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Original Article

Serologic screening and molecular surveillance of Kaposi sarcoma herpesvirus/human herpesvirus-8 infections for early recognition and effective treatment of Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome in solid organ transplant recipients

Alessandra Mularoni [1], Andrea Cona [1,*], Matteo Bulati [2], Rosalia Busà [2], Monica Miele [2,3], Francesca Timoneri [2,3], Mariangela Di Bella [2,3], Salvatore Castelbuono [2,4], Floriana Barbera [5], Daniele Di Carlo [5], Lorenzo Volpe [2], Alessia Gallo [2], Anna Maria de Luca [1,6], Giulia Coniglione [1,7], Francesca Todaro [8], Patrizia Barozzi [9], Giovanni Riva [10], Giada Pietrosi [11], Salvatore Gruttadauria [11], Alessandro Bertani [12], Patrizio Vitulo [13], Alessandra Fontana [14], Manlio Cipriani [14], Sergio Rizzo [15], Antonio Arcadipane [16], Angelo Luca [17], Malgorzata Mikulska [18,19], Pier Giulio Conaldi [2], Paolo Antonio Grossi [20], Mario Luppi [9]

[1] *Unit of Infectious Diseases and Infection Control, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy*

[2] *Department of Research, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy*

[3] *Ri MED Foundation, Palermo, Italy*

[4] *Department of Engineering, University of Palermo, Palermo, Italy*

[5] *Pathology Unit, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy*

[6] *Unit of Infectious Diseases, A.O.U.R. Dulbecco, Catanzaro, Italy*

[7] *Unit of Infectious Diseases, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy*

[8] *Dermatology Unit, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy*

[9] *Section of Hematology, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, AOU Modena, Modena, Italy*

[10] *Diagnostic Hematology and Clinical Genomics Laboratory, Department of Laboratory Medicine and Pathology, AUSL/AOU Modena, Modena, Italy*

[11] *Department for Treatment and Study of Abdominal Disease and Abdominal Transplantation, Abdominal Center Department, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy*

[12] *Division of Thoracic Surgery and Lung Transplantation, Chest Center Department, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy*

Abbreviations: Ab, antibody; CNI, calcineurin inhibitor; D, donor; DDI, donor-derived infection; HHV-8, human herpesvirus-8; HIV, human immunodeficiency virus; IL, interleukin; ISMETT, Mediterranean Institute for Transplantation and Advanced Specialized Therapy; KICS, Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome; IDO, indoleamine 2,3-dioxygenase; IFNα, interferon alfa; KS, Kaposi sarcoma; mTOR, mammalian target of rapamycin; R, recipient; SOT, solid organ transplant; TNFα, tumor necrosis factor alpha; Tx, transplant.

* Corresponding author. Andrea Cona, Unit of Infectious Diseases and Infection Control, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Via Tricomi 5, 90127 Palermo, Italy.

E-mail address: acona@ismett.edu (A. Cona).

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[13] Division of Pulmonology, Chest Center Department, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy
[14] Division of Cardiology, Heart Center Department, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy
[15] Medical Oncology Unit, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy
[16] Department of Anesthesia and Intensive Care, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy
[17] Department of Diagnostic and Therapeutic Services, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy
[18] Division of Infectious Diseases, Department of Health Sciences, University of Genoa, Genoa, Italy
[19] IRCCS, Ospedale Policlinico San Martino, Genoa, Italy
[20] Infectious and Tropical Diseases Unit, Department of Medicine and Surgery, University of Insubria-ASST-Sette Laghi, Varese, Italy

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ABSTRACT

Kaposi sarcoma (KS) herpesvirus/human herpesvirus-8 (HHV-8) neoplastic and nonneoplastic disease in solid organ transplant recipients can be life-threatening. We evaluated the seroprevalence of HHV-8 infection among donors (D) and recipients (R), the incidence of HHV-8 transmission/reactivation, and the clinical characteristics, management, and outcomes of HHV-8-related diseases, including KS herpesvirus-associated inflammatory cytokine syndrome (KICS), in consecutive SOT patients from 2011 to 2023. HHV-8 seroprevalence was 3.3% in 1349 donors and 8.4% in 1856 recipients screened ($P < .0001$). In the D+/R− group (n = 49), 13 patients developed HHV-8-related diseases: 7 liver recipients had KICS, and 1 lung recipient had KS with subsequent KICS. Four KICS patients treated with rituximab survived, whereas the 3 patients not treated with rituximab died. Within the D−/R− group, of 5 (0.3%) patients with non–donor-derived primary HHV-8 infection, 3 liver recipients developed KICS. Of the R+ patients (n = 155), 3 developed KS. In our cohort, 25/944 (2.6%) liver transplant recipients had a primary HHV-8 infection, and 10 of them (40%) developed KICS; 40% (4/10) of HHV-8 seropositive heart transplant recipients developed reactivation, and 2 of them (50%) had fatal KS. Serologic screening and molecular surveillance of D+/R− patient groups facilitate early recognition and effective therapy of KICS.

1. Introduction

In solid organ transplant (SOT) recipients, Kaposi sarcoma (KS) herpesvirus/human herpesvirus-8 (HHV-8)-related disease can be the result of a primary infection, either donor or non–donor-derived, or reactivation in recipients with pretransplant HHV-8-positive serology[1] and includes posttransplant (Tx) KS and, exceptionally, lymphoproliferative diseases.[1-3] KS herpesvirus-associated inflammatory cytokine syndrome (KICS) was first described in 10 human immunodeficiency virus (HIV) infected individuals with poor outcomes despite administration of liposomal doxorubicin and antivirals.[4] In SOT recipients, KICS was first described in a kidney-liver transplant (Tx) recipient following donor-derived infection (DDI) who was successfully treated with modification of immunosuppressive therapy, antivirals, and rituximab therapy.[5]

Both HHV-8 neoplastic and nonneoplastic disease in SOT recipients can be life-threatening, especially if unrecognized delay in treatment occurs. At our institution, the Mediterranean Institute for Transplantation and Advanced Specialized Therapy (ISMETT), HHV-8 serology screening has been routinely performed on all donors (D) and recipients (R) since 2011. In 2017, we implemented a protocol for the follow-up of recipients who were HHV-8 antibody (Ab) positive (D+/R+ and D−/R+) or had a serologic mismatch (D+/R−) with the aim of prompt detection and management of HHV-8 infections and related diseases.

The aims of this study were to evaluate (1) the seroprevalence of HHV-8 infection among donors and recipients; (2) the incidence of HHV-8 reactivation and primary infection; (3) the incidence, clinical characteristics, management, and outcomes of HHV-8-related diseases with a particular focus on KICS; and (4) the inflammatory response and cytokine expression patterns in recipients with KICS.

2. Materials and methods

2.1. Patients

A retrospective cohort study was conducted at ISMETT, an SOT center performing lung, liver, heart, kidney, and pancreas

Txs, located in Palermo, Italy. All consecutive patients who underwent SOT from 2011 to 2023 were included. KICS was defined as per Polizzotto et al,[4] which is based on high HHV-8 plasma viral load; evidence of systemic inflammation; clinical, laboratory, and imaging abnormalities; and lack of multicentric Castleman disease (Supplementary Materials). In HHV-8 Ab R+ patients, reactivation was defined by the presence of detectable HHV-8 DNAemia at any level. In D+/R− or D−/R−, primary infection was defined by the presence of detectable HHV-8 DNAemia at any level or by positive post-Tx HHV-8 serology confirmed in a second blood sample taken at least 4 weeks after the first positive results, thus confirming the seroconversion. The study was approved by our Institutional Review Board (IRRB/37/19) and conducted according to the guidelines of the Declaration of Helsinki. All patients gave written informed consent for the use of their anonymized data for research purposes.

2.1.1. Serologic and molecular methods

HHV-8 serology was performed using indirect immunofluorescence (Scimedx Corporation, Denville, NJ, USA), and the results were defined by concordance of 2 independent evaluations. HHV-8 DNAemia monitoring was performed using the HHV-8 ELITe MGB Kit (ELITechGroup, Puteaux, France). Cytokine assays were performed using ProcartaPlex Human Magnetic Luminex Kits (Affymetrix, Wien, Austria) (Supplementary Materials).

2.2. Protocol

ISMETT has developed a protocol to promptly detect HHV-8 infections and treat HHV-8-related diseases.

FIRST PHASE:

Since 2011, HHV-8 serology has been performed on all donors and recipients to stratify the risk of post-Tx HHV-8-related disease.

- Recipients with HHV-8 Ab mismatch (D+/R−) or those who are seropositive (R+) undergo HHV-8 DNAemia monitoring every 15 days for the first 3 months and monthly up to 1 year post-Tx; DNAemia is then checked at all subsequent in-hospital visits. HHV-8 Ab positive recipients receive dedicated instructions on skin self-examination for detection of KS-like lesions.
- Patients with persistent positive HHV-8 DNAemia and symptomatic infection are treated with an antiviral (foscarnet or cidofovir).

SECOND PHASE:

Since 2017, after the description of a case of KICS successfully treated with rituximab,[5] we established a protocol of strict clinical monitoring and early intervention in cases of primary HHV-8 infection (D+/R− and D−/R−) or reactivation (R+).

- The immunosuppression regimen is switched by replacing calcineurin inhibitors (CNIs) with mammalian target of rapamycin (mTOR) inhibitors, when feasible.
- In the case of KICS, we additionally provide rituximab plus an antiviral (foscarnet or cidofovir) as soon as the disease is diagnosed.
- Since 2018, in patients with HHV-8 DNAemia, cytokine expression levels are checked in different clinical disease phases.

All aspects of the first phase, including serologic screening of donors and recipients, clinical and molecular monitoring for high-risk patients, and antiviral treatment for persistent DNAemia and symptomatic infections, are also carried out during the second phase of the protocol.

3. Results

From January 1, 2011 to October 31, 2023, 1963 recipients underwent SOT from 1580 donors (see Table 1). Type and number of Txs are provided in the Supplementary Materials.

3.1. Seroprevalence of HHV-8 infection among donors and recipients

HHV-8 serology was performed on 1856 recipients (94.6%) and 1349 donors (85.4%) (Fig. 1). HHV-8 seroprevalence was higher among recipients than donors (8.4% [155/1856] vs 3.3% [45/1349], $P < .0001$). The highest seroprevalence was observed in liver recipients (10.2%) (Table 1). There were no discordant test results (defined as lytic positive and latent negative antibodies or vice versa) in the deceased donors. Among the recipients, 5 had discordant results: 3 of them repeatedly tested positive at subsequent controls and were considered HHV-8 positive, whereas the other 2 recipients repeatedly tested negative and were considered HHV-8 negative.

3.2. SOT recipients with HHV-8 mismatch (D+/R−) and DDI

Forty-nine (49/1856, 2.6%) recipients had HHV-8 Ab mismatch D+/R− (Table 2). Two patients died within 2 months from non–HHV-8-attributable causes. Twenty-two (22/49, 45%) patients developed a DDI; 21 (95.5%) were liver recipients (including one combined liver/kidney Tx) and one was a lung Tx recipient. No transmission was observed in kidney and heart recipients, whereas 21 of 33 (64%) liver recipients and 1 of 2 (50%) lung recipients with mismatch experienced HHV-8 transmission. DDI was detected by positive HHV-8 DNAemia plus seroconversion in 15 recipients, 4 patients had DNAemia only, and 3 patients had seroconversion only. These latter 3 patients could have experienced low-level, transient DNAemia that was not detected. Median time from Tx to first DNAemia was 71 days (95% CI, 32.5-98.5 days) with a median value of first HHV-8 DNA of 1325 cp/mL (95% CI, 547-2565 cp/mL). By Kaplan-Meier analysis, recipients with mismatch had a higher probability of viremia compared with R+ and D−/R− patients ($P < .0001$; Fig. 2).

Thirteen of 22 patients with primary infection developed HHV-8-related diseases: 1 lung recipient developed KS with subsequent KICS, and 12 liver recipients developed nonneoplastic inflammatory disease. Of these, 5 patients did not meet the criteria for KICS (Table 3), whereas 7 patients did (Table 4). Among the 7 patients with KICS, 3 patients did not receive

Table 1
Pretransplant seroprevalence of HHV-8 Ab among donors and recipients.

Type of Tx	All patients	Patients with HHV-8 Ab screening	Percent of patients screened	HHV-8 Ab−	HHV-8 Ab+	Seroprevalence (HHV-8 Ab+/screened)	*P*
Donors	1580	1349	85.4%	1304	45	3.3%	<.0001[a]
Recipients	1963	1856	94.6%	1701	155	8.4%	
Liver	984	944	95.9%	848	96	10.2%	<.0001[b]
Kidney	667	616	92.3%	577	39	6.3%	
Heart	158	151	95.5%	141	10	6.6%	
Lung	154	145	94.2%	135	10	6.9%	

Ab, antibody; HHV-8, human herpesvirus-8.

[a] Recipients vs donors.

[b] Liver transplant vs other organs.

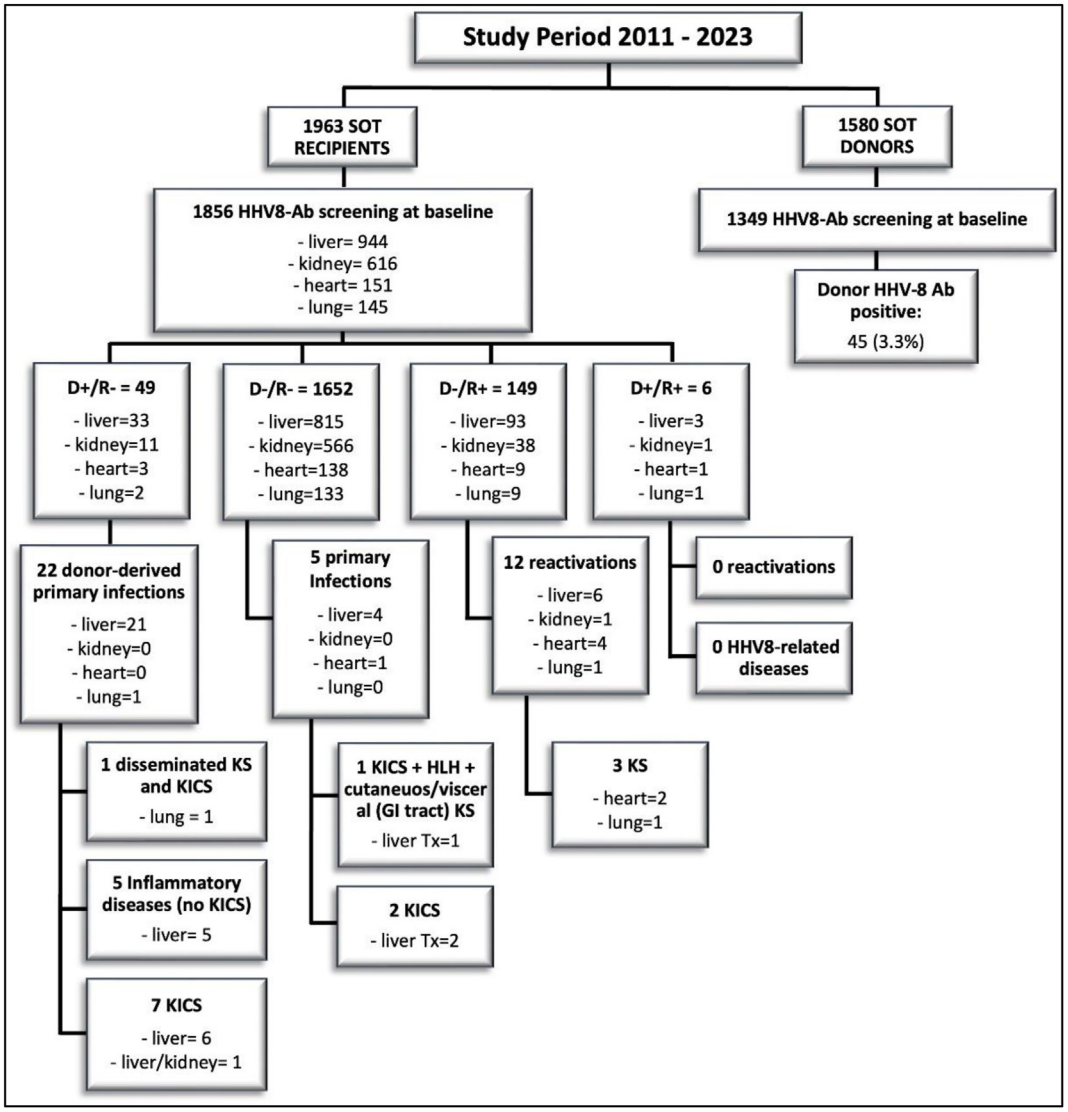

Figure 1. Study population. Ab, antibody; D, donor; GI, gastrointestinal; HLH, hemophagocytic lymphohistiocytosis; HHV-8, human herpesvirus-8; KICS, Kaposi sarcoma herpesvirus inflammatory cytokine syndrome; KS, Kaposi sarcoma; R, recipient; SOT, solid organ transplant.

Table 2
Stratification of recipients (n = 1856) according to HHV-8 Ab serostatus in both donors and recipients.

Type of Tx	HHV-8 Ab R− n = 1701 (91.6%)		HHV-8 Ab R+ n = 155 (8.4%)	
	D+/R−, n (%)	D−/R−, n (%)	D−/R+, n (%)	D+/R+, n (%)
Total Tx recipients	49 (2.6%)	1652 (89%)	149 (8%)	6 (0.4%)
Liver	33 (3.5%)	815 (86.3%)	93 (9.9%)	3 (0.3%)
Kidney	11 (1.7%)	566 (92%)	38 (6.2%)	1 (0.1%)
Heart	3 (2%)	138 (91.5%)	9 (5.8%)	1 (0.7%)
Lung	2 (1.4%)	133 (91.7%)	9 (6.2%)	1 (0.7%)

Ab, antibody; D, donor; HHV-8, human herpesvirus-8; R, recipient; Tx, transplant.

rituximab and died, whereas the remaining 4 were treated with rituximab and survived (Tables 4 and 5, Fig. 3).

In the first phase (2011-2016), when symptomatic patients were treated with antivirals only, 5 of 7 (71%) patients with DDI developed symptomatic infection, 4 of whom (80%) progressed to KICS. One was treated with rituximab and survived, whereas 3 patients were treated with antivirals only and died.

In the second phase (2017-2023), we performed, when feasible, an early switch to mTOR inhibitors at the first DNAemia (median time 21 days) and early treatment of KICS (median time from KICS to rituximab 6.5 days). Eight of 15 (53%) patients with DDI developed symptomatic infection, 4 of whom (50%) developed KICS. Three patients with isolated KICS were treated with rituximab and survived. In the fourth patient, a lung Tx recipient who developed disseminated KS and concomitant KICS, the early switch to mTOR was deemed infeasible by the primary team. He was treated with antivirals, chemotherapy, and rituximab but died of progressive KS.

3.3. D−/R− SOT recipients with primary HHV-8 infection

A total of 1652 recipients were HHV-8 Ab negative with an HHV-8 Ab negative donor (D−/R−). Five of them (0.3%) developed a non–donor-derived primary HHV-8 infection (Fig. 2). Three liver recipients developed disease: 2 had KICS and 1 had KICS complicated by hemophagocytic lymphohistiocytosis and was treated with high doses of steroids with subsequent development of cutaneous and gastrointestinal KS after 2 months. All these patients were treated with a switch to mTOR inhibitors, foscarnet and rituximab; the KS patient also received liposomal doxorubicin, and none of them died (Table 6).

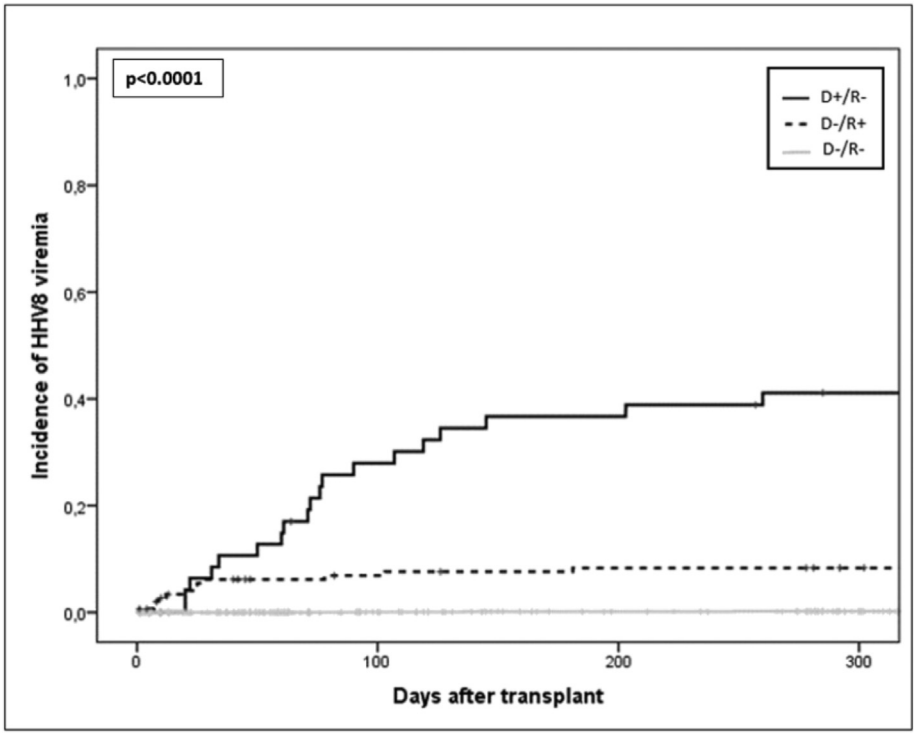

Figure 2. Incidence of HHV-8 viremia divided by donor/recipient match. Black line, D+/R−; dotted line, D−/R+; gray line D−/R−. No cases occurred in 6 D+/R+ patients nor in 107 patients with no available serostatus data. D, donor; HHV-8, human herpesvirus-8; R, recipient.

Table 3
Clinical and virologic characteristics, treatment, and outcomes of patients with HHV-8 inflammatory disease.

Pt, sex, age at Tx	Type of Tx, phase	HHV-8 Ab serostatus	First HHV-8 DNAemia, time from Tx	Max value HHV-8 DNAemia, time from Tx	Manifestations nonneoplastic inflammatory diseases	KICS, time of symptoms/ signs from SOT	Switch to mTOR inhibitor/ antiviral therapy	Attributable death, time from Tx	Death at end of follow-up, time from Tx
1, F, 1 y	Liver, first phase	D+/R− DDI	2630 cp/mL, 126 d	16,200 cp/mL, 132 d	anemia, thrombocytopenia, hypoalbuminemia	No, 132 d	Yes/No	No	No, alive after 11 years from event
2, M, 68 y	Liver, second phase	D+/R− DDI	697 cp/mL, 34 d	697 cp/mL, 34 d	edema, thrombocytopenia, hyponatremia, elevated CRP	No, 34 d	No/Yes	No	No, alive after 8 years from event
3, F, 50 y	Liver, second phase	D+/R− DDI	676 cp/mL, 60 d	3732 cp/mL, 133 d	thrombocytopenia	No, 95 d	Yes/Yes	No	No, alive after 8 years from event
4, M, 56 y	Liver, second phase	D+/R− DDI	816 cp/mL, 60 d	35,675 cp/mL, 177 d	anemia, thrombocytopenia, elevated CRP	No, 195 d	Yes/Yes	No	No, alive after 7 years from event
5, M, 64 y	Liver, second phase	D+/R− DDI	1,325 cp/mL, 61 d	3,346 cp/mL, 68 d	Thrombocytopenia, elevated CRP	No, 68 d	Yes/Yes	No	No, alive after 6 years from event

Ab, antibody; D, donor; DDI, donor-derived infection; F, female; HHV-8, human herpesvirus-8; KICS, Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome; M, male; mTOR, mammalian target of rapamycin; Pt, patient; R, recipient, SOT, solid organ transplant; Tx, transplant.

3.4. HHV-8 Ab positive SOT recipients: D−/R+ and D+/R+ with HHV-8 reactivation

At pre-Tx screening, 155 recipients were found to be HHV-8 Ab positive (8.4%): 6 were D+/R+, whereas 149 were D−/R+. Twelve patients (8%) developed HHV-8 DNA reactivation, with the highest rate in heart (40%), followed by lung (10%), liver (6%), and kidney (3%) Tx recipients. Median time to first DNAemia from transplant was 22 days (Table 7, Fig, 2). Only 3 cases of KS occurred: 2 heart recipients developed visceral KS and were treated with chemotherapy (1 with liposomal doxorubicin and 1 with gemcitabine), but both died due to KS. The third patient, a lung Tx recipient with cutaneous KS, was successfully treated by switching from CNIs to mTOR inhibitors (Supplementary Materials). No cases of KICS or other HHV-8-related diseases were observed in this cohort (Table 7).

3.5. Characteristics, management, and outcomes of KICS pre/postimplementation of protocol

Overall, 16 patients developed HHV-8-related inflammatory disease; most of these patients received antivirals (15/16, 94%) and were switched to mTOR inhibitors (14/16, 87.5%).

Table 4
Clinical and virologic characteristics, treatment, and outcome of patients with KICS.

Pt, sex, age at Tx	Type of Tx, phase	HHV-8 Ab serostatus	First HHV-8 DNAemia, time from Tx	Max value HHV-8 DNAemia, time from Tx	Manifestations of KICS	Exclusion of MCD[a]	KICS, time of symptoms/signs from SOT	Switch to mTOR inhibitor/ antiviral therapy	Anti-CD20 therapy	Attributable death, time from Tx	Death at end of follow-up, time from Tx
1, M, 68 y	Liver, first phase	D+/R− DDI	106 cp/mL, 31 d	231 000 cp/mL, 111 d	fever, edema, anemia, thrombocytopenia, hypoalbuminemia, splenomegaly, body cavity effusions, elevated CRP	NA	Yes, 55 d	No/Yes	No	Yes, 217 d	Yes
2, F, 37 y	Liver/ Kidney, first phase	D+/R− DDI	7050 cp/mL, 260 d	595 000 cp/mL, 455 d	fever, fatigue, edema, anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, lymphadenopathy, splenomegaly, body cavity effusions, elevated CRP	Yes	Yes, 387 d	Yes/Yes	Yes (5 doses)	No	No, alive after 11 y from event
3, F, 67 y	Liver, first phase	D+/R− DDI	65 780 cp/mL, 107 d	76 900 cp/mL, 141 d	fever, fatigue, edema, respiratory symptoms, altered mental state, anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, body cavity effusions, elevated CRP	NA	Yes, 107 d	Yes/Yes	No	Yes, 144 d	Yes
4, M, 49 y	Liver, first phase	D+/R− DDI	1475 cp/mL, 71 d	17 129 cp/mL, 86 d	fever, fatigue, edema, respiratory symptoms, anemia, thrombocytopenia, hyponatremia, body cavity effusions, elevated CRP	NA	Yes, 99 d	Yes/Yes	No	Yes, 111 d	Yes

(*continued on next page*)

Table 4 (*continued*)

Pt, sex, age at Tx	Type of Tx, phase	HHV-8 Ab serostatus	First HHV-8 DNAemia, time from Tx	Max value HHV-8 DNAemia, time from Tx	Manifestations of KICS	Exclusion of MCD[a]	KICS, time of symptoms/signs from SOT	Switch to mTOR inhibitor/ antiviral therapy	Anti-CD20 therapy	Attributable death, time from Tx	Death at end of follow-up, time from Tx
5, M, 48 y	Liver, second phase	D−/R− Non-DDI	3469 cp/mL, 136 d	200 171 cp/mL, 178 d	fever, fatigue, anemia, thrombocytopenia, hypoalbuminemia, body cavity effusions, elevated CRP	NA	Yes, 178 d	Yes/Yes	Yes (4 doses)	No	Yes, death after 5 y from event
6, F, 57 y	Liver, second phase	D+/R− DDI	4332 cp/mL, 22 d	275 428 cp/mL, 63 d	fever, fatigue, edema, respiratory symptoms, anemia, thrombocytopenia, hypoalbuminemia, splenomegaly, body cavity effusions, elevated CRP	NA	Yes, 43 d	Yes/Yes (foscarnet)	Yes (4 doses)	No	No, alive after 5 y from event
7, F, 62 y	Liver, second phase	D+/R− DDI	418 cp/mL, 119 d	52 175 cp/mL, 154 d	fever, fatigue, respiratory symptoms, anemia, thrombocytopenia, hypoalbuminemia, lymphadenopathy, splenomegaly, body cavity effusions, elevated CRP	Yes	Yes, 127 d	Yes/Yes (foscarnet)	Yes (4 doses)	No	No, alive after 5 y from event
8, M, 65 y	Liver, second phase	D−/R− Non-DDI	418 919 cp/mL, 91 d	733 332 cp/mL, 95 d	fever, fatigue, edema, anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, splenomegaly, body cavity effusions, elevated CRP	NA	Yes, 96 d	Yes/Yes (foscarnet)	Yes (4 doses)	No	No, Alive after 10 mo from event

(*continued on next page*)

9, M, 65 y	Liver, second phase	D+/R− DDI	535 507 cp/mL, 72 d	535 507 cp/mL, 72 d	fever, fatigue, edema, anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, elevated CRP	NA	Yes, 72 d	Yes/Yes (foscarnet)	Yes (4 doses)	No	No, alive after 8 mo from event
10, M, 41 y	Lung, second phase	D+/R− DDI	1362 cp/mL, 20 d	2 666 088 cp/mL, 399 d	fever, fatigue, edema, respiratory symptoms, anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, lymphadenopathy, body cavity effusions, elevated CRP	Yes	Yes (with disseminated KS), 334 d	Yes/Yes (foscarnet)	Yes (5 doses)	Yes, 432 d	Yes
11, M, 51 y	Liver, second phase	D−/R− Non-DDI	1 058 998 cp/mL, 248 d	7 178 990 cp/mL, 264 d	fever, fatigue, edema, respiratory symptoms, anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, splenomegaly, body cavity effusions, elevated CRP	NA	Yes (with cutaneous and gastrointestinal KS), 247 d	Yes/Yes (foscarnet)	Yes (4 doses)	No	No, alive after 1 y from event

Ab. antibody; CRP, C-reactive protein; D, donor; DDI, donor-derived infection; F, female; HHV-8, human herpesvirus-8; KICS, Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome; KS, Kaposi sarcoma; M, male; MCD, multicentric Castleman disease; mTOR, mammalian target of rapamycin; NA, not applicable; R, recipient; SOT, solid organ transplant; Tx, transplant.

[a] Histopathologic assessment of lymphadenopathy.

Table 5
Characteristics of 49 solid organ transplant recipients with HHV-8 mismatch D+/R−.

Characteristic	HHV-8 Ab D+/R− n = 49
Demographics	
Sex, M (%)	33/49 (67%)
Age at Tx (y), median (IQR)	57.5 (50-64)
Type of transplant	
Liver and combined liver/kidney	33/49 (67%)
Kidney, pancreas, and kidney/pancreas	11/49 (23%)
Lung	2/49 (4%)
Heart and heart/kidney	3/49 (6%)
Donor-derived primary HHV-8 infections: HHV-8 DNA in blood or HHV-8 Ab seroconversion	
Donor-derived primary HHV-8 infections on total mismatch	22/49 (45%)
Liver and combined liver/kidney	21/33 (64%)
Kidney	0/11 (0%)
Lung	1/2 (50%)
Heart	0/3 (0%)
Patients with detectable HHV-8 DNAemia	19/22 (86%)
Liver and combined liver/kidney	18/21 (86%)
Lung	1/1 (100%)
HHV-8 DNA: characteristics of DNAemia	
Value of first detectable DNAemia (cp/mL), median (IQR)	1325 (547-2565)
Time from Tx to first DNAemia (d), median (IQR)	71 (32.5-98.5)
Max value of DNAemia (cp/mL), median (IQR)	16 200 (3037-153 000)
Time from Tx to max DNAemia (d), median (IQR)	120 (74-166)
Clinical syndromes of patients with donor-derived primary HHV-8 infections	
Asymptomatic	9/22 (41%)
HHV-8-associated KS and KICS	1/22[a] (4%)
Time from Tx to first episode of KS (d)	132
Time from Tx to relapse of KS and KICS (d)	334
HHV-8-associated nonneoplastic manifestations (non-KICS)	5/22 (23%)
Time from Tx to symptoms (d), median (IQR)	95 (68-132)
KICS	7/22 (32%)
Time from Tx to KICS (d), median (IQR)	85 (52-112)
Treatment of patients with donor-derived primary HHV-8 infections	
Switch to mTOR inhibitors	15/22 (68%)
Antiviral therapy	12/22 (55%)
Anti-CD20 therapy/patients with KICS	5/7 (71.4%)
Outcomes	
Attributable death/ all patients with donor-derived primary HHV-8 infections	4/22 (18%)
Attributable death/ patients with KICS	3/7 (57%)
Attributable death/ patients with KICS not treated with anti-CD20 therapy	3/3 (100%)
Attributable death/ patients with KICS treated with anti-CD20 therapy	0/4 (0%)
Attributable death/ patient with disseminated KS + KICS treated with doxorubicin and anti-CD20	1/1[a] (100%)

Ab, antibody; D, donor; HHV-8, human herpesvirus-8; KICS, Kaposi sarcoma herpesvirus inflammatory cytokine syndrome; KS, Kaposi sarcoma; M, male; mTOR, mammalian target of rapamycin; R, recipient; Tx, transplant.

[a] Lung transplant recipient with disseminated KS + KICS treated with doxorubicin and anti-CD20.

Eleven patients met the diagnostic criteria for KICS. Of note, only 3 patients had lymphadenopathy among KICS manifestation, and multicentric Castelman disease was excluded by biopsy. In the remaining patients, lymphadenopathy was not present and therefore biopsy was not performed. In 2 cases, KICS was associated with KS: one lung D+/R− recipient developed disseminated KS 4 months after Tx, complicated by KICS 7 months later, and died of progressive KS. One liver HHV-8 D−/R− recipient with non–donor-derived primary infection developed KICS complicated by hemophagocytic lymphohistiocytosis, which resolved on treatment with high-dose steroids. Two months later, he developed KS and received 4 cycles of liposomal doxorubicin with a favorable outcome.

Nine patients, all liver recipients, had isolated KICS as a manifestation of primary infection (7 donor-derived and 2 non–donor-derived): 6 were switched to mTOR inhibitors and treated with rituximab and antivirals and survived, whereas the remaining 3 patients were treated with antivirals alone without rituximab in the first phase of the protocol and died (Table 4).

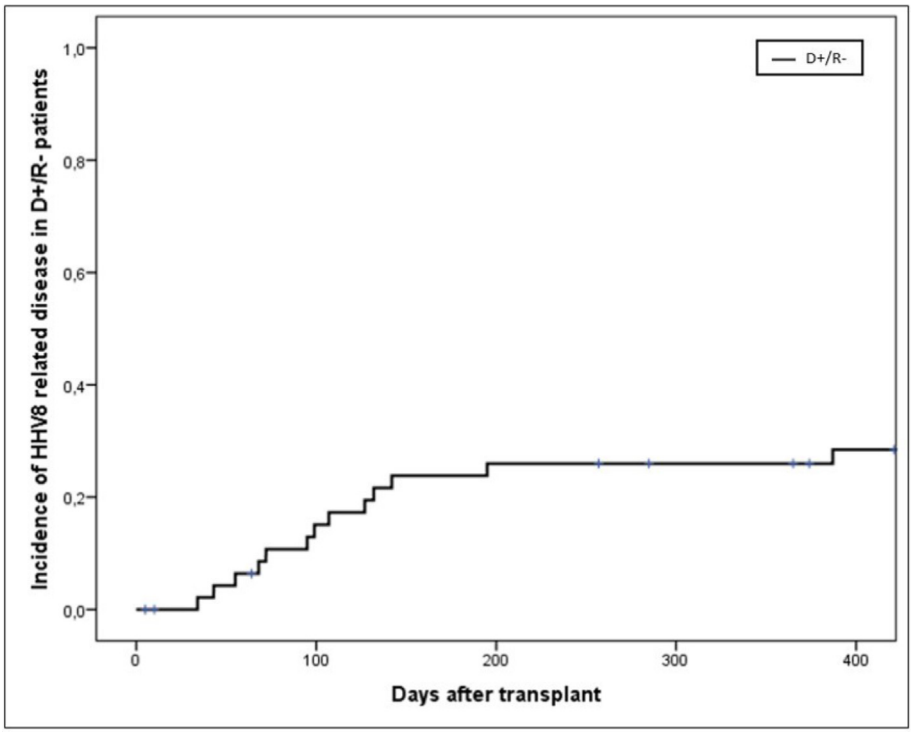

Figure 3. Incidence of HHV-8-related disease in 49 recipients with D+/R- serostatus. Black line, D+/ R-. D, donor; HHV-8, human herpesvirus-8; R, recipient.

3.6. Cytokine levels in asymptomatic, KICS, and KS HHV-8 patients

Fifty-one different cytokines and immune checkpoint proteins were measured in plasma samples from 16 cases with DNAemia. We divided the cases into 3 groups according to clinical manifestations: 6 asymptomatic/mildly symptomatic with HHV-8 DNAemia, 6 with KICS, and 4 with KS. For each case, we measured 3 different time points (T0: first DNAemia, T1: highest DNAemia, T2: descending phase/resolution). By performing correlation analysis on DNAemia vs cytokine levels at all time points, we obtained a significant positive correlation ($P < .05$ and $r > 0.5$) only with interleukin (IL)-10, IL-6, tumor necrosis factor alpha (TNFα), IL-17A, and interferon alfa (IFNα) and a negative correlation with inducible T cell costimulator (Fig. 4), whereas no significant correlations were found with the other cytokines (Supplementary Materials). We compared cytokine levels at T0, T1, and T2 in the 3 groups with different clinical manifestations and found, only at T1, a statistically significant increase of IL-10 and IL-6 in patients with KICS compared to both patients with DNAemia and KS; higher levels of TNFα, IL-1β, IFNα, IL-17A, and indoleamine 2,3-dioxygenase (IDO) in KICS than in DNAemia patients; and a trend toward higher values in KICS than in KS patients. Moreover, we found a marked elevation of programmed cell death-1 in KICS than in the other 2 groups, which only reached significance when compared with KS patients (Fig. 5).

4. Discussion

We provide extensive data on the clinical features and outcomes of the largest available cohort of KICS patients in the SOT setting. Serologic screening and active follow-up of all SOT recipients allowed us to describe (1) the rate of seroprevalence among donors (3.3%) and recipients (8.4%); (2) the rate of HHV-8 transmission (45%), related disease (26.5%), and outcome (mortality, 8.2%) in patients with mismatch (D+/R−); and (3) the rate of HHV-8 reactivation (8%), related disease (2%), and outcome (mortality, 1.3%) in HHV-8 seropositive recipients (R+). These findings significantly extend and refine the previously reported data on HHV-8 in SOT.[6-9]

We observed 11 cases of KICS exclusively as a result of primary infection, both donor- and nondonor-derived, whereas KS occurred after either primary infection in R− or reactivation in R+ patients. In our cohort, KICS was associated with KS in only 2 cases. Conversely, in the first series of 10 patients with HIV and KICS described by Polizzotto and colleagues,[4] all patients had concomitant KS and 2 also had primary effusion lymphoma.

Due to its nonspecific clinical features and lack of characteristic skin lesions, in the SOT setting, KICS may be misdiagnosed and confused with other clinical conditions characterized by fever, pancytopenia, and a dysregulated inflammatory response, such as sepsis and other viral infections. In a recent survey, only 33% of SOT centers reported screening for HHV-8 infection, whereas HHV-8-related complications were reported by 67% of centers.[10] This could explain the underdiagnosis and underreporting of KICS in the literature. However, left unrecognized and therefore untreated, KICS can rapidly lead to death by multiorgan failure. Relevant to this, during the period 2011-2016 (first phase), patients were treated only with antivirals at a late stage of the disease, and 5 of 7 (71%) DDIs evolved to symptomatic infections. Of these, 4 patients (80%) progressed to KICS, 3 of whom received antivirals alone without

Table 6
Characteristics of solid organ transplant D−/R− with nondonor-derived primary HHV-8 infection.

Nondonor-derived primary HHV-8 infections: HHV-8 DNA in blood or HHV-8 Ab seroconversion	HHV-8 Ab D−/R− n = 5
Demographics	
Sex, M (%)	5/5 (100%)
Age at Tx (y), median (IQR)	51 (48-63)
Type of transplant	
Liver and combined liver/kidney	4/5 (80%)
Kidney, pancreas, and kidney/pancreas	0/5 (0%)
Lung	0/5 (0%)
Heart and heart/kidney	1/5 (20%)
Patients with detectable HHV-8 DNAemia	3/5 (60%)
HHV-8 DNA: characteristics of DNAemia	
Value of first detectable DNAemia (cp/mL), median (IQR)	418 000 (211 000-738 000)
Time from Tx to first DNAemia (d), median (IQR)	136 (113.5-192)
Max value of DNAemia (cp/mL), median (IQR)	733 000 (466 000-3 956 000)
Time from Tx to max DNAemia (d), median (IQR)	178 (136.5-221)
Clinical syndromes of patients with non-donor-derived primary HHV-8 infections	
Asymptomatic	2/5 (40%)
HHV-8-associated KICS and cutaneous and visceral KS	1/5[a] (20%)
Time from Tx to KICS and KS (d)	232
KICS	2/5 (40%)
Time from Tx to KICS (d), median (IQR)	178 (137-212.5)
Treatment of patients with non–donor-derived primary HHV-8 infections	
Switch to mTOR inhibitors	5/5 (100%)
Antiviral therapy	3/5 (60%)
Anti-CD20 therapy/patients with KICS	3/3 (100%)
Outcomes	
Attributable death/ patients with non–donor-derived primary HHV-8 infections	0/5 (0%)

Ab, antibodies; D, donor; HHV-8, human herpesvirus-8; KICS, Kaposi sarcoma herpesvirus inflammatory cytokine syndrome; KS, Kaposi sarcoma; M, male; mTOR, mammalian target of rapamycin; R, recipient; Tx, transplant.

[a] Liver transplant recipient developed KICS and subsequently disseminated KS.

Table 7
Characteristics of HHV-8 Ab-positive solid organ transplant recipients (D−/R+ and D+/R+).

Characteristic	HHV-8 Ab R+ n = 155
Sex, M (%)	89/155 (57%)
Age at Tx (y), median (IQR)	58 (49-62)
HHV-8 reactivations: HHV-8 DNA in blood	
HHV-8 reactivations	12/155 (8%)
Liver and combined liver/kidney	6/96 (6%)
Kidney, pancreas, and kidney/pancreas	1/39 (3%)
Lung	1/10 (10%)
Heart and heart/kidney	4/10 (40%)
Value of first detectable DNAemia, median (IQR)	1000 (499-1712)
Time from Tx to first DNAemia (d), median (IQR)	22 (8.75-40.5)
Max value of DNAemia, median (IQR)	1930 (1030-3017)
Time from Tx to max DNAemia (d), median (IQR)	24.5 (18-126)
Clinical syndromes of patients with HHV-8 reactivations	
Asymptomatic	9/12 (75%)
KS, n (%)	3/12 (25%)
Time from Tx to KS (days), median (IQR)	383 (293.5-1104.5)
Outcomes	
Attributable death in patient with KS, n (%)	2/3 (66%)

Ab, antibody; D, donor; HHV-8, human herpesvirus-8; KS, Kaposi sarcoma; M, male; R, recipient; Tx, transplant.

rituximab and died, whereas 1 patient was treated with antivirals, switched to mTOR inhibitor and rituximab, and survived[5]. After this experience, we decided to change our protocol by introducing an early intervention, with a switch to mTOR inhibitors in cases of primary infection and treatment of KICS with rituximab. In the second phase (2017-2023), 8 of 15 (53%) DDIs evolved into symptomatic infections and 4 (50%) developed KICS. Three of these patients with isolated KICS were treated with rituximab and survived. Available therapeutic strategies include modification of the immunosuppressive regimen, antivirals, and immunomodulatory agents. Conversion from CNIs to mTOR inhibitors, beyond the antiproliferative effect on KS,[11] has been associated with early recovery of HHV-8-specific cytotoxic T cells,[2] which may lead to better control of infection. Antivirals may be useful in reducing HHV-8 viral load, but when given alone, are likely to be insufficient due to the uncontrolled and dysregulated inflammatory response of the host. Some cases of HHV-8-associated nonneoplastic disease, possibly KICS with

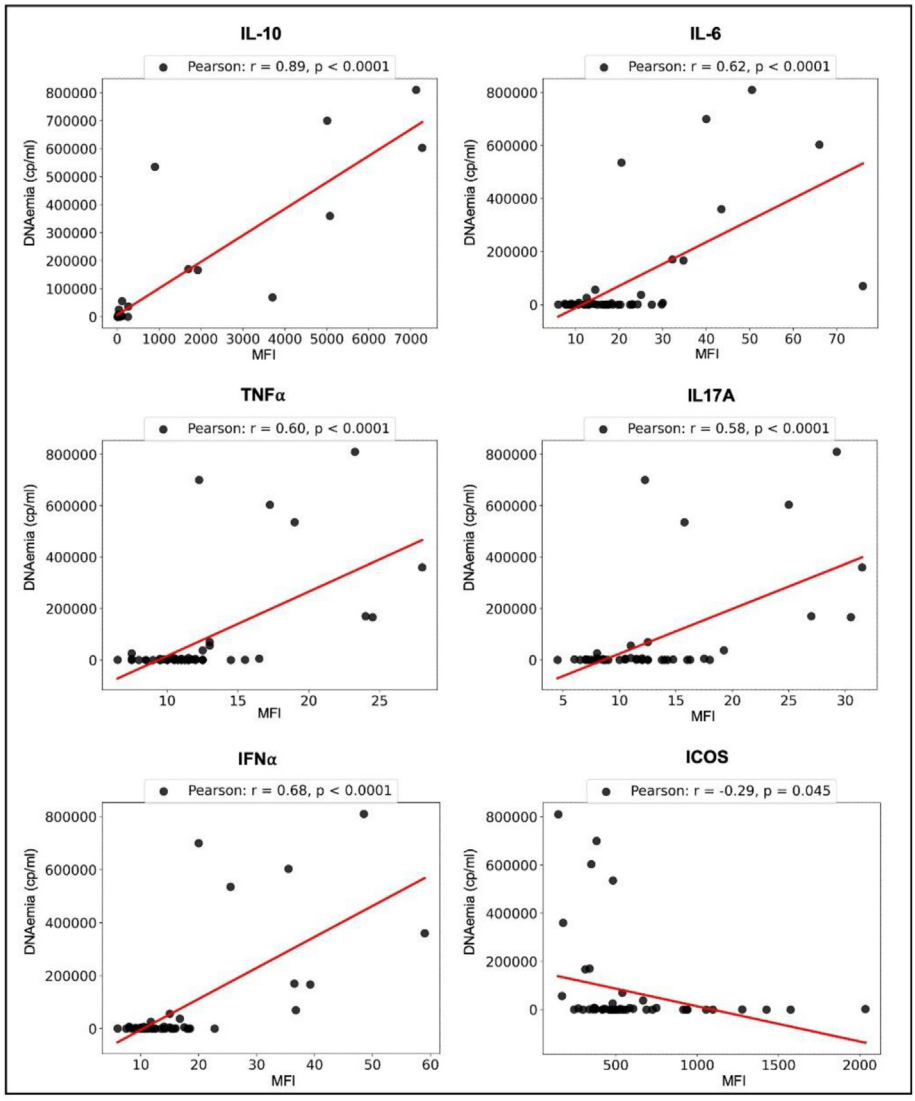

Figure 4. Correlation analysis of DNAemia vs cytokine levels in 16 cases (14 patients), including 6 asymptomatic/mildly symptomatic with HHV-8 DNAemia patients, 6 with KICS, and 4 with KS. Pearson's rank correlation (two-tailed) was obtained using cumulative parameters obtained for all time points analyzed (T0, T1, and T2). The significance (*P* and *r* values) is indicated in each panel. HHV-8, human herpesvirus-8; KICS, Kaposi sarcoma herpesvirus inflammatory cytokine syndrome; KS, Kaposi sarcoma; ICOS, inducible T cell costimulator; IL, interleukin; IFNα, interferon alfa; MFI, mean fluorescence intensity; TNFα, tumor necrosis factor alpha.

the currently available diagnostic criteria, have been described in the literature.[6,8,12-14] Most patients treated with antivirals alone died,[6,7,12] whereas those treated with rituximab survived.[5,13,15] Our study is the first to suggest that the systematic use of rituximab is associated with improved outcomes in SOT patients with KICS. Consistent with this, Ramaswami and colleagues[16] presented a prospective study of 44 patients with HIV and KICS, 18 of whom were treated with rituximab, which was beneficial in 55% of the patients. In our study, KICS patients exhibited markedly elevated levels of proinflammatory cytokines (IL-10, IL-6, TNFα, IL-1β, IFNα, and IL-17A) compared with both infected controls and KS patients. The higher levels of serum programmed death-1 and IDO reported in other infectious diseases[17-20] may represent a potential biomarker for KICS severity. Dysregulated IDO activity, crucial for T cell proliferation, may contribute to immune dysfunction and disease progression in KICS, as reported in HIV and hepatitis infections.[21-26] Conversely, a negative correlation was found between DNAemia and inducible T cell costimulator, suggesting a possible regulatory function in controlling viral replication. Our study extends the findings of Polizzotto et al[4] who, in a cohort of patients with HIV and HHV-8 coinfection, demonstrated higher elevations of IL-6 and IL-10 in KICS patients. We suggest that the use of rituximab may result in a wider blockade of the cytokine cascade through the potential eradication of HHV-8-infected CD20+ B cells and thus contribute to limiting viral proliferation by reducing the reservoir.[2]

Among D−/R− patients, 5 recipients developed a non–donor-derived primary HHV-8 infection. The median value of first DNAemia was higher (418 000 cp/mL) than that observed in patients with HHV-8 Ab mismatch (1300 cp/mL). These data might be explained by the fact that these patients received a delayed diagnosis because they were not included in the protocol for HHV-8 monitoring. Within this group of patients, 3 developed KICS, but none died. Even though these patients had higher DNAemia at the time of KICS diagnosis, prompt introduction of rituximab and antivirals led to clinical recovery. It is possible that the patients with non–donor-derived primary infection were misclassified, and the donor had a false negative HHV-8 serology. However, a high index of suspicion for HHV-8 infection in SOT

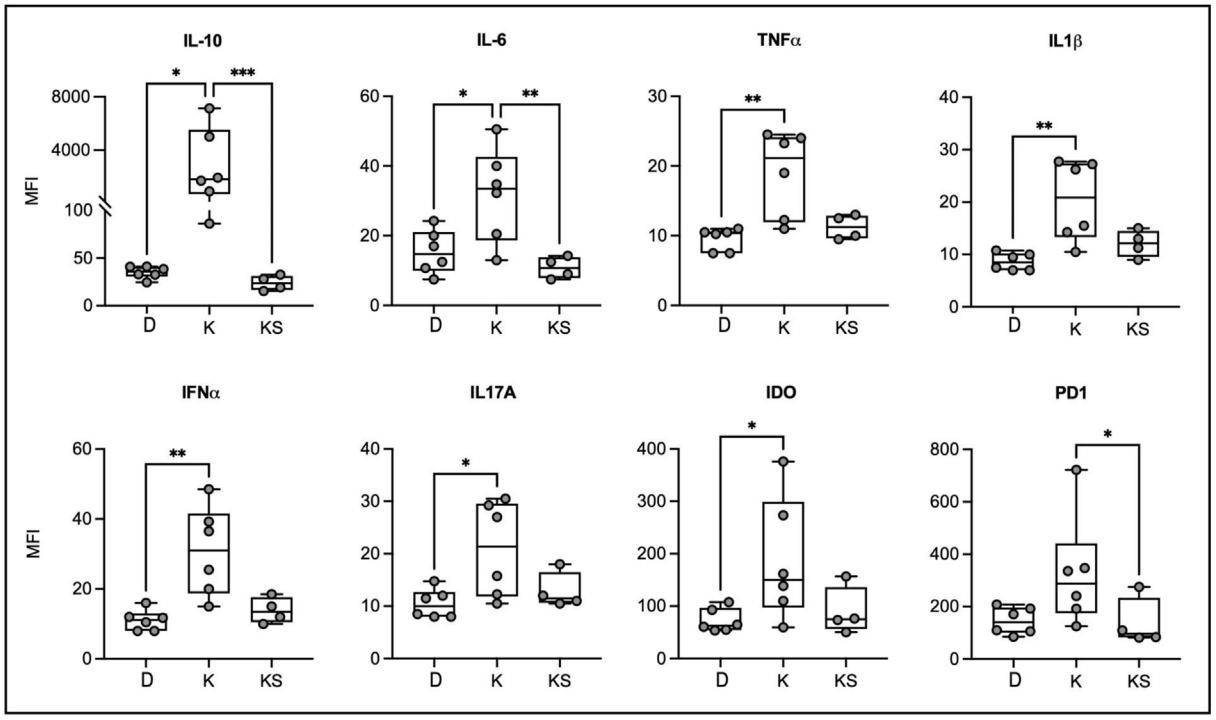

Figure 5. Plasma levels of IL-10, IL-6, TNFα, IL1β, IFNα, IL17A, IDO, and PD-1 during higher DNAemia (T1) in patients with DNAemia (D), Kaposi sarcoma herpesvirus inflammatory cytokine syndrome(K), and Kaposi sarcoma (KS). *$P \leq .05$, ** $\leq .01$, ***$P \leq .001$. IDO, indoleamine 2,3-dioxygenase; IL, interleukin; IFNα, interferon alfa; MFI, mean fluorescence intensity; PD-1, programmed death-1; TNFα, tumor necrosis factor alpha.

recipients with an unexplained fever may prompt an early diagnosis of KICS and avoid a potentially fatal outcome.

In our cohort, HHV-8 seroprevalence was 8.4% in recipients and 3.3% in donors. Seroprevalence was higher among liver Tx recipients (10.2%) than in other organ recipients (lung 6.9%, heart 6.6%, kidney 6.3%). A similar discrepancy between donors and recipients has already been reported in a study by Chiereghin et al[7] describing seroprevalence rates of 18% and 4% in Italian recipients and donors, respectively. Our hypothesis is that the difference in HHV-8 seropositivity among donors and recipients could be explained by the different comorbidities in the 2 populations, with the latter possibly being more exposed to factors potentially associated with HHV-8 infection such as coinfections with other viruses (hepatis B or C virus, etc) which may share the same methods of transmission with HHV-8. Among 45 donors in our cohort, high-risk sexual activity was reported in only 2 cases and use of blood products in 3 other cases, and none were injecting drug users. Factors associated with seropositivity among donors and recipients and by organ type should be evaluated in further studies.

Current guidelines do not support universal screening mainly due to the lack of standardized serologic assays for anti-HHV-8 Ab, and just a few centers perform serology in recipients, donors, or both.[10] The only serologic assay available at the present time is an immunofluorescence test, which is time-consuming and requires expertise in interpreting the results. We believe that an uncertain serologic result should be assumed positive to consider the patient at high risk and allow molecular and clinical monitoring for HHV-8-related disease, ensuring prompt diagnosis and management. The lack of an optimal serologic assay should not be a limitation because organs should not be excluded based on HHV-8 serology results. Nonetheless, information on the HHV-8 donor/recipient serostatus could provide an opportunity for clinical and virologic monitoring of patients at risk of HHV-8-related disease.

In our cohort, 25/944 (2.6%) liver Tx recipients had a primary HHV-8 infection, and 10 of them (40%) developed KICS; 1 of 2 lung Tx recipients with mismatch (50%) developed KS and concomitant KICS. Among 10 HHV-8 seropositive heart Tx recipients, 4 (40%) developed reactivation, and 2 of them (50%) had fatal KS. Because the median time of onset of DDI was 71 days after SOT, samples for serology could be sent to reference laboratories for risk stratification. Adequate follow-up and detection of HHV-8 DNA positivity allows the clinician to modulate immunosuppression and improve the timely recognition and treatment of HHV-8 disease.

The limitations of this study are inherent to its observational and retrospective nature, including the absence of a control arm of patients with KICS not receiving rituximab. However, data can be extrapolated from comparison with the preintervention period when rituximab was not systematically used. Due to the small number of KICS cases reported worldwide, randomized controlled trials might be difficult to conduct. Moreover, as this is a monocentric study conducted in an HHV-8 endemic region, our results may not be fully generalizable to other settings. In our cohort, the majority of donor-derived transmissions occurred in liver Tx recipients; this finding differs from that published by Dollard et al[27] in which lung recipients appeared most susceptible to HHV-8 infection. In our cohort, the vast majority of SOTs were represented by liver Tx recipients, whereas lung Tx

recipients were the minority. Larger cohorts of comparable numbers of either liver or lung and heart recipients are needed to investigate whether transmission rates can be influenced by the type of transplanted organs. In addition, the different transmission rates could be explained by the different designs of the 2 studies: in our cohort, all high-risk patients were prospectively followed up with clinical and virologic monitoring, and this allowed us to describe the actual rate of transmission. Unlike our study, in the study by Dollard et al,[27] recipients' data were retrieved starting from a case series of KS patients due to donor-derived transmission, and cases of nonsevere infection could have been underestimated.

Currently available serologic assays show variable performance rates worldwide, and misclassification of patients' serologic status in our study cannot be ruled out. Furthermore, because blood products are not screened for HHV-8 in Italy, it cannot be formally excluded that some patients were seropositive because of transmission by blood transfusion.[28-30] The impact of HHV-8 screening may vary, based on the actual prevalence of HHV-8 infection, but even if a limited number of D+/R− patients are identified, the impact on outcomes in liver recipients is potentially highly beneficial.

In summary, our protocol for diagnosis and prompt treatment of HHV-8-related nonneoplastic disease allowed mitigation of the impact of HHV-8 infection on recipient outcomes.

We suggest that further studies should assess the clinic utility of serologic assays for screening of donors and recipients and identify factors associated with seropositivity. Molecular surveillance of patients with HHV-8 Ab mismatch may allow early recognition of HHV-8-related nonneoplastic diseases and KICS. Indeed, diagnosis of these diseases can be challenging due to the absence of characteristic skin lesions and may be attributed to sepsis if HHV-8 DNAemia is not performed. Our data on KICS cytokine patterns provide new insights into the pathogenesis of virus-related cytokine storms in SOT patients and potential targets for therapeutic intervention. The optimal therapeutic strategy for KICS is still under investigation. We have proposed a protocol for the management of HHV-8 infection based on the early introduction of mTOR inhibitors in patients with positive DNAemia and the use of rituximab in cases of KICS, in addition to antivirals. The usefulness of our protocol should be tested in prospective multicenter studies that include centers from different geographic areas.

Data availability

The data presented in this study will be available from the corresponding author upon reasonable request.

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Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2024.11.013.

ORCiD

Alessandra Mularoni https://orcid.org/0000-0001-8612-5581
Andrea Cona https://orcid.org/0000-0002-2084-6535
Matteo Bulati https://orcid.org/0000-0002-3269-935X
Rosalia Busà https://orcid.org/0000-0002-7546-7209
Monica Miele https://orcid.org/0000-0002-1606-651X
Francesca Timoneri https://orcid.org/0000-0002-1634-1809
Mariangela Di Bella https://orcid.org/0000-0001-5502-4841
Salvatore Castelbuono https://orcid.org/0009-0002-8262-8223
Floriana Barbera https://orcid.org/0000-0001-6732-1923
Daniele Di Carlo https://orcid.org/0000-0003-0352-3993
Lorenzo Volpe https://orcid.org/0009-0009-6116-1565
Alessia Gallo https://orcid.org/0000-0001-6737-9770
Anna Maria de Luca https://orcid.org/0009-0001-8136-0619
Giulia Coniglione https://orcid.org/0009-0006-5629-9998
Francesca Todaro https://orcid.org/0009-0007-1789-5743
Patrizia Barozzi https://orcid.org/0000-0002-8936-1114
Giovanni Riva https://orcid.org/0000-0003-2089-6230
Giada Pietrosi https://orcid.org/0000-0002-2299-7118
Salvatore Gruttadauria https://orcid.org/0000-0002-9684-8035
Alessandro Bertani https://orcid.org/0000-0003-1684-3259
Patrizio Vitulo https://orcid.org/0000-0003-1699-0208
Alessandra Fontana https://orcid.org/0009-0000-7484-3754
Manlio Cipriani https://orcid.org/0000-0002-0632-0561
Sergio Rizzo https://orcid.org/0009-0000-9460-3627
Antonio Arcadipane https://orcid.org/0000-0001-6521-3806
Angelo Luca https://orcid.org/0000-0001-6859-4915
Malgorzata Mikulska https://orcid.org/0000-0002-5535-4602
Pier Giulio Conaldi https://orcid.org/0000-0003-1994-8005
Paolo Antonio Grossi https://orcid.org/0000-0003-2883-5061
Mario Luppi https://orcid.org/0000-0002-0373-1154

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