Fatal Disseminated Kaposi's Sarcoma Following Human Herpesvirus 8 Primary Infections in Liver-Transplant Recipients

Anne-Geneviève Marcelin,[1] Anne-Marie Roque-Afonso,[2*] Monika Hurtova,[3] Nicolas Dupin,[4] Micheline Tulliez,[5] Mylène Sebagh,[6] Zaïna Ait Arkoub,[1] Catherine Guettier,[6] Didier Samuel,[3] Vincent Calvez,[1] and Elisabeth Dussaix[2]*

Human herpesvirus 8 (HHV-8) is associated with the development of Kaposi's sarcoma (KS) and rare lymphoproliferative disorders in immunosuppressed patients. The risk of HHV-8 transmission by liver transplantation and the clinical manifestations of primary infection in this setting have yet to be determined. In order to evaluate this risk, we measured the seroprevalence of HHV-8 among 122 liver donors and their respective recipients before and after transplantation. Molecular methods and immunohistochemical analyses were performed to study the features of HHV-8 infection. Antibodies to HHV-8 were detected in sera of 4 donors before transplantation (3.3%) and of 3 recipients (2.4%). None of the 3 recipients, who were HHV-8 seropositive before transplantation, developed a KS during the follow-up. Four primary HHV-8 infections were detected among the 4 HHV-8 seronegative recipients who received a liver from an HHV-8 positive donor. Among these 4 recipients, 2 particularly immunosuppressed patients developed symptomatic diseases and died a few months after transplantation, harboring disseminated KS and HHV-8 positive lymphoproliferation. In these 2 patients, HHV-8 DNA genome sequences were detectable in peripheral blood mononuclear cells and other tissues with high viremia levels before and at the beginning of HHV-8–related diseases. In conclusion, in liver transplantation recipients, HHV-8 primary infection can be associated with fatal outcome. This study raises the question of screening liver donors for HHV-8 — even in low HHV-8 infection prevalence countries—not systematically to exclude the graft but to monitor, clinically and biologically, patients who received a graft from an HHV-8–infected donor. (*Liver Transpl 2004;10:295–300.*)

Introduction

Human herpesvirus 8 (HHV-8; also known as Kaposi's sarcoma–associated herpesvirus) has been associated with all forms of Kaposi's sarcoma (KS), primary effusion lymphomas (PEL), and multicentric Castleman disease.[1,2,3] These malignancies have been described most frequently among patients infected with human immunodeficiency virus (HIV), but they have also been reported in transplant recipients.[4–9] Posttransplant KS is a relatively common malignancy of solid-organ transplant recipients, occurring 1000-fold more often than in age-matched control subjects with an incidence of 0.5–5%, and KS is more common among transplant recipients from areas associated with classic and endemic forms of KS.[10] One of the main approaches in the management of transplant-related KS is the reduction or discontinuation of immunosuppression, which is usually associated with regression of lesions. This approach may, however, be more difficult in non-renal transplant recipients (heart, lung, liver) in whom the loss of the graft due to reduction in immunosuppression could mean death unless retransplantation is performed.

Two mechanisms have been observed in post-kidney transplantation KS: HHV-8 reactivation, as a result of immunosuppressive treatment in patients infected before the graft, and in some cases primary HHV-8 infection transmitted via organ transplantation.[5,9,11–14]

In liver transplantation, whether primary HHV-8 infection, reactivation of infection, or both means led to KS or other HHV-8–related diseases has yet to be determined. We conducted a monocentric retrospective study among 122 liver donors and their respective recipients to assess the risk of HHV-8 transmission via liver donor and the subsequent occurrence of KS or other HHV-8–related diseases.

Abbreviations: HHV-8, human herpesvirus 8; KS, Kaposi's sarcoma; HIV, human immunodeficiency virus; LANA, latent nuclear antigen; IFA, immunofluorescence assay; PBMCs, peripheral blood mononuclear cells; HCMV, human cytomegalovirus.

From the Department of [1]Virology (UPRES 2387), Pitié-Salpêtrière Hospital, Paris, France; Departments of [2]Virology, [3]Hepatology, and [6]Pathology (UPRES 3541), Paul Brousse Hospital, Villejuif, France; Departments of [4]Dermatology and [5]Pathology, Cochin Hospital, Paris, France.

**Have equally contributed to this work.*

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Address reprint requests to Anne-Geneviève Marcelin, Department of Virology, Pitié-Salpêtrière Hospital, 83 Boulevard de l'hôpital, 75013 Paris, France. Telephone: 3314-217-7401; FAX: 3314-217-7411; E-mail: anne-genevieve.marcelin@psl.ap-hop-paris.fr.

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Methods

Patients and Specimens

From January 1999 to June 2001, 178 liver transplantations were performed at the Paul Brousse University Hospital Transplant Unit (Villejuif, France). Serum samples obtained on the day of transplantation from 122 recipients and their respective donors were available for analysis. The mean age of transplant recipients was 46 years (range 8–69) and the sex ratio was 2.7 (89 men and 33 women). Twelve of the recipients underwent both liver and kidney transplantation. Major indications of liver transplant were alcohol (21%) and hepatitis C–related cirrhosis (20.5%). Posttransplant immunosuppression included a calcineurin inhibitor (cyclosporine or tacrolimus) plus steroids. In cases of renal dysfunction, azathioprine or mycophenolate mofetil were added to lower the amount of calcineurin inhibitors. Twelve recipients died in the early postoperative period. Posttransplant sera were available for 99 of the remaining 110 recipients (4 to 6 months posttransplant). Follow-up visits were scheduled every month during the first year after transplantation and every 3 months subsequently for at least 2 years.

HHV-8 Antibody Detection

Antibodies to a latent nuclear antigen (LANA) of HHV-8 were detected using an immunofluorescence assay (IFA) on a PEL cell line (BC-3). The immunofluorescence assay was performed using a sera dilution of 1:100 as previously described in other studies in the context of organ transplantation.[5,12,14,15] The samples were read in a double-blind fashion. Samples showing specific reactivity at a 1:100 were considered positive for HHV-8 antibodies. Antibodies to HHV-8 lytic antigens were searched in posttransplant sera from HHV-8 seronegative recipients who received a graft from HHV-8 seropositive donors using an immunofluorescence assay (HHV8 IgG IFA, Biotrin).

Histopathological and Immunohistochemical Studies

Paraffin-embedded blocks of formalin fixed from a number of tissues were obtained from recipients. Standard hematoxylin/eosin staining was performed on all sections and the histology was reviewed.

Paraffin-embedded sections (3–5 μm) were cut onto sialin-coated slides. Sections were deparaffinized with xylene and 100% ethanol and were heated in a 750 W microwave oven in citrate buffer, pH 6.0, for 30 minutes. In order to identify cell types infected latently by HHV-8, we used monoclonal antibody (mAb) LN53 against LANA.[16,17] After treatment with 20% acetic acid, sections were incubated with mAb LN53 (dilution 1 in 1500 in phosphate buffer saline [PBS] for 1 hour at 20°C). Slides were then washed twice with 0.1% Tween in PBS. Incubation of the primary antibody was followed by a streptavidin-phosphatase complex (Dako, High Wycombe, UK) and the sections were counterstained with hematoxylin. Endothelial cells were stained with mAb to CD31 (Dako). Lymphocyte subpopulations were stained with mAb to CD20 (Dako). Detection of EBER 1,2 messenger RNAs was performed using fluorescein isothiocyanate (FITC)–labeled specific peptide nucleic acid probes. The hybridization product was detected with a mouse monoclonal anti-FITC antibody (Dako). Surgical wedge biopsies of the grafted liver were routinely performed on day 0 of the transplantation and used for the detection of cells infected latently by HHV-8, as described previously.

HHV-8 Genome Detection by Real-Time PCR

DNA was extracted from sera, peripheral blood mononuclear cells (PBMCs), and paraffin-embedded tissues using QIAamp systems (QIAgen, Chatsworth, Calif.), according to the manufacturer's instructions, with specific handling for fixed tissues. Five 4μm sections of each fixed specimen were deparaffinized with xylene and 100% ethanol. Overnight tissue digestion and DNA extraction were then carried out with the QIAamp tissue kit. Extracted DNA was then subjected to a real-time PCR assay. Quantification within tissue specimens was done by combining the quantification of HHV-8 and albumin gene DNA as previously described.[18] This was performed thanks to fluorescent TaqMan methodology on ABI Prism 7700 Sequence Detection System (PE Applied Biosystems, Forster City, Calif.). Negative controls for all assays included two reactions that contained no DNA. KSHV viral load in PBMCs or tissues was expressed as the absolute viral copies of KSHV genome in 150,000 human diploid cells and the lower limit of quantification was 10 copies per 150,000 cells.

Results

Prevalence of HHV-8 Antibodies in Donors and Recipients

Among the 122 tested donors, 4 (3.3%) were positive for HHV-8 antibodies. Their liver was given to 4 HHV-8 seronegative recipients (patients #1–4).

Three out of the 122 recipients (2.5%) were positive for HHV-8 antibodies at the time of transplantation and sera from their donors were HHV-8 negative. HHV-8-positive recipients remained positive 6 months after transplantation. With the latent LANA IFA, no seroconversion event was observed in the 99 posttransplant sera examined 4 to 6 months posttransplantation, even in the cases in which liver from HHV-8 positive donors was given to HHV-8 seronegative recipients. However, we detected antibodies against lytic HHV-8 antigens in the posttransplant sera of the 4 HHV-8 seronegative recipients who received a liver from an HHV-8 positive donor.

Outcome of HHV-8 Seropositive Recipients

None of the 3 liver recipients who were HHV-8 seropositive before the transplantation developed a KS or any HHV-8–related disease during the clinical follow-up for at least 2 years. Two of them are well 2 and 3 years, respectively, after transplantation. The third one developed pulmonary and cutaneous aspergillosis and died of septic shock at month 6 after transplantation.

Outcome of HHV-8 Seronegative Recipients who Received a Graft from HHV-8 Seropositive Donors

A 63-year-old-patient (recipient #1) was transplanted for post–hepatitis C cirrhosis. Hepatocellular carcinoma was discovered on the explanted liver. On day 21, an acute rejection was diagnosed and treated by 1 gram of steroids. He received an immunosuppressive treatment based on steroids tapered to 0 by month 4 and tacrolimus with trough levels 6 to 10 ng/ml. The donor of recipient #1 also had antibodies to the hepatitis B core antigen (HBc). This recipient was therefore given long-term prophylaxis with anti-HBs immunoglobulins to prevent HBV transmission. Posttransplant HHV-8 serology remained negative at 6 months using the latent IFA test but became positive using the lytic IFA test, and HHV-8 PCR in PBMCs was negative at 1 year posttransplant. He is well 21 months posttransplant.

A 33-year-old woman (recipient #2) was transplanted for HHV-6–associated fulminant hepatitis. She received an immunosuppression by steroids, tacrolimus with trough levels 5 to 15 ng/ml, and mycophenolate mofetil. Posttransplant course was without complications. Four months posttransplant HHV-8 serology was always negative using the latent IFA test but became positive using the lytic IFA test, and no HHV-8 sequences were detected in PBMCs. She is well 16 months posttransplant.

A 40-year-old man (recipient #3) was transplanted for fulminant B-Delta hepatitis. He received an immunosuppressive treatment based on steroids and tacrolimus with trough levels 10 to 22 ng/ml. An episode of acute rejection was diagnosed one month posttransplant, which was treated by a flash of 1 gram of steroids. At month 2, he developed a biliary stricture that was operated at month 4. Before the surgery, a second episode of acute rejection was treated by a flash of 1 gram of steroids and increasing tacrolimus doses. At month 5, he presented with rash, polyadenopathy, fever at 39°C, anemia, and thrombopenia. Bone marrow aspiration was performed showing absence of erythroblasts, normal megakaryocytes, and excessive rate of plasmocytes (11%), suggestive of viral infection. Lymph node biopsy showed massive haemorrhagic necrosis and capsular spindle cells were positive for HHV-8 (Fig. 1a and 1b) . HHV-8 sequences were detected in PBMCs (407,140 copies/150,000 cells), lymph nodes (53,175 copies/150,000 cells), and serum (560,000 copies/ml) (Table 1). A few days later, a pulmonary infection was diagnosed and HHV-8 sequences were detected in the bronchoalveolar fluid. Rapidly, the patient got worse and died of multiorgan failure at month 5 posttransplant. Autopsy showed a diffuse Epstein-Barr virus (EBV)–negative but HHV-8 positive and CD20 positive large-cell lymphoproliferation with high plasmacytoid differentiation in pulmonary, splenic, and gastric samples. In abdominal lymph nodes, endothelial and spindle cells of typical KS also were associated.

A 30-year-old man (recipient #4) received a liver transplant for amyloid polyneuropathy. Standard immunosuppression by steroids and tacrolimus was applied with tacrolimus trough levels between 12 and 22 ng/ml. At month 1, he developed a biopsy-proven lobular hepatitis. Human cytomegalovirus (HCMV) viremia was positive but immunolabeling of the liver biopsy specimen was negative for HCMV. HHV-8 sequences were detected in PBMCs (49 copies/150,000 cells) (Table 1). This episode resolved spontaneously and liver function tests returned to normal. At month 6, he presented with fever and polypnea, rapidly evolving to infectious shock. HCMV was detected in bronchoalveolar fluid and ganciclovir therapy was started. The patient ultimately developed multiorgan failure and died two weeks later at month 6 posttransplant. HHV-8 sequences were detectable in PBMCs (1.08×10^6 copies/150,000 cells) and plasma (300,000 copies/ml) (Table 1). On autopsy, ischaemic lesions were observed in most organs. The detection of HHV-8 LANA antigen was positive in the peripancreatic and liver's hilar lymph nodes with classical aspect of KS (Fig. 1c and 1d). LANA antigen positive lymphoproliferation was seen in pulmonary, splenic, and lymph node samples. HHV-8 sequences were detectable in pulmonary biopsy (1980 copies/150,000 cells).

Detection of HHV-8 in Liver Grafts from HHV-8 Positive Donors

HHV-8 sequences were detected neither in day 0 graft biopsies nor in day 0 donors' sera. No HHV-8 antigen

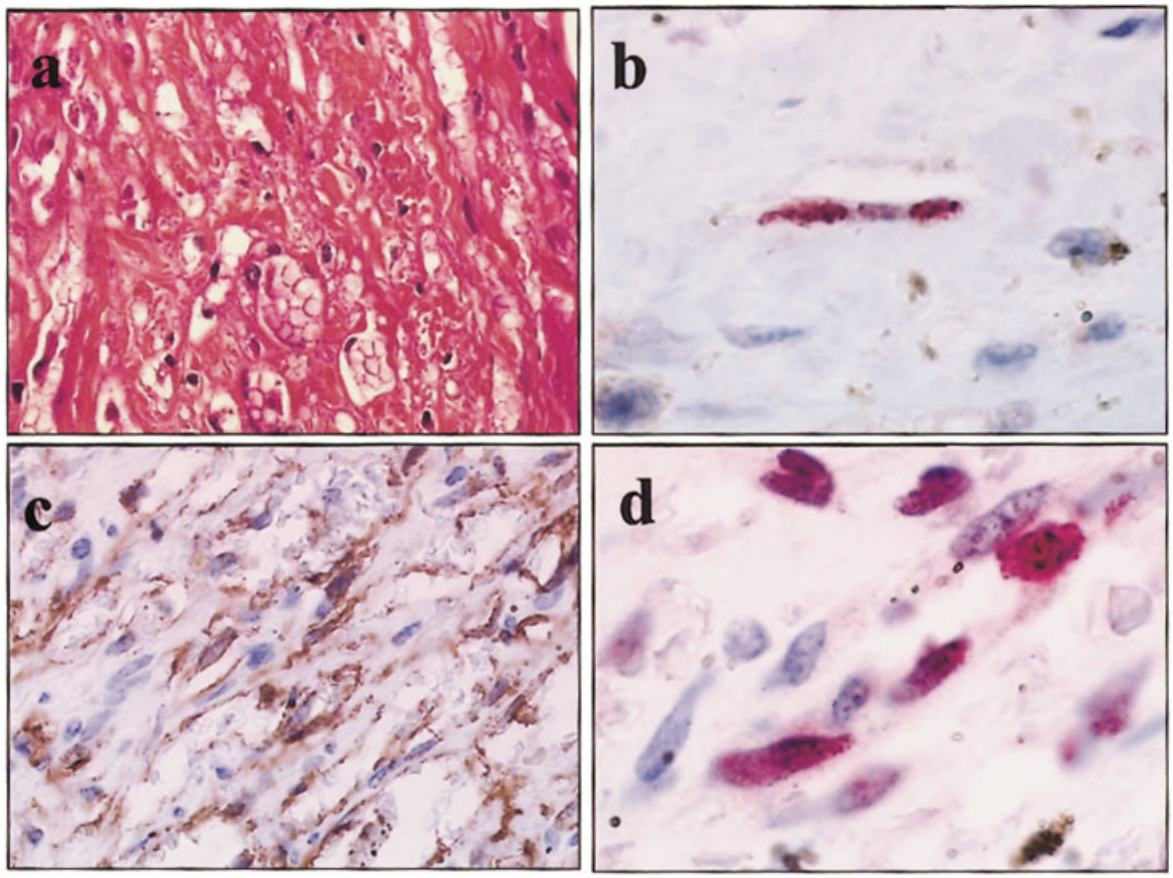

Figure 1. Lymph node biopsies from Patient 3 (panels a and b) and 4 (panels c and d). Lymph node biopsy stained with hematoxylin and eosin showed capsular spindle cells (panel a, ×200). Lymph node biopsy stained with LN43 showed LANA positive cells with typical nuclear stippling (panel b, ×1000). Postmortem lymph node biopsy stained with anti CD31 (panel c, ×400). Postmortem lymph node biopsy stained with LN43 showed LANA positive cells (panel d, ×1000).

Table 1. HHV-8 Viral Load in Different Compartments of Recipients Who Developed HHV-8–Related Diseases

Compartments	Recipient 3	Recipient 4
Plasma (copies/mL)		
Month 6	560,000	300,000
PBMCs (copies/150,000 cells)		
Month 1	NA	49
Month 6	407,140	1.08×10^6
Tissues (copies/150,000 cells)		
Bronchoalveolar fluid	positive	NA
Pulmonary biopsy	NA	1980
Lymph node	53,175	NA

PBMCs: peripheral blood mononuclear cells; NA: not available.

was detected by immunohistochemical analysis in day 0 graft biopsies.

Discussion

HHV-8 has been linked to malignant diseases in immunosuppressed patients. Nonneoplastic complications associated with primary or reactivation of HHV-8 infection can also be observed, such as bone marrow failure with blood stem cell and renal transplantations[13] and multiorgan dissemination of HHV-8 without KS manifestations in primary immunodeficiencies.[19] In this study, we analyzed serum samples from 122 liver recipients and their respective donors for the presence of antibodies to HHV-8 on the day of transplantation and a few months later. The overall HHV-8 seroprevalence in liver-transplant patients and in donors were respectively 2.5% and 3.3%, close to the rate (2%)

observed in healthy subjects in Paris.[20] We observed 4 cases of HHV-8 primary infections in liver recipients, 2 of which were symptomatic. Disseminated KS and LANA positive lymphoproliferation was observed in both recipients. These 2 patients with symptomatic HHV-8 primary infections died a few weeks after transplantation in a context of multiorgan failure. In both cases, a stronger immunosuppression compared to the other recipients who received livers from HHV-8 positive donors, was induced by higher tacrolimus trough levels and use of steroid boluses.

This study showed that severe diseases associated with HHV-8 primary infection can be observed and may not be so rare, even in a low HHV-8–infection prevalence country. These results are in accordance with clinical findings suggesting that posttransplantation KS in liver recipients is associated with a high rate of graft involvement and mortality.[21] In this study, no seroconversion event was observed using latent IFA assay even in the 2 patients who developed documented symptomatic primary HHV-8 infection. However, using lytic IFA assay, all the patients who received grafts from HHV-8 infected donors seroconverted for HHV-8. This finding can be related to the fact that antibodies targeted against lytic antigens appeared before antibodies directed against latent antigens, a fact well known for EBV. HHV-8 seroconversions have been demonstrated with the latent IFA assay for renal and heart patients within the first posttransplant year. In this study, the absence of seroconversion, using this test, in the 4 exposed liver patients suggests that, at least in the context of liver transplantation, HHV-8 lytic serological assay and PCR should be used and combined to monitor recipients who have received an organ from an HHV-8 positive donor.[14,15,22] In this study, in the 2 cases of symptomatic HHV-8 primary infection, HHV-8 DNA sequences were detectable in PBMCs and other tissues with high viremia levels. The detection and the quantification of HHV-8 DNA in PBMCs and plasma could be useful to predict the onset of severe HHV-8–related disease, as suggested by its evolution in patient #4 who harbored an increase of 5 logs of HHV-8 viral load within 5 months, announcing the development of a disseminated KS and HHV-8 lymphoproliferation. The level of HHV-8 DNA viremia has been shown to be associated with the onset of HHV-8–related disease in contexts of immunosuppression.[23,24,25] HHV-8 DNA sequences and antigens were not detected in any of the liver grafts from the 4 HHV-8 seropositive donors. These results suggest that testing for the presence of HHV-8 in graft is probably not efficient enough to prevent HHV-8 contamination from donor to recipient in the context of liver transplantation, as has been demonstrated before for other viruses.[26]

This study raises the question of systematic screening of donors for HHV-8, not to exclude the graft but to know the HHV-8 serologic status and to monitor the recipient adequately. Currently, routine virological assessment of organ donors includes HIV, HCV, and HTLV1 serology, where positivity excludes from organ donation. HBV testing comprises HBsAg, anti-HBs, and anti-HBc detection. While HBsAg positivity excludes from organ donation, anti-HBc positive donors may be used under certain life-threatening circumstances, although their infectivity is clearly established.[26] However, HBV prophylaxis with antiviral agents or immunoglobulins may prevent HBV reactivation from the liver graft.

A similar strategy could be developed for HHV-8 in the context of organ transplantation to avoid the occurrence of severe HHV-8–related disease, combining use of serological assays in donors and recipients and molecular detection of HHV-8 DNA sequences in recipients of positive donors. Reduction or discontinuation of immunosuppressive drugs is usually associated with regression of lesions. This strategy could also be proposed preventively in cases of high risk of development of HHV-8–related disease, for example in patients harboring a positivation and/or increase of HHV-8 viral load.

Two recent studies reported remission of multicentric Castleman disease using anti-CD20 monoclonal antibody infusion correlating with reduction of HHV-8 DNA viral load in PBMCs.[27,28] The use of anti-CD20 monoclonal antibody should be evaluated in cases of documented primary HHV-8 infection with the aim of decreasing the risk of disseminated KS or HHV-8 lymphoproliferation.

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