Rapidly Fatal Hemophagocytic Lymphohistiocytosis Developing Within Six Days Following Deceased-Donor Renal Transplantation: Case Report

E.J. Filippone[a,*], P. Singh[a], A.M. Frank[b], A. Gupta[c], and J.L. Farber[d]

[a]Division of Nephrology, Department of Medicine, Sydney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania; [b]Department of Surgery, Sydney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania; [c]Department of Medicine, Albert Einstein Medical Center, Philadelphia, Pennsylvania; and [d]Department of Pathology, Sydney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an often fatal hyperinflammatory syndrome that may complicate malignancy, infection, rheumatic disease, or immunosuppression. HLH after kidney transplantation is most often triggered by infection, usually Herpes viruses such as cytomegalovirus and Epstein-Barr virus (EBV). It usually occurs early after transplantation. We present a case of HLH triggered by reactivation of EBV that pursued a rapidly fatal course within 6 days of receiving a deceased-donor kidney transplant. This case serves to remind transplant clinicians to consider HLH when cytopenias and hyperinflammation are atypical for the usual post-transplantation course. We discuss pitfalls in diagnosis and suggestions for treatment in this setting.

HEMOPHAGOCYTIC lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by an overly aggressive yet ineffective immune response [1]. Both cytotoxic CD8+ T lymphocytes (CTLs) and natural killer cells (NKs) have impaired cytolysis. CTLs proliferate and produce large amounts of interferon-γ and other cytokines. The result is a proliferation of benign macrophages with hemophagocytosis and tissue invasion by both macrophages and CTLs. A substantial production of proinflammatory cytokines occurs ("cytokine storm"). Patients are febrile with organomegaly, pancytopenia, and end-organ dysfunction (central nervous system, liver, kidney, lung,). Laboratory abnormalities include hyperferritinemia, hypofibrinogenemia, coagulopathy, hypertriglyceridemia, and abnormal liver function. Histiocytes (macrophages) that phagocytize various cellular elements are frequently found in bone marrow aspirates and in the liver, spleen, or lymph nodes.

HLH may occur as a primary form with a genetic basis due to recessive mutations in one of several genes involved in the function of cytotoxic degranulation of CTLs and NKs [2], where it is called familial HLH (FHL). HLH may also complicate other inherited immunodeficiency syndromes [2]. A reactive form of HLH (rHLH) can occur at any age, usually in response to one or more triggers, including infections, malignancy, immune deficiency (human immunodeficiency virus infection or transplantation), or autoimmune/autoinflammatory diseases [3]. In the latter case, HLH is known as the macrophage activation syndrome (MAS).

HLH has been described in the setting of kidney transplantation. In 1979, Risdall et al reported 19 patients with rHLH, 13 of whom were kidney transplant recipients (KTRs) [4]. An editorial review in 2009 by Ponticelli and Alberighi [5] identified 76 reported cases in KTRs, with 53% mortality. Subsequently, additional case reports have appeared [6–11]. HLH in KTRs was triggered most commonly by infection, but also by malignancy. Typically, it occurred early after transplantation, with the earliest reported case being 10 days [12]. We present here a rapidly fatal case that developed within a week after a deceased-donor kidney transplantation. Reactivation of Epstein-Barr virus (EBV) was the trigger. This case highlights the difficulty of both suspecting and diagnosing HLH in the immediate post-transplantation period.

*Address correspondence to Edward J. Filippone, MD, 2228 South Broad St, Philadelphia, PA 19145. E-mail: kidneys@comcast.net

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CASE REPORT

A 53-year-old African-American man with beta-thalassemia and sickle cell trait had hypertension-induced end-stage kidney disease and had been on hemodialysis for 9 years. Stable splenomegaly (15.7 cm) was present on serial computerized tomographic (CT) scans over a period of 3 years. He received a compatible 6-antigen-mismatched allograft from an African-American woman who died of anoxic brain injury. The terminal serum creatinine was 1.5 mg/dL with a Kidney Donor Profile Index of 77%. Cytomegalovirus (CMV) serology was D+/R−, and EBV serology was D+/R+, the recipient being EBV viral capsid antigen (VCA) IgG+, EBV-VCA IgM-, and EBV nuclear antigen IgG+, indicating latent infection. The donor was not at high risk for infectious disease transmission. Induction consisted of 1.5 mg/kg antithymocyte globulin (ATG) and 500 mg intravenous methylprednisolone. Subsequent ATG dosing was decreased owing to low platelet count, but was continued daily. The cumulative ATG dose was 450 mg (~4.5 mg/kg). Total steroid dosage included 3.75 g methylprednisolone and 260 mg prednisone. The steroids were discontinued on postoperative day 5. Maintenance immunosuppression consisted of tacrolimus (trough of 8–11 ng/mL) and 1,000 mg mycophenolate mofetil twice daily. Prophylaxis included trimethoprim-sulfamethoxazole and valgancyclovir. Hemodialysis was required for delayed function. Renal ultrasound revealed normal appearance of the transplant without perinephric collections. *Clostridium difficile*–positive diarrhea developed with prompt response to oral vancomycin. A fever to 103.1°F occurred perioperatively, but subsequent temperatures were normal or hypothermic.

Exacerbation of chronic back pain developed on day 5. Morning laboratory tests on day 6 revealed a drop in hemoglobin to 7.5 mg/dL with worsening leukopenia and thrombocytopenia (Table 1). Repeated complete blood count 6 hours later revealed a hemoglobin of 5.1 mg/dL. Two units of packed red cells (PRBCs) were administered, with minimal response of the hemoglobin. Because of hemodynamic instability, the dialysis treatment that afternoon was shortened. A CT scan again showed splenomegaly (17.6 cm) and nodular bibasilar pulmonary opacities, but no bleeding was apparent. The hemolysis profile and direct antiglobulin testing were negative. The patient rapidly deteriorated and experienced a cardiac arrest. Despite multiple transfusions, he was unable to be resuscitated and died 2 hours later. Peak aspartate transaminase was 476 IU and peak alanine transaminase 389 IU. Ferritin was not measured. D-Dimers were 10,500 ng/mL (normal, <281 ng/mL), the international normalized ratio 1.6, and fibrinogen 225 mg/dL.

An autopsy was performed. The spleen was enlarged (1.4 kg) and prominently congested. Microscopically, loss of white pulp, marked congestion, and erythrophagocytosis were present. The liver weighed 1.9 kg with congestion of the sinusoids and hypertrophic Kupffer cells with erythrophagocytosis. The lungs were congested with interstitial macrophages also showing erythrophagocytosis. Immunohistochemistry for CD68 showed increased numbers of macrophages in all 3 organs. CD163-positive hemophagocytosing macrophages were numerous in the spleen (Fig 1). The heart had left ventricular hypertrophy with patent coronary arteries. The transplanted kidney had intact anastomoses and multiple small cortical infarcts. No surgical or gastrointestinal bleeding was present. Examination of the brain revealed only neuronal injury. Immunohistochemical staining for EBV-encoded RNA (EBER in situ hybridization) was positive in the spleen and lungs. In summary, the cause of death was rHLH with severe anemia that resulted from EBV reactivation.

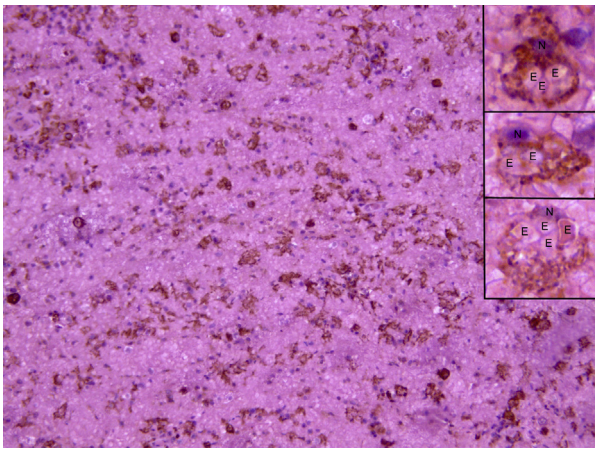

Fig 1. Photomicrograph of the spleen at autopsy. A marked depletion of white pulp is present, with replacement by erythrocytes and CD163 + macrophages (× 200). At higher magnification (insets, × 1,000), numerous macrophages contain cytoplasmic erythrocytes (*E*). *N* marks the macrophage nuclei. Macrophage cytoplasm is immunoreactive for CD163 (*brown*).

DISCUSSION

HLH represents a hyperinflammatory state with many potential inciting causes. There is no pathognomonic finding or test result that confirms the diagnosis. In 1991, The Histiocyte Society published criteria for the diagnosis of pediatric FHL, with an update in 2004 (HLH-2004) [13] (Table 2). Our patient did not satisfy these criteria, but 4 of the 8 were not evaluated, owing to his rapid demise. Had he not expired, a serum ferritin and bone marrow aspiration

Table 1. Patient Laboratory Data

Laboratory Values	Postoperative Day										
	Pre op	0	1	2	3	4	5	6, 4 am	6, 10 am	6, 5 pm	6, 8 pm
Hb, g/dL	12.4	10.2	8.9	8.8	9.3	9.7	8.9	7.6	5.1	5.6	4.0
Platelets, X1000/mcL	113	63	50	46	65	76	78	25	14		26
Leukocytes, X1000/mcL	5.7	3.2	6.7	7.1	7.3	4.1	3.3	1.6	2.1	8.2	6.8
Absolute Neutrophil/absolute lymphocyte, X1000/mcL			6.45/0.06			3.62/0.21		1.16/0.23			
Creatinine, mg/dL	10.5	10.1	10.8	12.7	8.5	10.1	7.9	9.3			7.9
Potassium, mmol/L	3.8	4.3	3.9	5.3	4.4	4.6	4.0	4.4			6.2
Bicarbonate, mmol/L	18	21	24	21	24	22	26	19			13