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Hemophagocytic Lymphohistiocytosis in Solid Organ Transplants

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Received 25 June 2024; revised 24 November 2024; accepted 2 December 2024; published online 6 December 2024

Kidney Int Rep (2025) **10,** 960–963; https://doi.org/10.1016/j.ekir.2024.12.003

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal, and underrecognized syndrome in solid organ transplant (SOT) recipients.[1-3] It is a heterogeneous clinicopathological entity, and the presentation mimics common conditions (fever, cytopenia, lymphadenopathy, hepatosplenomegaly, sepsis, and multiorgan failure).[1-3] Owing to this, the diagnosis is often missed or delayed, contributing to poor prognosis and mortality rate of 40% to 50%.[1-3] It is divided into primary or familial HLH and acquired (secondary, reactive) forms. The primary condition is commonly seen in the pediatric population and is caused by genetic mutations.[1-3] Whereas secondary HLH (sHLH) is triggered by an underlying disorder and is the focus of our study.[1-3]

sHLH is characterized by excessive but ineffective immune activation.[3] In SOTs, sHLH can be triggered by various events that disrupt immune homeostasis, such as systemic infections, neoplasia, autoimmunity, and immunosuppression.[3,4] Abnormal T lymphocyte activation in this situation leads to interleukin (IL)-2 and interferon secretion, which in turn activates the macrophages and production of proinflammatory cytokines (tumor necrosis factor, IL-1, and IL-6).[3] A cytokinin storm then causes tissue infiltration (bone marrow, spleen, hepatic cytolysis, and lymph nodes) by phagocytizing histiocytes and direct cytotoxicity of activated macrophages.[3] Fever, cachexia, hyperferritinemia, and inflammatory syndrome are secondary to elevated serum IL-1 and tumor necrosis factor–concentration.[3] Revised HLH-2004 diagnostic criteria require 5 of the following 8 features: (i) fever; (ii) splenomegaly; (iii) cytopenia involving 2 of 3 lineages; (iv) hypertriglyceridemia (> 3 mmol/l) and hypofibrinogenemia (2400 U/ml); (v) hemophagocytosis in bone marrow, spleen, or lymph nodes; (vi)) reduced or absent natural killer cell activity; (vii) hyperferritinemia (> 500 ng/ml); and (viii) elevated soluble IL-2 receptor.[5] Bone marrow biopsy is considered the most sensitive diagnostic test, but is not universally positive.[5,6] Our case series aims to assess the incidence, management, and prognosis of sHLH in SOT. Key teaching points of this case are presented in Table 1.

CASE PRESENTATIONS

Six SOT recipients diagnosed with sHLH (4 kidneys, 1 liver, and 1 heart) formed the final study group (Supplementary Methods). Baseline characteristics, presentation, immunosuppression, management, and outcomes of the study group are listed in Table 2, and laboratory values are in Supplementary Table S1. Based on the chart review, the estimated prevalence of HLH at our center was 0.15%. Induction agents were antithymocyte globulin in all kidney recipients and IL-2 receptor antagonist (basiliximab) for liver and heart transplants. Initial maintenance agents posttransplant were calcineurin inhibitors (cyclosporin and tacrolimus) and Myfortic in all the recipients. The median time to diagnosis posttransplant was 2 years (1 month–2.6 years). All recipients were Caucasians, 83% were male, and the median age of diagnosis was 50 (28–72) years.

Table 1. Teaching points

1. As presentation of HLH can be nonspecific, high index of clinical suspicion is important.
2. Early recognition and treatment initiation can decrease mortality.
3. Management involves reducing immunosuppression, treating the trigger and immunomodulatory therapy are the cornerstone for management of HLH.

HLH, hemophagocytic lymphohistiocytosis.

Table 2. Baseline characteristics, presentation, management, and prognosis of HLH in six solid organ transplants

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Type & time since transplant, yrs	Kidney (LDKT), 4.2	Kidney (DDKT), 6.7	Kidney (DDKT), 5.2	Kidney (LDKT), 12	Liver (OLT), 6.9	Heart (OHT), 11.4
Approximate time posttransplant when HLH was diagnosed	6 mo	1 mo	1.8 yrs	1.6 yrs	2.6 yrs	2.2 yrs
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Etiology of end-stage organ disease	Diabetes	IgA nephropathy	Hypertension	Adult polycystic kidney disease	Autoimmune hepatitis	Nonischemic cardiomyopathy
Immunosuppression - Induction	ATG	ATG	ATG	ATG	basiliximab	basiliximab
Immunosuppression (Maintenance at the time of transplantation)	tacrolimus, Myfortic	tacrolimus, Myfortic	tacrolimus, Myfortic	Neoral, Myfortic	tacrolimus, Myfortic	tacrolimus, Myfortic
Immunosuppression post HLH	tacrolimus, prednisone	tacrolimus, mycophenolate	tacrolimus, mycophenolate	rapamune	everolimus, tacrolimus	prednisone, sirolimus
Rejection (Y/N), treatment given	No	No	No	Yes, ATG, steroid, plasmapheresis, i.v. Ig	No	Yes, pulse prednisone
Clinical presentation	Fever, headaches	Fever, diarrhea	Diarrhea, cramps	Fever, headaches	Fever, mastoid pain	Sepsis, pancytopenia, AKI
Etiology	*Ehrlichia chafeensis*	*Clostridium difficile*	CMV	EBV	EBV/PTLD	EBV
Management along with immunosuppression reduction	dexamethasone, doxycycline	dexamethasone, oral vancomycin	dexamethasone, ruxolitinib, anakinra	dexamethasone, anakinra, rituximab, ganciclovir	dexamethasone, R-EPOCH ×6 cycles, intrathecal chemotherapy	rituximab 375 mg/m^2 weekly ×4, prednisone 1 mg/kg
Outcomes (graft failure, i.e., need for KRT or retransplantation)	No	No	Yes, return to hemodialysis	Yes, return to dialysis	No	No
Age at diagnosis of HLH, outcome, cause of death (if any)	50 yrs at diagnosis of HLH, alive and 53 yrs now	49 yrs at diagnosis of HLH, alive and 55 yrs now	72 yrs at diagnosis of HLH and deceased. Muti-organ failure because of HLH	59 yrs at diagnosis of HLH and deceased. Muti-organ failure because of HLH	26 yrs at diagnosis of HLH, alive and 30 yrs now	65 yrs at diagnosis of HLH, died at 71 yrs from COVID-19

AKI, acute kidney injury; ATG, antithymocyte globulin; DDKT, deceased donor kidney transplant; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; KRT, kidney replacement therapy; LDKT, living donor kidney transplant; OHT, orthotopic heart transplantation; OLT, orthotopic liver transplantation; PTLD; posttransplant lymphoproliferative disorder; R-EPOCH, [rituximab, etoposide phosphate, prednisone, vincristine sulfate (oncovin), cyclophosphamide, and doxorubicin hydrochloride.

The presentation (Table 2) included constitutional (fever, weight loss), respiratory (acute hypoxic respiratory failure), neurological (altered mental status, hemiplegia, tremors, mastoid pain, and hearing loss), and end-organ failure (shock). Laboratory abnormalities were hyperferritinemia, elevated IL-2 receptor, hypertriglyceridemia, transaminitis, coagulopathy, and pancytopenia. Bone marrow biopsy demonstrated hemophagocytosis in 66% of patients; it was not performed in 1 recipient and was negative in another. This is consistent with previous reports in which 25% could have a negative biopsy. None of these patients had a personal or familial history of hematologic disease or HLH. The triggers for HLH were Epstein-Barr virus (EBV)–positive posttransplant lymphoproliferative disorder (3 cases) and 1 case each of cytomegalovirus, *Ehrlichia*, and *Clostridium difficile*. Treatment modalities used were immunomodulatory agents (dexamethasone, anakinra, ruxolitinib), posttransplant lymphoproliferative disorder–guided treatments (rituximab, etoposide phosphate, prednisone, vincristine sulfate [oncovin], cyclophosphamide, and doxorubicin hydrochloride) and treatment of inciting illness (doxycycline for the ehrlichiosis and ganciclovir for cytomegalovirus). Both patients who died were kidney transplant recipients and died with HLH during hospital admission. Overall, mortality because of sHLH was 33%, which was lower than the previously reported mortality of 50%. This could be due to early treatment initiation. Patient 6 died 6 years later from COVID-19.

In our case series (Supplementary case series), advanced age, rapid viral turnover or load, central nervous system involvement, and failure of therapy to induce remission were poor prognostic markers. For example, patient 3 was a 72-year-old man with a high titer of tissue invasive cytomegalovirus. Despite being treated with ganciclovir, dexamethasone, and immunomodulatory agents, including anakinra (IL-1 inhibitor) and ruxolitinib (Janus kinase protein inhibitor), he did not survive and died during the same hospital admission. Similarly, patients 5 and 6 with high EBV titers died despite being treated with various combinations of rituximab; steroids; rituximab, etoposide phosphate, prednisone, vincristine sulfate (oncovin), cyclophosphamide, and doxorubicin hydrochloride; and anakinra. Conversely, patient 4 was diagnosed with EBV-positive posttransplant lymphoproliferative disorder at the age of 26 years and survived, despite having a very high EBV viral load.

DISCUSSION

Our case series emphasizes the importance of a high index of clinical suspicion and early recognition or treatment to decrease the morbidity and mortality associated with sHLH. Therapy should not be delayed while awaiting specialized immunologic testing or genetic analysis. The management involves reducing immunosuppression, treating the trigger, and early initiation of immunomodulatory therapy to prevent long-term tissue damage and even death. A search for triggering agents, for example, infection (HIV, influenza, COVID-19, hepatitis viruses, and parvovirus B-19), malignancy (leukemia and lymphoma), macrophage activation syndrome, and rheumatologic conditions, should be done.[7] In our case series, inciting pathogens for sHLH were EBV, cytomegalovirus, *Ehrlichia*, and *Clostridium difficile*. In one of our patients, the treatment of rejection led to high EBV viremia. It is inconclusive if the trigger for HLH was rejection or EBV. To our knowledge, there is only 1 case report where an episode of rejection led to the development of HLH.[8] The hyperinflammatory presentation being nonresponsive to standard therapy should prompt consideration for sHLH.[7] For example, the first patient of our case series was treated with doxycycline for *Ehrlichia*; however, his delirium, transaminitis, and acute kidney injury did not improve. Nevertheless, he has shown drastic improvement in all these parameters with early steroid administration. Survival can be dramatically increased with early HLH-specific therapy. Current guidelines recommend initiating the HLH-2004 protocol or enrollment in a clinical trial. HLH-2004–based treatment includes etoposide and dexamethasone given at tapering doses over 8 weeks, with intrathecal methotrexate and hydrocortisone for those with central nervous system involvement.[9] The response to initial treatment is a major factor in determining the need for additional therapy, including hematopoietic cell transplantation.[9] Allogenic hematopoietic cell transplantation is reserved for refractory disease, central nervous system involvement, and hematologic malignancies that cannot be cured.[S1,9] For patients with refractory or recurrent HLH, emapalumab (interferon gamma blocking antibody) and alemtuzumab (anti-CD52 monoclonal antibody) have been utilized.[S1,9] Depending on the clonality, rituximab and chemotherapy are commonly used as first-line agents for posttransplant lymphoproliferative disorder.[9] A multidisciplinary approach and consultation with a hematology or oncology specialist is highly recommended.

In conjunction with the paucity of cases, there is a lack of prospective randomized controlled trials for the therapeutic management of HLH in SOT recipients. In the past decade, sHLH has been reported approximately 18 times in adult SOT patients (Supplementary Table S2).[S2–S14] Our case series highlights the largest single-center cohort of 6 adult SOT recipients with secondary HLH over 10 years. In our series, the observed mortality because of sHLH was 33%, which is lower than the previously reported case series in the general population. This might be secondary to early initiation of treatment specific to trigger and immunomodulatory therapy. Future clinical trials focusing on biomarker, genetic profiling, and mechanistic basis of sHLH are warranted.

The limitations of our study are that it is a single-centered, nonblinded, retrospective analysis with small sample size.

CONCLUSION

Early initiation of corticosteroids, immunomodulatory therapies, and treatment of underlying trigger are the cornerstone to the management of HLH in SOT recipients.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

All data were collected according to our institutional review board-approved protocol [#2020E1191]. This study was a retrospective chart review, involving existing data with no or minimal risk to participants. This study's institutional review board granted patient consent "exempt" status under human subject regulations.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary Case Series.

Supplementary References.

Table S1. Laboratory testing in 6 solid organ transplants at the time of diagnosis.

Table S2. Detailed cases of hemophagocytic lymphocytosis globally from 2011 to 2021.

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