Fatal donor-derived Kaposi sarcoma following liver transplantation

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SUMMARY

Human herpesvirus-8 (HHV8) is a recognised precursor for a number of neoplastic and non-neoplastic processes. Immunosuppressed recipients of both solid organ and haematopoietic stem cell transplants are at risk of life-threatening lytic reactivations of HHV8-infected B-lymphocytes, primary infections after receiving grafts from HHV8-seropositive donors and more rarely by the direct transplantation of malignant Kaposi sarcoma cells seeded within graft tissue. We describe the case of an HHV8-seronegative patient with confirmed, post-orthotopic liver transplant transmission of HHV8 from a seropositive donor with quantitative evidence of viraemia and subsequent development of disseminated visceral and cutaneous Kaposi sarcoma with a rapidly fatal outcome.

BACKGROUND

Human herpesvirus-8 (HHV8), also known as Kaposi sarcoma herpesvirus presents a number of clinical difficulties in the post-transplant period. In immunosuppressed solid organ recipients, latent human gamma-herpesvirus, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV) and HHV8 are responsible for a number of oncogenic processes.[1] EBV and HHV8 have the ability to infect B-lymphocytes, persisting lifelong in latent form.[1] From time-to-time, the virus reactivates its lytic replicative cycle, because of a decrease in virus-specific cell-mediated immunity, producing an acute viraemia.

Iatrogenic immunosuppression plays a fundamental role in reducing the risk of graft rejection; however, it may precipitate HHV8 lytic reactivations causing clonal expansion of latently infected lymphoid cells. Alternatively, as in the case of our patient, HHV8-related post-transplant diseases may result from acute primary infection, followed by rapid seroconversion after receiving graft tissue from an HHV8-seropositive donor. Within the immunocompromised individual, impaired CD8+ T lymphocyte responses mean HHV8 replication is unchecked, favouring oncogenic processes. Furthermore, Kaposi sarcoma may directly originate from donor-derived HHV8-positive cells, seeded within graft tissue.[1 2]

CASE PRESENTATION

We present the case of a 69-year-old woman with a history of primary biliary cholangitis with liver cirrhosis. She underwent orthotopic liver transplant (OLT) following a donation after brainstem death (DBD). Pre-transplant donor variables: blood group, O Rh–; CMV status, positive; EBV status, negative and toxoplasmosis status, negative. Recipient variables: blood group, O Rh–; CMV status, negative; EBV status, positive and toxoplasmosis status, negative. The patient received oral valganciclovir for 3 months post-transplant as per standard protocol. Post-transplant immunosuppression was prednisolone and tacrolimus.

Five months following OLT she presented with an acute kidney injury (AKI), hyponatraemia, dyspnoea, fever and night sweats. Examination identified a well-defined, non-tender neck lump, in addition to a palmar/planter non-blanching maculopapular rash. Throughout her admission, there were a number of transient clinical manifestations such as (a) intermittent constitutional/inflammatory 'B-cell' type symptoms (fever, rigors, malaise, anorexia, polymyalgia and cutaneous manifestations), (b) transfusion-dependant pancytopenia, (c) respiratory symptoms (initially felt to be in keeping with an interstitial pneumonitis), (d) AKI (initially felt to be in keeping with a tubulointerstitial nephritis), (e) pleural effusions and (f) lymphadenopathy.

INVESTIGATIONS

Contrast-enhanced CT identified pulmonary nodules, lymphadenopathy and pleural effusions. In light of this, a provisional diagnosis of post-transplant lymphoproliferative disorder was made.

Core needle biopsy was carried out on the neck lump. Histopathological examination identified medullary lymphoid tissue with prominent vascular structures, scattered lymphocytes and plasma B-cells (figure 1). Small aggregates of lymphocytes were also present with no cytological abnormality. Immunohistochemistry with CD20, CD3, MIB1 and CD30 demonstrated no abnormal localisation. EBV-encoded RNA in situ hybridisation was negative. Initial histopathological features were non-diagnostic, with no evidence of lymphoma or metastatic malignancy. In light of the prominence of vascular structures, HHV8 immunostain was performed and was positive—conclusively identifying the presence of Kaposi sarcoma (figure 2). There were no features to suggest multicentric Castleman disease.

Following histopathological confirmation of Kaposi sarcoma, sirolimus was commenced. After 2 weeks, our patient was unable to tolerate side effects associated with sirolimus and was switched back to prednisolone and tacrolimus.

Positron emission tomography demonstrated increased tracer uptake within multiple lymph nodes and the liver (figure 3).[3] There was also evidence of a painless cutaneous Kaposi sarcoma,

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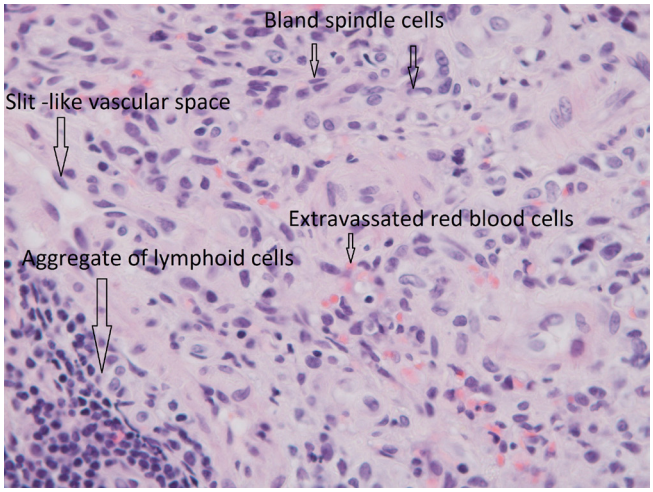

Figure 1 Histopathological specimen of lymphatic tissue (×40 magnification) illustrating an abnormal area of vascular proliferation, composed of bland spindle cells with many slit-like vascular spaces. There are extravasated red blood cells.

unusually within and overlying the scar of her OLT (figure 4). Cutaneous biopsy was not preformed because histopathological confirmation of Kaposi sarcoma had been obtained from the patient's lymph node. A diagnosis of disseminated visceral and cutaneous HHV8 Kaposi sarcoma was made.

Thoracentesis was performed on the pleural effusion. Flow cytometry identified erythrocytes and lymphocytes. Lymphocytes were almost exclusively T-cells with a normal CD4:CD8 ratio. There was no clonal B-cell population and no evidence of a B-cell non-Hodgkin lymphoma infiltrate. This excluded HHV8-neoplastic intracavity primary effusion lymphoma.

Clotted blood was tested for HHV8 viral load (quantitative DNA PCR) and immunofluorescence for HHV8 lytic antibodies. Samples taken from the donor at the time of donation tested positive for HHV8 lytic antibodies and HHV8 DNA was detected at a low copy number by PCR. Results demonstrate that the patient had detectable virus in blood within 3 weeks of OLT and was seroconverting by that time also (table 1).

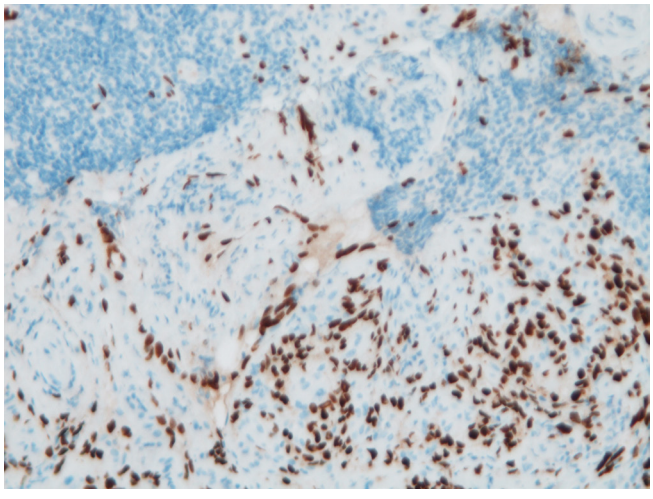

Figure 2 Histopathological specimen with HHV8 immunostain illustrating strong nuclear positivity.

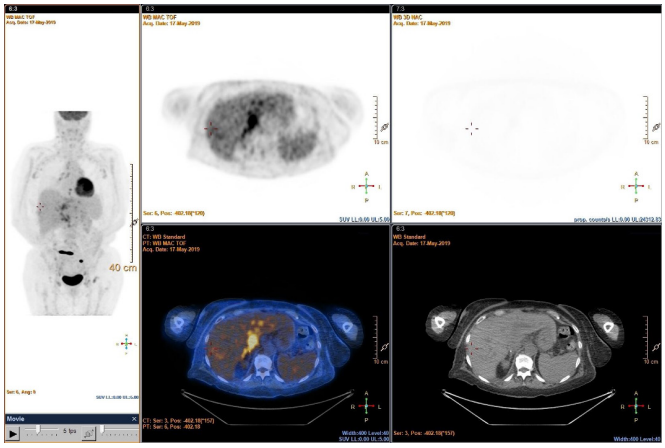

Figure 3 Staging PET illustrating increased nodal uptake within multiple lymph nodes in addition to inhomogeneous liver uptake. PET, positron emission tomography.

OUTCOME AND FOLLOW-UP

Retrospectively, we now know that within a 6month period post transplant our patient underwent primary HHV8 infection and seroconversion. The resultant oncogenic nature of HHV8, coupled with post-transplant immunosuppression resulted in the development of disseminated visceral and cutaneous Kaposi sarcoma. Within 3 weeks of diagnosis, the patient died.

DISCUSSION

This clinical case demonstrates transmission of HHV8 from a seropositive donor to a seronegative recipient with quantitative evidence of evolving viraemia and the subsequent development of disseminated visceral and cutaneous Kaposi sarcoma. Vijgen *et al*[4] conducted a detailed literature review of all cases associating more than one HHV8-related pathology after solid organ transplant. Recipients included the following: two heart transplants, five liver transplants and six kidney transplants. Kaposi sarcoma was present in all cases, however, only five demonstrated a cutaneous manifestation. In 38% of cases, HHV8 infection was considered as donor-derived, by serological and/or molecular diagnostics. To our knowledge, this is the first case to demonstrate cutaneous Kaposi sarcoma within a post-OLT scar (figure 4).

Unlike EBV and CMV, HHV8 is considered geographically restricted because seroprevalence is higher in certain regions of the world. Seropositivity is highest in sub-Saharan Africa (up to 50%) and the Mediterranean (up to 35%), while it is intermediate in South America (up to 16%) and Asia (up to 24%). In

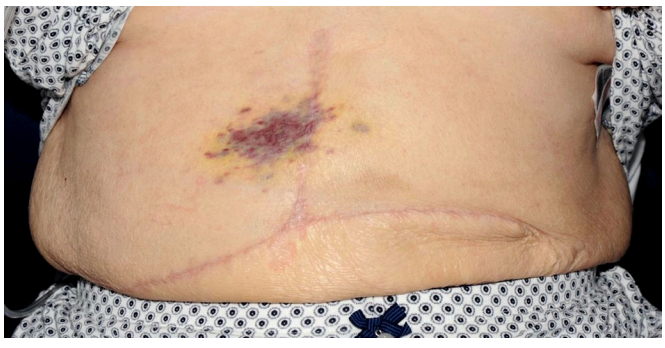

Figure 4 Image of cutaneous Kaposi sarcoma within the post-transplant scar.

Table 1 Illustration of the temporal evolution of post-transplant HHV8 viraemia and resultant seroconversion

Date	HHV8 lytic antibodies (immunofluorescence)	HHV8 DNA PCR
07/08/2018 (*pre-transplant*)	Negative	Not detected
19/11/2018 (*post-transplant*)	Negative	Not detected
30/11/2018	Weak +/–	Detected 100 cp/mL
26/12/2018	Positive 2+	Detected 57 cp/mL
22/01/2019	Positive 1+	Detected 720 cp/mL
18/04/2019	Positive 2+/1+	Detected 6400 cp/mL
09/05/2019	Weak +/–	Not tested
14/05/2019	Positive 2+	Not tested

Europe and North America (<6%), seropositivity is comparatively lower, however, studies have indicated substantially elevated seroprevalence in certain adult subgroup populations such as men who have sex with men (MSM), intravenous drug users and HIV-infected individuals.[2 4–6]

As previously discussed, HHV8 infection following solid organ transplant may occur either as primary infection in seronegative recipients or as secondary infection resulting from reactivation of latent virus within lymphoid cells. The incidence of primary HHV8 seroconversion following solid organ transplant is variable depending on the geographic area.[6] One French prospective study found a cumulative incidence between 28% and 29% in 454 solid organ recipients. HHV8 viraemia was detected in 4 of 89 liver transplant recipients, 2 of which developed Kaposi sarcoma.[7]

Another prospective French study found four primary HHV8 infections detected among the four HHV8-seronegative recipients who received a liver from an HHV8-positive donor. Among these four recipients, two particularly immunosuppressed patients died following disseminated Kaposi sarcoma and HHV8-positive lymphoproliferation.[8] Overall, however, reported incidences of Kaposi sarcoma in solid organ transplant recipients vary from as low as 0.5% in North America to as high as 28% in the Middle East.[9] HHV8 seroconversion within the haematopoietic stem cell transplant setting appears to be relatively uncommon in comparison to solid organ transplant, possibly because of chemotherapy and total body irradiation.[1] One Italian study, involving 187 bone marrow recipients reported no cases of HHV8 post-transplant Kaposi sarcoma.[10]

Risk factors associated with HHV8 infection following solid organ transplantation include (a) residence in an HHV8 endemic area, (b) receipt of an organ from a donor from an endemic region, (c) high-risk behaviours (MSM), (d) pre-transplant HHV8 seropositivity (latency), (e) iatrogenic immunosuppression (particularly with anti-lymphocyte agents) and (f) older age.[5 11]

The outcome of HHV8 syndromes is profoundly poor and is often associated with post-transplant immunosuppression.[4 5 12] Management of HHV8-related diseases goes beyond the scope of this case, yet we are keen to highlight that it elucidates the clinical predicament clinicians face when titrating immunosuppressive therapy—balancing the risks between graft rejection and overwhelming immunosuppression.

Evidence suggests that management strategies for post-transplant Kaposi sarcoma include immune reconstitution, for example, the reduction of immunosuppression and switching from calcineurin inhibitors to sirolimus.[2 13 14] Research indicates that sirolimus has anti-tumour effects, mediated by inhibition of the mechanistic target of rapamycin (mTOR), as well as anti-angiogenic effects mediated by impairing production of vascular endothelial growth factor.[15]

This case highlights that the identification of post-transplant HHV8 viraemic syndromes is challenging—often because of the temporal evolution and overlapping symptomatology between neoplastic (Kaposi sarcoma, multicentric Castleman disease and primary effusion lymphoma) and non-neoplastic diseases (HHV8-positive plasmacytic B-lymphocyte proliferations, bone marrow failure and acute hepatitis). In any case, HHV8-related illness should be suspected in the post-transplant setting in patients who present with constitutional, systemic symptoms or lymphadenopathy.[4] We also feel that diagnostic importance should be placed on obtaining histopathological diagnosis early, so far as possible. We have also demonstrated the importance of obtaining evidence of HHV8 viraemia—currently by detecting HHV8 DNA by PCR. Evidence suggests that the quantification of HHV8 viral load has usefulness in the prediction of HHV8 non-neoplastic processes and is also found to be associated with disease progression in the context of Kaposi sarcoma.[1 16 17] There is also scope for the use for flow cytometry in the identification and quantification of infected B-lymphocytes and as in our patient we found this clinically useful in the assessment of her pleural effusion.[18]

In conclusion, this case serves to demonstrate the risk posed by HHV8 in the post-transplant period. It also illustrates that HHV8-related post-transplant diseases can result from acute primary infections from seropositive donors, secondary infection from latently infected recipients, and that there is scope to consider the use of HHV8 serology during the pre-transplant evaluation of donors and recipients. Following this, HHV8 PCR may be used to detect acute viraemia which may facilitate timely diagnosis or consideration of HHV8 neoplastic and non-neoplastic syndromes; affording clinical teams the opportunity to track viral titres and adjust immunosuppression accordingly.

Learning points

- Human herpesvirus-8 (HHV8) viraemic syndromes should be suspected in the post-transplant period where a patient displays evolving and transient constitutional symptoms or lymphadenopathy.
- If available, consideration should be given to HHV8 serology and HHV8 DNA PCR testing.
- Clinical outcomes relating to HHV8 viraemic syndromes are poor, demonstrating the importance of early consideration and diagnosis with prompt reduction of immunosuppression.

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