Post-Transplantation Hairy Cell Leukemia with Hemophagocytic Lymphohistiocytosis in an Adult Kidney Transplant Recipient: A Case of Rare Occurrence

Maryam Ghazizadeh,[1] Mohammad Moini,[2*] Matin Ghazizadeh[3]

[1]Assistant Professor of Hematology-Oncology, Department of Hematology-Oncology, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, [2]MD Student, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran [3]Associate Professor of Otolaryngology, Head and Neck Surgery, Department of Otolaryngology, Head and Neck Surgery, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Keywords. Epstein-Barr virus infections; Hemophagocytic lymphohistiocytosis; Kidney transplantation; Hairy cell Leukemia; Transplant recipients; Lymphoproliferative disorders; Neoplasms; Immunosuppressive therapy

Post-transplant lymphoproliferative disorder (PTLD) is a rare and severe complication that occurs after kidney transplantation. Most cases of PTLD are associated with reactivation of the Epstein-Barr virus (EBV), which often happens during the early phases following transplantation. Hemophagocytic lymphohistiocytosis (HLH) is an inflammatory syndrome characterized by a cytokine storm originating from activation of the reticuloendothelial system, leading to multi-organ failure (MOF). Herein, we present a case of late-onset EBV-positive hairy cell leukemia in a kidney transplant recipient who concurrently developed HLH. Diagnosing and managing HLH can be particularly challenging, as it can mimic sepsis. This is especially true for transplant recipients, where diagnosing and treating such conditions are difficult. Immunosuppressive therapy, malignancies like lymphoma, and EBV infection are recognized risk factors for developing HLH. However, very few cases have reported the simultaneous occurrence of HLH and PTLD.

IJKD 2025;19:243-7
www.ijkd.org
DOI: 10.52547/ijkd.8943

Case Report

INTRODUCTION

Post-transplantation lymphoproliferative disorder (PTLD) is a rare complication that occurs after kidney transplantation. Approximately 85% of PTLD cases after kidney transplantation are B-cell lymphomas.[1] The risk factors for the development of PTLD include Epstein-Barr virus infection and immunosuppression. The prevalence of PTLD after kidney transplantation is estimated to be between 0.4% and 0.5%.[2] The highest incidence of PTLD after kidney transplantation occurs within the first year post-transplantation.[3] Epstein-Barr Virus (EBV) is present in over 90% of early-onset B-cell PTLD cases.[4] Conversely, EBV-negative PTLD tends to arise later and is associated with a poor prognosis.[5] Hairy cell leukemia (HCL) is an indolent B-cell leukemia characterized by pancytopenia, monocytopenia, splenomegaly, and hair-like projections on lymphocytes.[6] It possesses distinct morphological, immunophenotypic, and genetic characteristics, including central nuclei, abundant cytoplasm, and expression of CD20, CD22, CD11c, CD123, CD25, CD103, T-box transcription factor 21 (TBX21), annexin A1 (ANXA1), Fluorescein-conjugated Monoclonal Clone 7 (FMC7), CD200, and weak cyclin D1 (CCND1).[7] HCL is rare and has an annual incidence of about 0.3 cases per 100,000, which accounts for around 2% of all leukemias.[8] Patients often experience nonspecific symptoms and an increased susceptibility to infections, whereas rare manifestations include cutaneous symptoms, bone infiltration, and central nervous system (CNS) involvement.[7] Hemophagocytic Lymphohistiocytosis (HLH) is

an inflammatory, fatal syndrome characterized by fever, hepatosplenomegaly, Pancytopenia, hypofibrinogenemia, hypertriglyceridemia, and hemophagocytosis in the bone marrow, spleen, and lymph nodes. It is also associated with low natural killer (NK) cells, ferritin level > 500 ng/ml, elevated soluble CD25, and liver dysfunction.[9,10] HLH is characterized by cytokine storm resulting from activation of the reticuloendothelial system.[11] It is a septic-like inflammatory syndrome that rapidly progresses to multi-organ failure (MOF). HLH is also associated with infectious conditions such as infectious mononucleosis (IM) caused by EBV and malignancies such as lymphoma; however, few cases have described an association between HLH and EBV-negative PTLD.[2] Since HLH can present similarly to sepsis, it can be challenging for clinicians to distinguish between the two conditions, especially in PTLD patients. In this article, we describe an adult kidney transplant recipient who developed HLH associated with post-transplantation hairy-cell leukemia.

CASE PRESENTATION

A 37-year-old woman, a known case of kidney transplantation since 22 years ago, was admitted to Modarres Hospital, Tehran, Iran, with complaints of weakness and fatigue, fever, vertigo, vomiting, and oliguria. She also mentioned a weight loss of approximately four kilograms in the last 6 months and episodes of night sweats. Her symptoms began 20 days before admission, and in recent days, she has experienced both epistaxis and vaginal bleeding. She had a history of end-stage kidney disease (ESKD) of unknown cause from 1997 to 2001, during which she underwent hemodialysis and eventually received a kidney transplant from a living donor in 2001. Her transplanted kidney was rejected in 2008 due to drug interruptions caused by poor medical adherence; however, after improving her adherence to treatment, a second kidney transplantation from a deceased donor was performed in the same year. The patient had received immunosuppression induction therapy with Thymoglobulin (1.5 mg/kg/day for 7 days), Methylprednisolone (500mg/day for 3 days), and Intravenous Immunoglobulin (IVIG) (20 g/day for 5 days). Afterward, she received Azathioprine (1.5 mg/kg/day), Cyclosporin (75 mg/day), and Prednisolone (30 mg/day) as maintenance therapy.

Physical examination showed an ulcerative lesion in the mouth, petechia, and purpura on the skin. No lymphadenopathy was detected in the cervical, axillary, inguinal, and paraaortic regions. On abdominopelvic examination, splenomegaly and positive shifting dullness were detected, along with bilateral edema in the lower extremities. On abdominopelvic sonography, the liver appeared normal in size and echogenicity, and the spleen size was 155 mm; mild to moderate ascites were also observed. The native kidneys were seen with increased echogenicity, but the transplanted kidney was detected in the left lower quadrant (LLQ) with normal echogenicity and size. The lung computed tomography (CT) scan revealed bilateral patchy ground-glass infiltration, accompanied by atelectasis and nodules located in the peripheral regions of the right middle lobe (RML) and right lower lobe (RLL), which could be indicative of fungal infections such as aspergillosis. Additionally, minimal bilateral pleural effusion was seen, but without mediastinal lymphadenopathy. In the abdominopelvic CT scan, splenomegaly, atrophic native kidney, and free fluid in the abdominopelvic cavity were noted. A sclerotic focus was detected in pelvic bones. Blood tests revealed elevated liver enzymes, lactate dehydrogenase (LDH), triglycerides, and Epstein-Barr virus (EBV) antibodies, along with thrombocytopenia, anemia, and decreased fibrinogen. (Table 1) Urinalysis showed 1-2 white blood cells (WBC) and 0-1 red blood cells (RBC).

Five days after admission, the patient developed pancytopenia and severe anemia (Hemoglobin level of 6/5 g/dl). A bone marrow aspiration and biopsy revealed fibrotic bone marrow containing numerous histocytes with evidence of hemophagocytosis, lymphoid cells, and some atypical cells. (Figure 1,2)

Furthermore, positive Dako B-cell Antibody 44 (DBA-44), CD45, CD20, CD11c, and B-Raf proto-oncogene, serine/threonine kinase (BRAF) in the immunohistochemistry (IHC) study indicated the diagnosis of hairy cell leukemia (HCL). Fever, pancytopenia, elevated ferritin levels, splenomegaly, Hypertriglyceridemia, hypofibrinogenemia, and Hemophagocytosis in the bone marrow confirmed a diagnosis of Hemophagocytic Lymphohistiocytosis (HLH). High-dose Dexamethasone (8 mg TDS) and etoposide (100 mg/m^2/week) were administered as initial treatment for HLH. Additionally, the patient received IVIG (20 g/day) for 5 days

Table 1. Blood test results showing elevated triglycerides, LDH, and liver enzymes

Parameter	Measured Value	Units	Standard Range
White Blood Cells (WBC)	1,700	/µL	4,000–11,000 /µL
Triglycerides	432	mg/dL	< 150 mg/dL
Hemoglobin (Hb)	9.1	g/dL	12.0–16.0 g/dL
Platelets (Plt)	77,000	/µL	150,000–400,000 /µL
Prothrombin Time (PT)	14.5	seconds	11–13.5 seconds
Partial Thromboplastin Time (PTT)	34	seconds	25–35 seconds
Creatinine (Cr)	1.65	mg/dL	0.6–1.2 mg/dL
International Normalized Ratio (INR)	1.29	None	0.8–1.2
Lactate Dehydrogenase (LDH)	2,160	U/L	140–280 U/L
Epstein-Barr Virus (EBV) IgM	71.9	AU/mL	< 36 AU/mL (negative); > 40 AU/mL (positive)
Epstein-Barr Virus (EBV) IgG	30.9	AU/mL	< 18 AU/mL (negative); > 22 AU/mL (positive)
Haptoglobin	0.01	g/L	0.3–2.0 g/L
A Disintegrin And Metalloproteinase with Thrombospondin Motifs 13 (ADAMTS13)	10	%	≥ 67%
Ferritin	> 1,000	ng/mL	20–200 ng/mL (for women)
Parvovirus B 19 PCR	Negative	None	Negative
Fibrinogen	60	mg/dL	200–400 mg/dL
CD25	2,800	U/mL	0–1,000 U/mL
Alanine Aminotransferase (ALT)	193	U/L	7–35 U/L (for women)
Aspartate Aminotransferase (AST)	265	U/L	8–33 U/L
Erythrocyte Sedimentation Rate (ESR)	91	mm/hr	0–20 mm/hr
Reticulocytes (Retic)	0.2	%	0.5–2.5% of total RBC

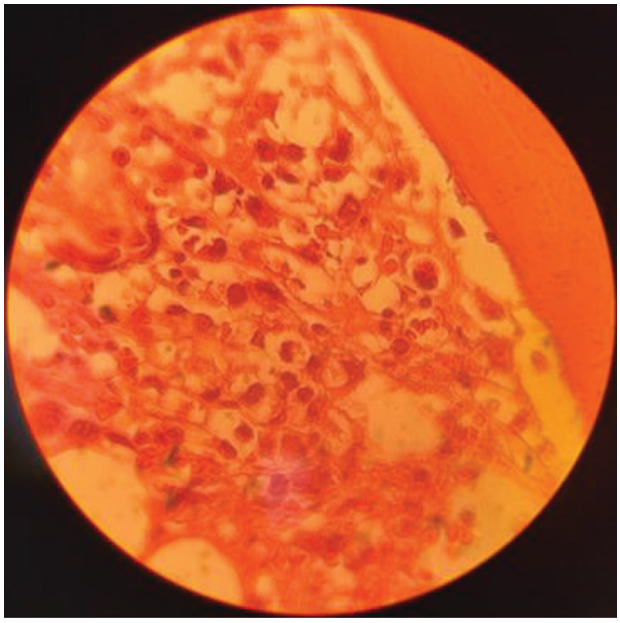

Figure 1. Bone marrow biopsy at high magnification (×1000) shows diffuse infiltration by lymphoid cells with pale cytoplasm and occasional “fried egg” appearance.

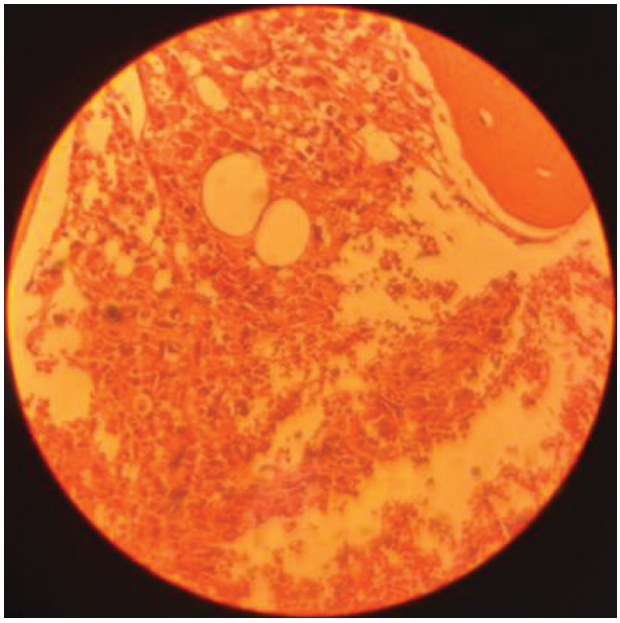

Figure 2. Bone marrow biopsy at 400× magnification displaying a dense interstitial infiltration of atypical lymphoid cells replacing normal hematopoietic elements.

and plasmapheresis for 6 sessions. She was also administered amphotericin B (3 mg/kg liposomal) due to radiologic evidence of a fungal infection seen in the lung CT scan; however, due to the patient’s low platelet count, a bronchoscopy could not be performed. In the following days, she developed worsening of pancytopenia, fever, night sweats, hypotension, and respiratory failure that required mechanical ventilation. Within hours, she developed hyperbilirubinemia (total bilirubin level of 4 mg/dl), elevated LDH (3100 U/L), and eventually multiorgan failure (MOF),

disseminated intravascular coagulation (DIC), and anuria. Continuous renal replacement therapy was started. Due to the suspicion of fungal infection, Cladribine or rituximab was not being prescribed for the treatment of Hairy cell leukemia. Despite the treatments for HLH and broad-spectrum antibiotics, the patient died after several days.

DISCUSSION

Hemophagocytic Lymphohistiocytosis (HLH) is a hyperinflammatory syndrome resulting from cytokine release from the activated reticuloendothelial system. Since HLH has a nonspecific presentation and overlaps with sepsis and other diseases, diagnosis is challenging. It has a high mortality rate of 40%-50%. In most patients, HLH is triggered by infections, autoimmune diseases, and malignancies like lymphoma. HLH associated with lymphoma has a worse prognosis than HLH triggered by infections or autoimmune diseases.[12] In a Swedish study about malignancy-associated HLH, the author concluded that lymphoma-associated HLH is more prevalent in men than women, and the median age of lymphoma-associated HLH at the time of diagnosis was 60 years. However, patients with T non-Hodgkin lymphoma (T-NHL) associated with HLH were younger in comparison to B non-Hodgkin lymphoma (B-NHL) with HLH.[13] In contrast to these findings, our patient was a young woman (36 years old) with HLH associated with hairy-cell leukemia. Another study indicated prior iatrogenic or acquired immunosuppression, including that induced by the immunodeficiency virus or medications like steroids and azathioprine, was identified as a risk factor for HLH.[12] In our study, the patient had received azathioprine and steroids for kidney transplantation, which is also considered as a risk factor for HLH. In the mentioned study,[10] the author concluded that, based on the Ann Arbor classification,[14] which stratifies disease by number and location of nodal regions, extranodal involvement, and systemic (B') symptoms, nearly all lymphoma-associated HLH cases present in stages III and IV. Additionally, over half of these patients had lymphoma infiltrations in their bone marrow.[10] In our case, the patient also presented in an advanced stage and exhibited bone marrow involvement with malignant lymphocytes infiltration. The cohort study on lymphoma-associated hemophagocytic lymphohistiocytosis (LA-HLH) demonstrated that the survival of LA-HLH is less than one month without treatment or if only HLH-directed treatment is administered,[15] which is in line with our patient's survival of less than one month despite receiving treatment for HLH. In a study involving 225 patients with LA-HLH, approximately 60% of the participants presented with pancytopenia and elevated ferritin levels were found in 90% of these patients. Additionally, 62% of the patients exhibited high triglyceride levels, while 42% had decreasing fibrinogen levels. In this study, 98% of patients had elevated CD25 levels, and the CD25/ferritin ratio was higher in patients with HLH induced by B-NHL.[10] Another study found that an association between lymphoma pathophysiology and EBV tropism increases HLH development.[16] In our study, the patient presented with pancytopenia, elevated ferritin level more than1000 ng/ml, elevated soluble CD25 (more than 2600 U/ml), elevated triglyceride (432 mg/dl), decreased fibrinogen (60 mg/dl), and a positive EBV polymerase chain reaction (PCR). The laboratory findings of our patient were similar to those of the mentioned studies. The pathology of PTLD is heterogeneous; the most common pathology is diffuse large B-cell lymphoma and, less commonly, Burkitt lymphoma and plasma cell neoplasms.[4] However, hairy cell leukemia (HCL) is an infrequent B-cell malignancy consistent with pancytopenia and splenomegaly. The incidence of HCL after solid organ transplantation is very low. HCL has only been documented in two solid organ transplant recipients: one patient after a kidney transplant and another after a cardiac transplant.[17] There have been no documented cases of concurrent HCL and HLH following kidney transplantation. This report presents the first case of the simultaneous occurrence of HCL and HLH after kidney transplantation.

CONCLUSION

We report a rare case of an adult kidney transplant recipient who developed Epstein-Barr virus (EBV)-positive Hairy Cell Leukemia (HCL) concurrent with Hemophagocytic Lymphohistiocytosis (HLH) 14 years post-transplantation. To the best of our knowledge, this is the first documented case of an adult kidney transplant recipient experiencing simultaneous HCL and HLH. Given the poor prognosis associated with HLH in the context of

PTLD and the overlap of its symptoms with sepsis and multi-organ failure (MOF), diagnosing and treating this condition poses a significant challenge for physicians, particularly in transplant recipients. HLH should be included in the differential diagnosis of sepsis and MOF to ensure the timely initiation of treatment.

FUNDING SOURCES

No funding sources, financial support, or in-kind contributions were received for this study.

FINANCIAL DISCLOSURES

The authors have no financial disclosure relevant to this manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

REFERENCES

1. Cho JM, Kim YC, Min S, Kim TM, Lee H. T cell posttransplant lymphoproliferative disorder after kidney transplantation progressing to acute liver failure: a case report. Korean J Transplant. 2023 Dec 31;37(4):299-305.
2. Mazzola Poli de Figueiredo S, Johnson JC, Lyapichev KA, Stevenson HL, Lea A, Hussain S, et al. Fatal Case of EBV-negative Posttransplant Lymphoproliferative Disorder With Hemophagocytic Lymphohistiocytosis in an Adult Kidney Transplant Recipient. Transplant Direct. 2022 Sep;8(9):e1368.
3. Leblond V, Davi F, Charlotte F, Dorent R, Bitker MO, Sutton L, et al. Posttransplant lymphoproliferative disorders not associated with Epstein-Barr virus: a distinct entity? J Clin Oncol. 1998 Jun;16(6):2052-9.
4. Allen U, Preiksaitis J. Epstein-barr virus and posttransplant lymphoproliferative disorder in solid organ transplant recipients. Am J Transplant. 2009 Dec;9 Suppl 4:S87-96.
5. Bakanay SM, Kaygusuz G, Topçuoğlu P, Sengül S, Tunçalı T, Keven K, et al. Epstein-barr virus-negative post-transplant lymphoproliferative diseases: three distinct cases from a single center. Turk J Haematol. 2014 Mar;31(1):79-83.
6. Troussard X, Maitre E. Untangling hairy cell leukaemia (HCL) variant and other HCL-like disorders: Diagnosis and treatment. J Cell Mol Med. 2024 Feb;28(3):e18060.
7. Robak T, Robak M, Majchrzak A, Krawczyńska A, Braun M. Atypical Hairy Cell Leukemia-The Current Status and Future Directions. Eur J Haematol. 2025 May;114(5):747-62.
8. Grever MR, Abdel-Wahab O, Andritsos LA, Banerji V, Barrientos J, Blachly JS, et al. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. Blood. 2017 Feb 2;129(5):553-60.
9. Karras A, Thervet E, Legendre C. Hemophagocytic syndrome in renal transplant recipients: report of 17 cases and review of literature. Transplantation. 2004 Jan 27;77(2):238-43.
10. Knauft J, Schenk T, Ernst T, Schnetzke U, Hochhaus A, La Rosée P, et al. Lymphoma-associated hemophagocytic lymphohistiocytosis (LA-HLH): a scoping review unveils clinical and diagnostic patterns of a lymphoma subgroup with poor prognosis. Leukemia. 2024 Feb;38(2):235-49.
11. M D, P S, T P. Post-Transplant Lymphoproliferative Disorder as a Trigger for Hemophagocytic Lymphohistiocytosis in Solid Organ Transplant – Case Series [abstract]. American Transplant Congress: American Journal of Transplantation; 2021.
12. Birndt S, Schenk T, Heinevetter B, Brunkhorst FM, Maschmeyer G, Rothmann F, et al. Hemophagocytic lymphohistiocytosis in adults: collaborative analysis of 137 cases of a nationwide German registry. J Cancer Res Clin Oncol. 2020 Apr;146(4):1065-77.
13. Löfstedt A, Jädersten M, Meeths M, Henter JI. Malignancy-associated hemophagocytic lymphohistiocytosis in Sweden: incidence, clinical characteristics, and survival. Blood. 2024 Jan 18;143(3):233-42.
14. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971 Nov;31(11):1860-1.
15. Bigenwald C, Fardet L, Coppo P, Meignin V, Lazure T, Fabiani B, et al. A comprehensive analysis of Lymphoma-associated haemophagocytic syndrome in a large French multicentre cohort detects some clues to improve prognosis. Br J Haematol. 2018 Oct;183(1):68-75.
16. Marsh RA. Epstein-Barr Virus and Hemophagocytic Lymphohistiocytosis. Front Immunol. 2017;8:1902.
17. Zamfir A, Leymarie V, Galoisy A-C, Falkenrodt A, Epailly E, Fohrer C, et al. Successful Treatment af a Hairy Cell Leukemia (HCL) with Pentostatin in a Cardiac Transplant Recipient. Blood. 2004 2004/11/16/;104(11):4815.

*Correspondence to:
Mohammad Moini,
Postal address: Tehran University of Medical Sciences, Northern gate of the university, Poursina St., Qods St., Enqelab St., Tehran, Iran
E-mail: mohammadmoini1384@gmail.com
Postal Code: 1417613151
Phone: +989128165754

Received November 2024
Accepted July 2025