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Case Report

Successful Treatment of Kaposi Sarcoma–Associated Herpesvirus Inflammatory Cytokine Syndrome After Kidney–Liver Transplant: Correlations With the Human Herpesvirus 8 miRNome and Specific T Cell Response

A. Mularoni[1,*,†], A. Gallo[2,†], G. Riva[3,4,†], P. Barozzi[3,†], M. Miele[9], G. Cardinale[5], G. Vizzini[6], R. Volpes[6], P. Grossi[1,7], D. Di Carlo[2], A. Luca[8], T. Trenti[4], M. Luppi[3,†] and P. G. Conaldi[2,9,†]

[1]Infectious Disease and Infection Control Service, Department for the Treatment and Study of Abdominal Diseases and Abdominal Transplantation, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), Palermo, Italy
[2]Department of Laboratory Medicine and Advanced Biotechnologies, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), Palermo, Italy
[3]Section of Hematology, Department of Surgical and Medical Sciences, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy
[4]Department of Laboratory Medicine and Pathology USL, Modena, Italy
[5]Division of Hematology, Department of Oncology, A.R.NA.S. Civico-Benfratelli, G. Di Cristina e M. Ascoli, Palermo, Italy
[6]Department for the Treatment and Study of Abdominal Diseases and Abdominal Transplantation, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), Palermo, Italy
[7]Department of Infectious and Tropical Diseases, University of Insubria, University Hopital Ospedale di Circolo-Fondazioni Macchi, Varese, Italy
[8]Department of Diagnostic and Therapeutic Services, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione), Palermo, Italy
[9]Fondazione Ri.MED, Palermo, Italy
**Corresponding author: Alessandra Mularoni, amularoni@ismett.edu*
[†]These authors contributed equally to this study.

After transplant, patient infection with human herpesvirus 8 (HHV-8) and Kaposi sarcoma–associated herpesvirus (KSHV) is known to cause aggressive tumors and severe nonneoplastic complications. These latter syndromes are driven by HHV-8/KSHV lytic reactivations and related hyperinflammatory host responses typically characterized by high viral loads, elevated levels of cytokines and other inflammation biomarkers, cytopenia, organ failure, high fever, and worsening conditions (with no evidence of B cell neoplasias). These disorders are associated with a high mortality rate, often due to lack of prompt diagnosis, effective therapeutic approaches, and adequate follow-up. These features resemble most of those defining the so-called KSHV-associated inflammatory cytokine syndrome (KICS), which was recently recognized in patients positive for human immunodeficiency virus (HIV). In this report, we describe—for the first time—a case of a KICS-like nonneoplastic recurrent complication occurring after transplant in an HIV-negative patient that was successfully treated by a combination of anti-CD20 monoclonal therapy, antivirals, and modification of the immunosuppressive regimen. In addition to clinical and laboratory findings collected during 3-year follow-up, we report novel experimental data on HHV-8–specific T cell dynamics and circulating microRNA profile, showing correlations with clinical course and other laboratory markers (including viral load, C-reactive protein, and cytokine levels), providing useful information about abnormal cellular and cytokine dynamics underlying HHV-8–associated inflammatory disorders in posttransplant patients.

Abbreviations: CDV, cidofovir; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; DEX, dexamethasone; EVR, everolimus; FCN, foscarnet; GM-CSF, granulocyte-macrophage colony-stimulating factor; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; IFN, interferon; IVIG, intravenous immunoglobulin; KSHV, Kaposi sarcoma–associated herpesvirus; KICS, KSHV-associated inflammatory cytokine syndrome; MCD, multicentric Castleman disease; miRNA, microRNA; PBMC, peripheral blood mononuclear cell; PT-KICS, posttransplant KICS-like disorder; RTX, rituximab; TC, tacrolimus; vIL-6, virus-encoded IL-6 homolog; v-miRNA, viral microRNA

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Introduction

Human herpesvirus 8 (HHV-8) infection in solid organ transplant recipients can induce virus-driven neoplastic proliferations as well as uncommon but life-threatening nonmalignant complications (1). After primary infection, the HHV-8 life cycle exhibits a latent phase interrupted by lytic (viremic) reactivations, manipulating cellular pathways by expressing host-homolog cytokines, intracellular proteins, and microRNAs (miRNAs). HHV-8 lytic reactivations result in the production of high levels of proinflammatory cytokines and chemokines, which are responsible for a hyperinflammatory status causing potentially fatal organ damage. In particular, virus-encoded IL-6 homolog (vIL-6) and other host cytokines induced during the lytic phase are pivotal factors in the pathogenesis of multicentric Castleman disease (MCD), a systemic lymphoproliferative disorder with features including the presence of HHV-8–infected plasmablasts expressing vIL-6 in affected lymph nodes, high levels of HHV-8 viremia, and overproduction of inflammatory cytokines. Moreover, a distinct severe complication called KSHV-associated inflammatory cytokine syndrome (KICS) has recently been defined in patients positive for human immunodeficiency virus (HIV) who showed elevated HHV-8 viral loads, elevated C-reactive protein (CRP), no evidence of MCD, and at least two serious clinical abnormalities in three categories (symptoms, abnormal laboratory findings, and abnormal radiographic findings) (2) (Table 1). In the transplant setting, most nonneoplastic HHV-8–associated inflammatory manifestations seem to share main features with KICS described in HIV-positive patients (3–5). In this report, we describe the first case of successful treatment of recurrent posttransplant KICS (PT-KICS) in a kidney–liver transplant patient with onset after donor-derived HHV-8 primary infection. We also provide novel data and correlations obtained from the monitoring of specific immunological, inflammatory, and virological parameters.

Clinical case

A 38-year-old woman underwent liver and kidney transplantation for primary sclerosing cholangitis and chronic renal insufficiency of unknown origin. The donor was a 42-year-old woman whose cause of death was intracranial hemorrhage. Serological matches were as follows: cytomegalovirus (CMV), donor positive and recipient negative; Epstein–Barr virus, donor and recipient positive; HHV-8, donor positive and recipient negative; hepatitis B virus, donor and recipient negative; hepatitis C virus, donor and recipient negative; HIV, donor and recipient negative. Immunosuppressive therapy consisted of two doses of basiliximab and mycophenolate mofetil for 14 days and daily long-term tacrolimus. The postoperative course was uneventful. The recipient developed a primary CMV infection that spontaneously resolved without antiviral treatment. Monthly monitoring of HHV-8 DNA showed the first positive viral load 30 weeks after transplant. She was not treated but was closely monitored. During the subsequent 5 mo, HHV-8 replication continued with values of <20 000 copies/mL. She did not complain of any new symptoms except for progressive anemia. At week 55 after transplantation, she developed persistent fever, severe anemia, and worsening of renal function. Investigations for common bacterial, parasitic, and viral infections were negative, whereas HHV-8

Table 1: Working case definition of KICS

Clinical features	Radiographic or histological abnormalities	Laboratories parameters
Symptoms:	**Radiographic abnormalities:**	**HHV-8 viral activity (*):**
Fever (*)	Lymphadenopathy (*)	Elevated viral load in plasma (≥1000 copies/mL), in blood (≥ 2500 copies/mL), or in PBMCs (100 copies/10^6 cells)
Fatigue (*)	Splenomegaly (*)	
Edema (*)	Hepatomegaly	
Cachexia	Body cavity effusions	
Respiratory symptoms:		
Gastrointestinal disturbance (*)	**Histopathological assessment of lymphadenopathy:**	**Systemic inflammation (*):**
Arthralgia/myalgia	No Evidence of HHV-8 associated MCD (*)	C-reactive protein ≥3 g/dL
Neuropathy with or without pain		**Laboratories abnormalities:**
		Anemia (*)
		Thrombocytopenia (*)
		Hypoalbuminemia (*)
		Hyponatremia (*)

The working case definition of KICS requires the presence (V) of HHV-8 high viral activity and systemic inflammation and the exclusion of HHV-8 plus at least two categories of symptoms and radiological and laboratories abnormalities.
HHV-8, human herpesvirus 8; KICS, Kaposi sarcoma–associated herpesvirus inflammatory cytokine syndrome; MCD, multicentric Castleman disease; PBMC, peripheral blood mononuclear cell.
(*) clinical features of the patient at diagnosis

DNA was 189 750 copies/mL (Figure 1A). A computed tomography (CT) scan showed severe splenomegaly and small-sized generalized lymphadenopathy (Figure 1C). Bone marrow biopsy showed a picture of hypoplasia without lymphoproliferation; HHV-8 DNA on bone marrow aspirate was 20 000 copies/mL. Lymph node biopsy revealed a reactive node with no specific changes and no diagnostic evidence of malignancy. Consequently, a reduction of tacrolimus levels was started along with weekly cidofovir therapy for a total of five doses, resulting in the disappearance of fever but with only a transient decrease of HHV-8 viral load (Figure 1A). At week 64, fever suddenly relapsed, and the patient showed a significant increase in CRP, worsening of renal function, and severe pancytopenia. HHV-8 viremia had a rapid 1-log increase (from 45 700 to 630 000 copies/mL).

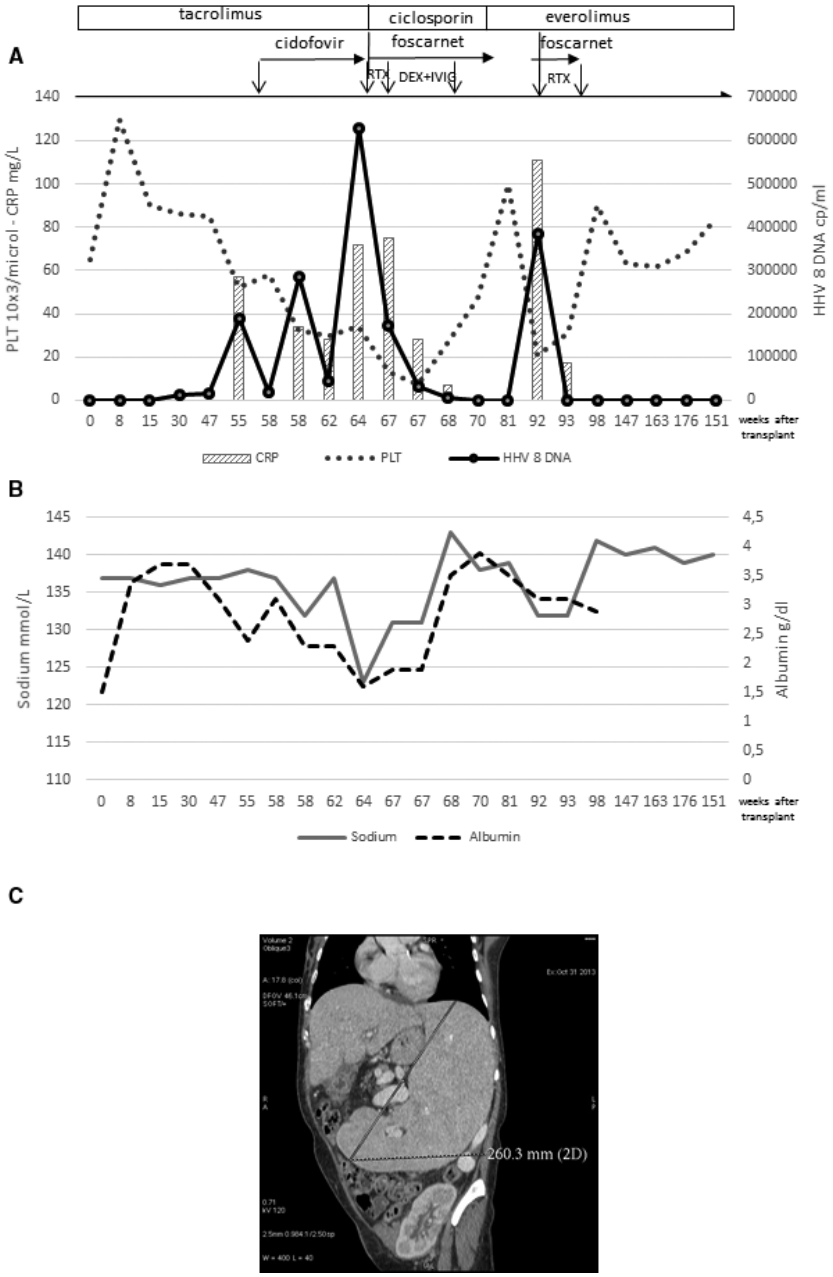

Figure 1: (A) Trends in human herpesvirus 8 (HHV-8) DNA viral load, platelet (PLT) count, and C-reactive protein (CRP) during weeks 0–151 after liver–kidney transplant. (B) Trend of sodium plasma level during weeks 0–151 after transplant and albumin plasma levels during weeks 0–98 after transplant. (C) Splenomegaly at computed tomography scan performed at week 65 after transplant. DEX, dexamethasone; IVIG, intravenous immunoglobulin; RTX, rituximab.

Treatment with foscarnet was introduced, and the first dose of rituximab was administered. The patient, however, soon experienced higher fever, worsening of general condition, body cavity effusion, hypoalbuminemia, edema, intestinal subocclusion, anemia, and thrombocytopenia (Figure 1B). She was immediately reassessed, and a diagnosis of hemophagocytic lymphohistiocytosis (HLH)/hemophagocytic syndrome (HPS) was made, in line with diagnostic guidelines for HLH (6), according to the following findings: fever 40°C, pancytopenia (hemoglobin, 7.8 g/dL; neutrophil count, 380/μL; platelet count, 21 000/μL), ferritin, 2180 μg/L; triglycerides, 445 mg/dL; and severe splenomegaly in the absence of histological evidence of hemophagocytosis. Consequently, the immunosuppressive treatment was switched from tacrolimus to cyclosporine, and dexamethasone and intravenous immunoglobulin (IVIG) were started (Figure 1A). After these treatments, inflammatory markers, fever, and HHV-8 DNA slowly decreased, general conditions gradually improved, and lactate dehydrogenase and triglycerides together with blood cell count normalized. Dexamethasone was tapered and then withdrawn, and the patient was finally discharged on everolimus immunosuppression. For the subsequent 18 weeks (weeks 71–89), she remained afebrile and in good clinical condition; monthly follow-up of HHV-8 DNA was negative, and blood cell counts gradually increased (Figure 1A). At week 92, the patient was admitted because of fever (40°C), asthenia, and worsening of general condition. Laboratory analyses showed pancytopenia and elevated CRP. The HHV-8 DNA value was 384 000 copies/mL. She underwent total body CT scan, EGDS esophagogastroduodenoscopy and colonoscopy, which ruled out MCD and Kaposi sarcoma (KS), but spleen size was significantly increased. Daily foscarnet treatment (14 days) and weekly rituximab (four doses) were restarted. After the second dose of rituximab, HHV-8 viremia promptly became undetectable, fever disappeared, and blood cell counts gradually returned to baseline parameters. Since then, the patient has remained afebrile and in good clinical condition, with HHV-8–negative DNA, stable blood cell counts, and normal kidney and liver functions (Figure 1A).

Experimental Investigations

After obtaining the patient's informed consent, we serially assessed plasma levels of several cytokines—interferon (IFN) α and γ, tumor necrosis factor α, IL-1a, IL-1b, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-17A, IP-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte chemoattractant protein 1, macrophage inflammatory proteins 1α and 1β, soluble platelet selectin, soluble E-selectin, and intercellular adhesion molecule 1—using commercially available ELISA kits for cytokine detection (Thermo Fisher Scientific, Waltham, MA). Of note, IL-6, IL-8, IL-10, and GM-CSF were found to be highly secreted in plasma in concomitance with viral load peaks (Table 2). In particular, IL-8, IL-10, and GM-CSF showed a significant direct correlation with HHV-8 viremia levels (Figure 2), and IL-6 appeared to be increased mainly before viremic events.

In parallel, we performed HHV-8–specific T cell monitoring with IFN-γ enzyme-linked ImmunoSpot assays on serial peripheral blood mononuclear cell samples by using, as antigenic stimulation, three different peptide pools derived from HHV-8 proteins, either lytic (K8.1) or latent (orf73 and K12), according to reported protocols (1,7). We observed that the first viremic peak, at week 64, was associated with very low or undetectable levels of latent responses but with the presence of significant lytic responses. The progressive decrease of HHV-8 viral

Table 2: Time-course follow-up measurement of IL-10, IL-6, IL-8, and GM-CSF levels in patient's plasma

Weeks after transplant	HHV-8, copies/mL	IL-10 pg/mL	IL-6 pg/mL	IL-8 pg/mL	GM-CSF pg/mL	Treatment
5	0	3.26	7.6	9.6	9.537	TC
6	0	2.7	17	9.6	27	TC
8	0	2.06	0	8.97	26	TC
10	0	2.4	7.6	9.18	22.5	TC
15	0	1.3	7.6	7.7	18	TC
19	0	2.6	7.06	7.7	11.5	TC
30	11 610	39	47	9.39	31	TC
37	7050	12	38	7.81	31	TC
47	13 900	39	13	6.41	11.5	TC
48	20 000	66	24	6.96	11.5	TC
58	18 050	66	31	7.91	42	TC + CDV
62	45 700	73	12	8.13	18	TC + CDV
64	630 000	2569	68	13.73	56.5	TC + RTX
92	384 000	60	7.06	14.36	38.5	EVR + FCN + RTX
98	0	1.5	33	9.18	9.537	EVR

The table reports treatment at every measurement. CDV, cidofovir; EVR, everolimus; FCN, foscarnet; GM-CSF, granulocyte-macrophage colony-stimulating factor; HHV-8, human herpesvirus 8; RTX, rituximab; TC, tacrolimus.

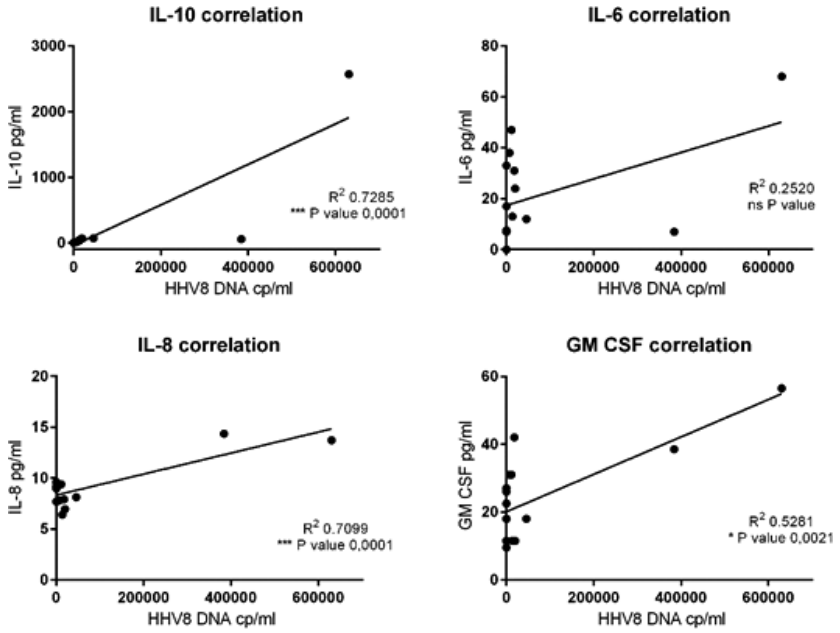

Figure 2: Correlations of plasmatic granulocyte-macrophage colony-stimulating factor (GM-CSF; pg/mL), IL-10 (pg/mL), IL-8 (pg/mL), and IL-6 (pg/mL) with human herpesvirus 8 (HHV-8) DNA (copies/mL). Spearman test was used to analyze the correlation between parameters.

loads was concomitant with an increase in latent responses and with the decrease in lytic responses. The persistent absence of HHV-8 viremia was associated with the presence of latent responses but with undetectable lytic responses. The second viremic peak was preceded by a new reduction in latent responses while increasing viral loads paralleled rising lytic responses (Figure 3A).

In addition, by considering the relevant modulatory effects of the viral miRNAs on infected cells, we decided to investigate the HHV-8 miRNome circulating in the peripheral blood of the patient for the first 24 mo after transplant by creating a viral miRNA (v-miRNA) expression profile with the Custom TaqMan Array MicroRNA Cards (Thermo Fisher Scientific). The HHV-8 genome encodes for 12 precursor miRNAs located within the latency-associated region and transcribed from the latent kaposin/K12 promoter, yielding 25 mature v-miRNAs (8). Of these 25, we detected the expression of the following five circulating v-miRNAs: kshv-miR-K12-10b, kshv-miR-K12-12* (Figure 3B) and kshv-miR-K12-1*, kshv-miR-K12-5, and kshv-miR-K12-3 (Figure 3C).

Discussion

We describe, for the first time, a clinical case of PT-KICS that presented with unexplained fever, markers of severe systemic inflammation, and elevated HHV-8 viral load, similar to the KICS originally defined by Polizzotto et al (2) in HIV-infected patients. The early manifestation of PT-KICS showed a partial, transient response to the reduction of immunosuppression combined with cidofovir antiviral therapy, similar to what we observed in our previous report (4). Later, in consideration of a diagnosis suggestive of HLH/HPS, initial treatments with rituximab and foscarnet were initiated, with later combination therapies of dexamethasone, IVIG, and tacrolimus-to-cyclosporine switch, obtaining a remarkable reduction of viral burden and reactive inflammatory state and then complete disease resolution; this approach also avoided the etoposide-based chemotherapy recommended for HLH. Four months later, our patient developed a PT-KICS relapse. Prompt treatment with rituximab and foscarnet, without modification of ongoing immunosuppressive therapy (everolimus), led to rapid, complete, and sustained clinical remission. The use of everolimus, which has a valuable role in the prevention and treatment of posttransplant KS, failed to prevent the recurrence of PT-KICS in this patient. This case further supports the notion that prompt CD20-targeted treatment may be a pivotal option in the management of HHV-8–driven inflammatory complications, which cannot be prevented by the sole use of antivirals (1,5). Contrary to the successful experience with rituximab-based therapy in HIV-positive patients with MCD (9), to our knowledge, there are no detailed reports regarding the use of CD20-targeted therapy in HIV-positive patients with KICS. Combination of cytotoxic chemotherapy with rituximab has been used in small groups of HIV-positive patients with resistant KS associated with KICS, leading to improvements in KSHV-

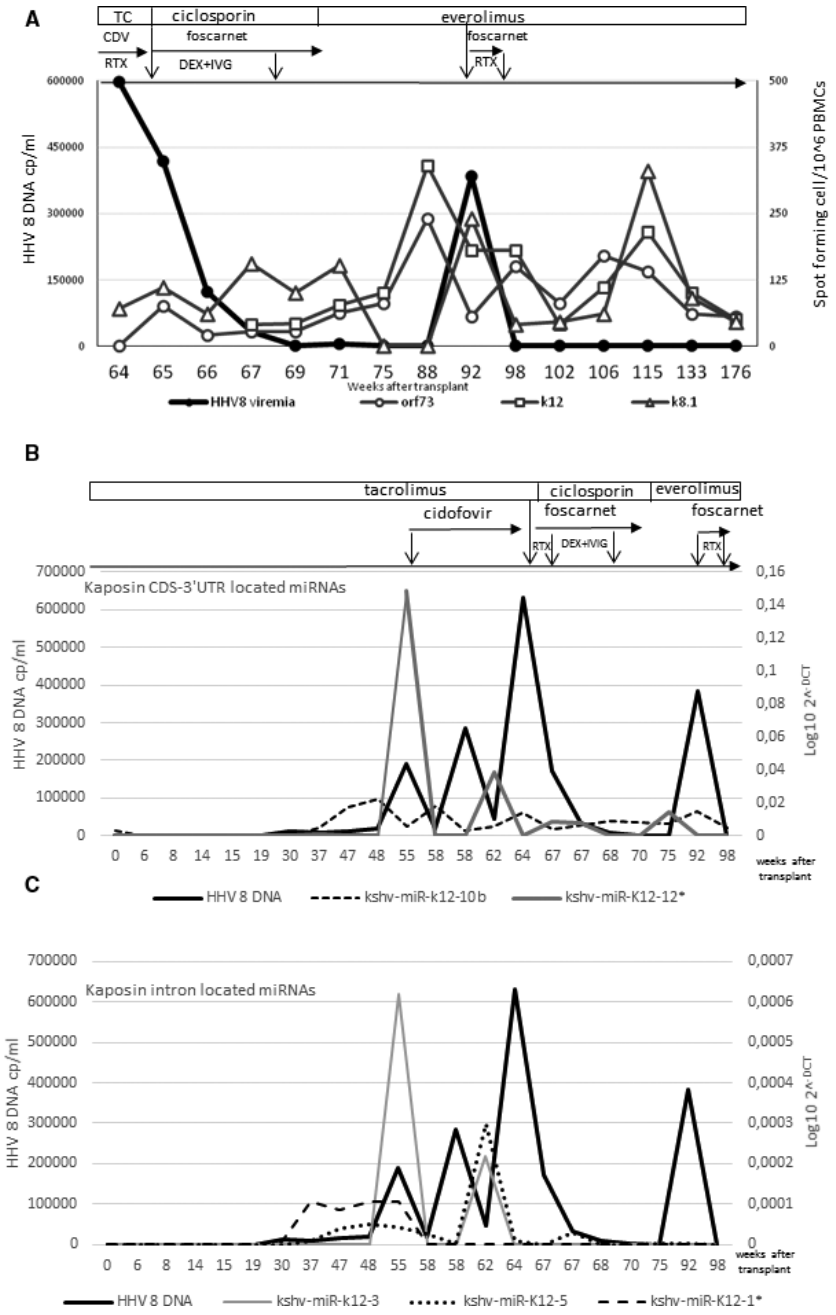

Figure 3: (A) Human herpesvirus 8 (HHV-8)–specific T cell monitoring by interferon γ enzyme-linked ImmunoSpot toward either lytic (orfK8.1) or latent (orf73/LANA or K12) peptide pools, with overlay of HHV-8 viral loads (black line). (B) Time-course expression profiles of HHV-8 microRNAs located either in the kaposin CDS-3′ untranslated region (UTR; kshv-miR-k12-10b and kshv-miR-k12-12*) or (C) in a kaposin intron (kshv-miR-k12-3, kshv-miR-k12-5, and kshv-miR-k12-1*), with overlay of HHV-8 DNA values (black line). CDV, cidofovir; DEX, dexamethasone; IVIG, intravenous immunoglobulin; miRNA, microRNA; PBMC, peripheral blood mononuclear cell; RTX, rituximab; TC, tacrolimus.

related tumors, but no specific information on the clinical course of KICS has been reported (10). The rational use of therapies that target KSHV cellular reservoirs needs to be explored further in both HIV-positive and posttransplant patients with KICS (2). It is conceivable that a massive elimination of B lymphocytes by close infusions of rituximab (weekly) may arrest HHV-8 replication events, leading to a switching off of the related inflammatory response. Such a therapeutic effect can be more evident when PT-KICS is treated early, as systemic

inflammation should be more reversible and strictly dependent on HHV-8 lytic activities.

In our patient, we found not only the KICS-defining IL-6/IL-10 signature but also plasma levels of IL-8 and GM-CSF correlated with HHV-8 reactivation events and inflammatory exacerbations. Analysis of single nucleotide polymorphisms revealed that patients with MCD and KICS have unusual KSHV miRNA sequences, suggesting an association between the observed sequence variations and the risk of developing either MCD or KICS (11). In the peripheral blood, we detected the presence of kshv-miR-K12-5, which was described as being involved in the regulation of the latency-lytic switch (12); kshv-miR-K12-3, inducing angiogenesis and cell migration (13); and kshv-miR-K12-10b and kshv-miR-K12-12*, known to promote the secretion of IL-10 and IL-6 (14). Of note, oncogenic v-miRNAs such as kshv-miR-K12-11 and kshv-miR-K12-1, which are involved in B cell differentiation and expansion (15), were not found circulating in this patient. Finally, as already proposed for patients with posttransplant KS (1), the immunological monitoring of HHV-8–specific T cell subsets may be an informative tool for PT-KICS patients. Indeed, the dynamics of T cell responses against different HHV-8 antigens suggest that latent responses may be protective, being associated with control of HHV-8 reactivation, whereas lytic responses may be surrogate markers of ongoing viral replication.

Further studies are needed to confirm these first observations, but our data may indicate that posttransplant monitoring of specific T cell immunity and inflammatory biomarkers can help in the management of HHV-8–induced nonneoplastic/inflammatory disorders, which typically require prompt recognition and start of combined treatments with anti-CD20 monoclonal therapy and antivirals as well as opportune modifications of immunosuppressive therapy and careful postremission follow-up.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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