LETTER TO THE EDITOR

Korean J Intern Med 2017;32:750-752
https://doi.org/10.3904/kjim.2015.124

# Development of Kaposi sarcoma and hemophagocytic lymphohistiocytosis associated with human herpesvirus 8 in a renal transplant recipient

Young Jae Park, Hyun Jin Bae, Ji-Yeun Chang, Chul Woo Yang, and Byung Ha Chung

Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

**Received: April 28, 2015**
**Revised : August 5, 2015**
**Accepted: August 12, 2015**

**Corresponding to**
**Byung Ha Chung, M.D.**
Department of Internal Medicine, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82-2-2258-6066
Fax: +82-2-599-3589
E-mail: chungbh@catholic.ac.kr

*To the Editor,*

Human herpesvirus 8 (HHV-8) infection is a typical opportunistic infection found in immunocompromised patients, such as organ transplant recipients. While HHV-8 is asymptomatic in immunocompetent individuals, it could result in the development of neoplastic disorders, such as Kaposi sarcoma (KS), in immunocompromised hosts. Hemophagocytic lymphohistiocytosis (HLH) is a very rare clinical syndrome characterized by excessive immune activation and inflammation [1]. Various causes of HLH have been suggested, but only a few case reports have shown the development of HLH associated with HHV-8 infection in kidney transplant recipients (KTRs). Here, we report the simultaneous development of KS and HLH, both of which are associated with HHV-8 infection in a KTR. We also provide a brief review of the literature.

A 60-year-old man visited our outpatient clinic with multiple nontender dark brown papules on the surgical scar of transplantation (Fig. 1A). He had been diagnosed with end-stage renal disease caused by diabetes mellitus, and had then started hemodialysis treatment 7 years ago. Five months before presentation at our outpatient clinic, he received kidney transplantation from a 70-year-old deceased male donor with 3 mismatched numbers of human leukocyte antigen. The renal allograft was 198 g. The patient's panel reactive antibody score was 0% for both class I and class II. Donor specific antibody was also negative. He had taken a triple regimen immune suppressants (IS), which was composed of tacrolimus, mycophenolate mofetil, and prednisolone. Trough serum level of tacrolimus was 6.5 ng/mL. The graft kidney function was stable with a serum creatinine level of 2.01 mg/dL and a Modification of Diet in Renal Disease estimated glomerular filtration rate (MDRD eGFR) of 36.19 mL/min/1.73 $m^2$ at presentation. The pathologic finding of the partially excised skin lesion was KS, which showed multiple Kaposiform spindle cells in connective tissues, with HHV-8 positivity in molecular pathology. Chest and abdomen computed tomography and colonoscopy only showed negative findings, but multiple shallow ulcerations at the gastric body were observed during upper endoscopy. These shallow ulcerations were also revealed to be Kaposiform spindle cell proliferations, suggestive of KS. We decided to convert tacrolimus to sirolimus with immediate discontinuation of mycophenolate mofetil. One month after IS conversion, the patient visited our emergency department with fever. His known KS



pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

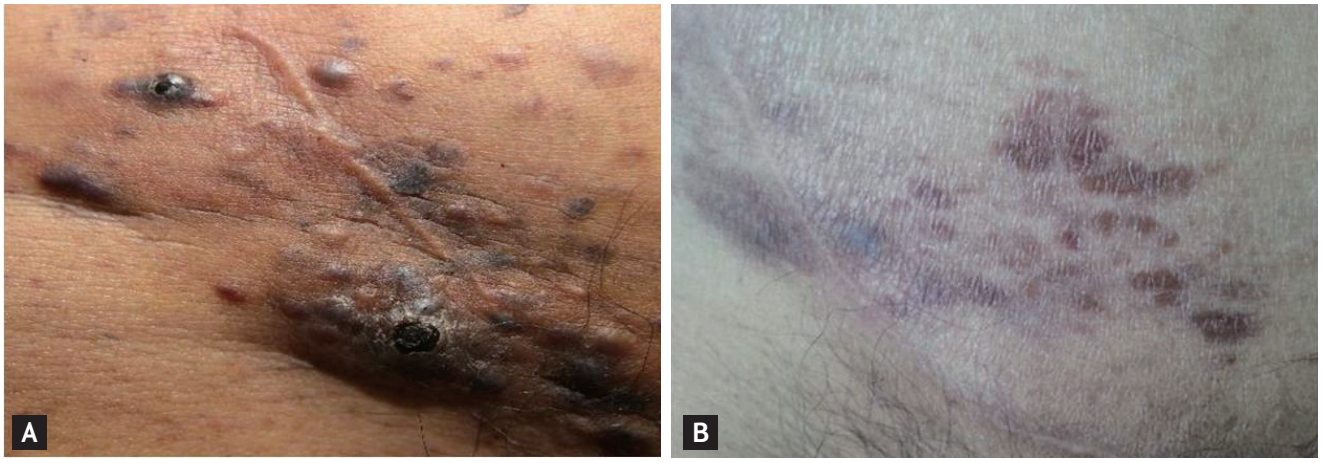


**Figure 1**. (A) Multiple nontender dark brown papules on the previous renal transplantation surgical scar, which were proven to be Kaposi sarcoma. (B) Remarkably improved Kaposi sarcoma, 1 month after the conversion of calcineurin inhibitor to sirolimus.

lesion of the surgical scar was remarkably improved (Fig. 1B). Trough serum level of sirolimus was stable between 4.5 and 4.9 ng/mL during that period. However, pancytopenia was newly detected (white blood cell count, 3,740/mm$^3$; hemoglobin, 8.3 g/dL; platelet count, 42,000/mm$^3$). Elevated serum alanine transaminase (69 IU/L), ferritin (1,948 ng/mL), and C-reactive protein (16.81 mg/dL) values were found as well. The result of bone marrow aspiration and biopsy showed 20% of cellularity without KS invasion, but active hemophagocytosis (Fig. 2) and HHV-8 positivity. At first, we continued reduced amount of IS to maintain the patient's kidney function. A few days later, we totally discontinued IS and attempted to control the HHV-8 infection using antiviral agents, such as acyclovir and foscarnet for 1 month. During this period, these antiviral therapies improved pancytopenia as well as the patient's general condition. Therefore we restarted IS with a very little dose. However, immediately after the restart of IS, pancytopenia recurred and antiviral therapies did not improve the bone marrow failure state anymore, despite the use of other conservative treatments including massive transfusion. Hence, we decided to start cytotoxic therapy according to the HLH-2004 protocol to treat HHV-8 infection-associated HLH, which is refractory to antiviral therapies, with IS discontinuation [2]. During the induction therapy, which consisted of etoposide and dexamethasone, septic shock occurred in combination with lobar pneumonia. Ultimately, the patient expired because of multi-drug resistant bacterial infection, which was refractory to aggressive antibiotic treatment.

The primary issue of this case was the determination of a proper treatment plan for both HHV-8 associated KS and HLH. In cases of KS associated with HHV-8 infection, the mainstay of treatment is the reduction of IS burden. By itself, however, IS reduction is associated with a low resolution rate for KS. Further, discontinuation of IS may increase the risk of allograft rejection. Hence, many studies have suggested conversion to a mammalian target of rapamycin inhibitor from a calcineurin inhibitor, which has been reported to provide an excellent outcome as treatment for KS [3]. In this context, we did sirolimus conversion with reduction of overall IS, which resulted in remarkable regression of the KS lesions.

However, this patient also presented bone marrow failure due to HLH associated with HHV-8 infection. The treatment for HLH is rather complex and has not been standardized. When the cause of HLH is clear, the corresponding therapy is needed. For example, when virus infection was found to be the cause of HLH, antiviral agents provided effective resolution of HLH in a few case reports. Indeed, foscarnet therapy was effective for the treatment of HHV-8-associated HLH developed in KTRs [4]. However, considering the excessive immune-activating nature of HLH, these conservative therapies may not be sufficient for the recovery of bone marrow failure in many cases. Accordingly, the use of cytotoxic therapy based on etoposide and dexamethasone is recommended in current guidelines [2].

In our case, HHV-8 was identified as the cause of both KS and HLH. Hence, we first attempted to treat HLH using an antiviral agent without cytotoxic therapy and IS

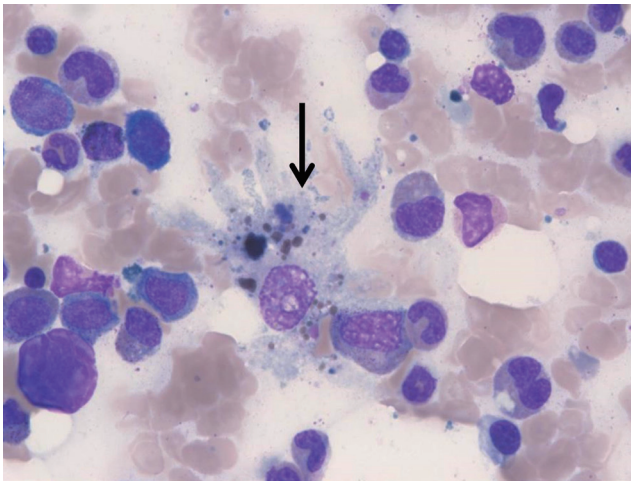

**Figure 2**. Hematoxylin and eosin staining showed active hemophagocytosis (arrow) in the patient's bone marrow (aspirated specimen, ×1,000).

reduction relevant to the development of infectious complication. However, the effect of the antiviral agent was limited and the state of bone marrow failure persisted. Hence, we decided to administer cytotoxic therapy and discontinue IS. Despite these treatments, the patient's bone marrow did not recover, and he ultimately died of serious infection. It remains unclear whether cytotoxic therapy is necessary for the treatment of HLH. Further, if cytotoxic therapy is necessary, the optimal timing of its administration is unknown. These uncertainties regarding the proper strategy for cytotoxic therapy led us to delay our decision to change the treatment plan; hence, the state of bone marrow failure persisted. However, it is clear that earlier drastic reduction of IS may be necessary to prevent serious infection in such a vulnerable state.

A secondary issue in this case was the route of HHV-8 infection. HHV-8 is usually transmitted through body secretions, but it can also be transmitted through blood transfusions and organ or tissue transplantations. Indeed, seroconversion of HHV-8 was detected in a significant proportion of KTRs [5]. Therefore, it is possible that HHV-8 was transmitted from the decreased donor to this patient and activated after the initiation of IS, which results in fatal diseases such as KS and HLH. This potential route of infection suggests that screening for HHV-8 serostatus in both donors and recipients may be necessary to prevent fatal HHV-8 infections. In HHV-8 endemic area like sub-Saharan Africa, HHV-8 serostatus can be evaluated by enzyme-linked immunosorbent assay or immunofluorescent antibody for blood or organ donors. But, in nonendemic area of HHV-8 infections such as Korea, there are no consensus or guideline about routine screening of HHV-8 serostatus, hence we also did not perform this study. However, in high-risk patients for HHV-8 primary infection or reactivation with donor or recipient seropositivity, continuous virological monitoring by HHV-8 DNA PCR is needed, and prophylactic or preemptive antiviral therapy, like ganciclovir, could be useful to prevent the incidence of posttransplant HHV-8 associated diseases [4].

In conclusion, HHV-8 infection rarely occurs in KTRs, but can cause several severe disorders, including both neoplastic diseases (such as KS) and nonneoplastic fatal disease (such as HLH). When treating both neoplastic and nonneoplastic disorders associated with HHV-8, careful management of the infection may be necessary to prevent mortality. In addition, screening for HHV-8 may be required for donors and recipients with high risks of HHV-8 infection.

**Keywords:** Kidney transplantation; Herpesvirus 8, human; Sarcoma, Kaposi

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

## REFERENCES

1. Karras A. What nephrologists need to know about hemophagocytic syndrome. Nat Rev Nephrol 2009;5:329-336.
2. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. Lancet Infect Dis 2007;7:814-822.
3. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005;352:1317-1323.
4. Riva G, Luppi M, Barozzi P, Forghieri F, Potenza L. How I treat HHV8/KSHV-related diseases in posttransplant patients. Blood 2012;120:4150-4159.
5. Lebbe C, Porcher R, Marcelin AG, et al. Human herpesvirus 8 (HHV8) transmission and related morbidity in organ recipients. Am J Transplant 2013;13:207-213.


https://doi.org/10.3904/kjim.2015.124