361–4. https://doi.org/10.1002/ajh.26783
39. Bower M, Powles T, Williams S, Davis TN, Atkins M, Montoto S, et al. *Brief communication: rituximab in HIV-associated multicentric Castleman disease. Ann Intern Med* 2007;**147**:836–9.
40. Bower M. *How I treat HIV-associated multicentric Castleman disease. Blood* 2010;**116**:4415–21. https://doi.org/10.1182/blood-2010-07-290213
41. Gérard L, Bérezné A, Galicier L, Meignin V, Obadia M, De Castro N, et al. *Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus-associated multicentric Castleman's disease: ANRS 117 CastlemaB trial. J Clin Oncol* 2007;**25**:3350–6.
42. Oksenhendler E, Boulanger E, Galicier L, Du MQ, Dupin N, Diss TC, et al. *High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. Blood* 2002;**99**:2331–6.
43. Gérard L, Michot JM, Burcheri S, Fieschi C, Longuet P, Delcey V, et al. *Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. Blood* 2012;**119**:2228–33.
44. Pria AD, Pinato D, Roe J, Naresh K, Nelson M, Bower M. *Relapse of HHV8-positive multicentric Castleman disease following rituximab-based therapy in HIV-positive patients. Blood* 2017;**129**:2143–7.
45. Polizzotto MN, Uldrick TS, Wyvill KM, Aleman K, Marshall V, Wang V, et al. *Clinical features and outcomes of patients with symptomatic Kaposi sarcoma herpesvirus (KSHV)-associated inflammation: prospective characterization of KSHV inflammatory cytokine syndrome (KICS). Clin Infect Dis* 2016;**62**:730–8.
46. Luppi M, Barozzi P, Schulz TF, Setti G, Staskus K, Trovato R, et al. *Bone marrow failure associated with human herpesvirus 8 infection after transplantation. N Engl J Med* 2000;**343**:1378–85.
47. Luppi M, Barozzi P, Rasini V, Riva G, Re A, Rossi G, et al. *Severe pancytopenia and hemophagocytosis after HHV-8 primary infection in a renal transplant patient successfully treated with foscarnet. Transplantation* 2002;**74**:131–3.
48. Karras A, Thervet E, Legendre C. *Hemophagocytic syndrome in renal transplant recipients: report of 17 cases and review of literature. Transplantation* 2004;**77**:238–43.
49. Cohen GM, Langer AL, Sima H, Chang C, Troy K, Taimur S. *Hemophagocytic lymphohistiocytosis due to primary HHV-8 infection in a liver transplant recipient. Transplant Direct* 2018;**4**:411.
50. Vijgen S, Wyss C, Meylan P, Bisig B, Letovanec I, Manuel O, et al. *Fatal outcome of multiple clinical presentations of human herpesvirus 8-related disease after solid organ transplantation. Transplantation* 2016;**100**:134–40.

51. Thaunat O, Mamzer-Bruneel MF, Agbalika F, Valensi F, Venditto M, Lebbe C, et al. *Severe human herpesvirus-8 primary infection in a renal transplant patient successfully treated with anti-CD20 monoclonal antibody [1]. Blood* 2006;**107**:3009–10. https://doi.org/10.1182/blood-2005-08-3213
52. Peri AM, Magro B, van den Bogaart L, Dalla Pria A, Giuffrida P, Gianatti A, et al. *Successful treatment of suspected donor-derived human herpesvirus-8 infection in a liver transplant patient with coronavirus disease-19. Transplantation* 2021;**105**:E65–7. https://doi.org/10.1097/TP.0000000000003684
53. Ramaswami R, Lurain K, Peer CJ, Serquiña A, Wang V, Widell A, et al. *Tocilizumab in patients with symptomatic Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Blood* 2020;**135**:2316–9. https://doi.org/10.1182/blood.2019004602