Hemophagocytic Lymphohistiocytosis as the Initial Presentation of Epstein–Barr Virus-Associated Post-Transplant Lymphoproliferative Disorder in a Kidney Transplant Recipient

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Abstract

Post-transplant lymphoproliferative disorder (PTLD) is one of the most serious malignancies following kidney transplantation and is strongly associated with Epstein–Barr virus (EBV) infection. Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome that only rarely presents as the initial manifestation of PTLD.

We report the case of a 41-year-old kidney transplant recipient who presented with persistent fever and progressive systemic inflammation despite broad-spectrum antimicrobial therapy. The combination of bicytopenia, hyperferritinemia, hypertriglyceridemia, and splenomegaly, together with an HScore of 231 and an elevated soluble interleukin-2 receptor level, supported the diagnosis of HLH. A markedly elevated EBV viral load prompted investigation for PTLD. Although ^{18}F-FDG PET/CT revealed no abnormal uptake, bone marrow biopsy established the diagnosis of EBV-positive monomorphic PTLD, diffuse large B-cell lymphoma type, with a germinal-centre B-cell phenotype and an isolated MYC rearrangement. Anakinra was initiated while the diagnostic investigation was ongoing, followed by attempted rituximab administration, obinutuzumab plus CHOP (Obino-CHOP) and reduction of immunosuppression. Clinical and laboratory improvement occurred in the context of these sequential interventions. The patient subsequently achieved complete haematological remission, documented by bone marrow assessment, with resolution of HLH and preservation of kidney allograft function.

This case highlights the importance of investigating the underlying cause of HLH in kidney transplant recipients. PTLD should be considered in patients with significant EBV viraemia, even in the absence of suggestive imaging findings. Management of hyperinflammation and investigation of its underlying cause should proceed in parallel to enable timely disease-specific treatment.

Keywords: Epstein-Barr Virus Infections; Kidney Transplantation/adverse effects; Lymphohistiocytosis, Hemophagocytic; Lymphoproliferative Disorders

What's already known about this topic?

- Hemophagocytic lymphohistiocytosis is a life-threatening hyperinflammatory syndrome that may mimic severe infection in solid organ transplant recipients.

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- Hemophagocytic lymphohistiocytosis is a rare presenting manifestation of Epstein–Barr virus-associated post-transplant lymphoproliferative disorder.

What does this study add?

- Post-transplant lymphoproliferative disorder may present as hemophagocytic lymphohistiocytosis several decades after kidney transplantation.
- Marked Epstein–Barr virus viremia may provide an important diagnostic clue, even when PET/CT reveals no abnormal ^{18}F-FDG uptake.
- This case illustrates the feasibility of initiating treatment for hyperinflammation while continuing the investigation of its underlying cause.

INTRODUCTION

Long-term immunosuppression is essential to prevent allograft rejection after kidney transplantation. However, it also increases the risk of infectious and malignant complications, among which post-transplant lymphoproliferative disorder (PTLD) is one of the most serious complications following solid organ transplantation.[1] PTLD comprises a heterogeneous group of lymphoid proliferations, predominantly of B-cell origin, occurring in both pediatric and adult transplant recipients. Epstein–Barr virus (EBV) infection is a major risk factor for its development.[1-3] Although PTLD remains relatively uncommon after kidney transplantation, it is associated with substantial morbidity and mortality, making early diagnosis crucial for improving outcomes. The incidence of PTLD is particularly high during the early post-transplant period, but cases may also occur many years after transplantation.[3-5]

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by uncontrolled immune activation and excessive cytokine release, which may rapidly progress to multiorgan failure. It is broadly classified as primary, resulting from inherited genetic defects, or secondary, the more common form, triggered by infections, autoimmune diseases or malignancies, particularly hematological neoplasms.[6-8] Among solid organ transplant recipients, HLH is an uncommon but potentially fatal complication. Its diagnosis is particularly challenging because its clinical presentation frequently mimics severe sepsis and multiorgan dysfunction, often leading to delayed recognition.[9,10]

The coexistence of PTLD and HLH is rare and has been reported almost exclusively in isolated case reports and small case series. Among these, HLH as the initial manifestation of PTLD is particularly uncommon and represents a major diagnostic challenge in kidney transplant recipients.[11-13] We report a case illustrating this rare presentation, highlighting the importance of early investigation of the underlying cause in transplant recipients presenting with persistent systemic inflammation of unclear origin.

CASE REPORT

A 41-year-old man underwent kidney transplantation 30 years earlier for end-stage kidney disease secondary to focal segmental glomerulosclerosis (inconclusive genetic testing). He was receiving maintenance immunosuppression with tacrolimus and mycophenolate mofetil (MMF) and presented to the emergency department with a 10-day history of asthenia, fever and cough. He had completed a seven-day course of oral amoxicillin–clavulanate for a presumed respiratory tract infection, without clinical improvement.

On admission (day 0), laboratory investigations revealed normocytic normochromic anemia (hemoglobin 9.5 g/dL), an elevated C-reactive protein level (185 mg/L), leukocytosis with neutrophilia (white blood cell count 20 847/µL; neutrophils 15 860/µL), and mild deterioration of kidney allograft function (serum creatinine 2.4 mg/dL; baseline approximately 1.5 mg/dL). Chest radiography showed no focal pulmonary consolidation. Given the suspicion of a respiratory infection unresponsive to outpatient antibiotic therapy, he was admitted and started on empirical piperacillin–tazobactam after samples had been collected for blood, urine and respiratory secretion cultures and respiratory virus testing. All these tests subsequently yielded negative results.

Despite treatment, the patient continued to experience daily fever, worsening asthenia, and rising inflammatory markers. On day 5, piperacillin–tazobactam was discontinued and antimicrobial therapy was switched to imipenem and vancomycin. From day 8 onwards, he began to develop thrombocytopenia (minimum 38 000/µL), worsening anemia (minimum hemoglobin 7.2 g/dL), hyperferritinemia (peak 6 870 ng/mL), hypertriglyceridemia (peak 407 mg/dL), and elevated AST (96 U/L), together with persistently elevated C-reactive protein, erythrocyte sedimentation rate, and serum amyloid A. Repeat blood and urine cultures remained negative.

Given the persistent fever despite antimicrobial therapy, contrast-enhanced computed tomography of the chest, abdomen and pelvis was performed. It showed small mediastinal and hilar lymph nodes and homogeneous splenomegaly, without other clinically significant abnormalities.

The combination of persistent fever, bicytopenia, hyperferritinemia, hypertriglyceridemia, hepatocellular injury, and splenomegaly raised suspicion of HLH. On day 9, the calculated HScore was 231, corresponding to a model-estimated probability of HLH of 98-99%, based on known immunosuppression related to kidney transplantation,

a temperature of 38.4ºC-39.4°C, splenomegaly, two cytopenias, ferritin > 6 000 ng/mL, triglycerides >354 mg/dL, and AST >30 U/L. An elevated soluble interleukin-2 receptor (sCD25) level of 6 311 U/mL provided additional support for the diagnosis. Investigation of the underlying trigger revealed an EBV DNA load exceeding 1 000 000 IU/mL in blood. Given the suspicion of EBV-associated HLH, anakinra was initiated on day 11 at a dose of 8 mg/kg/day. Rituximab was subsequently attempted on day 12 at a planned dose of 375 mg/m². During the infusion, after 118 mL had been administered, the patient developed dyspnoea, shivering, and vomiting of gastric contents. The infusion was stopped before completion, and rituximab was permanently discontinued.

In view of the patient's transplant status and the markedly elevated EBV viral load, further investigations were undertaken to exclude PTLD. Peripheral blood flow cytometry identified a monoclonal B-cell population expressing CD19, strongly positive CD20, CD10 and CD38, with reduced BCL2 expression. Bone marrow aspiration and biopsy were performed on day 12. The aspirate demonstrated a hypercellular marrow with 37% atypical lymphoid cells showing intensely basophilic, vacuolated cytoplasm and nuclei with finely dispersed chromatin. Flow cytometric analysis of the bone marrow confirmed a monoclonal B-cell population with an immunophenotype identical to that observed in peripheral blood. Bone marrow biopsy revealed infiltration by atypical large B cells. EBER-CISH was positive in more than 90% of neoplastic cells, the Ki-67 proliferation index exceeded 90%, and immunohistochemical findings supported a germinal-centre B-cell phenotype according to the Hans algorithm. The neoplastic cells expressed MYC, and fluorescence ***in situ*** hybridization (FISH) using a break-apart probe demonstrated a MYC rearrangement in 69% of analyzed nuclei. No BCL2 rearrangement was detected; FISH analysis for BCL6 was not performed. Integration of the morphological, immunophenotypic and molecular findings established the diagnosis of EBV-positive monomorphic PTLD, diffuse large B-cell lymphoma type, with a germinal-centre B-cell phenotype and an isolated MYC rearrangement. An ^{18}F-FDG PET/CT performed on day 14 showed no areas of abnormal ^{18}F-FDG uptake. Bone marrow uptake was not specifically reported.

After confirming the diagnosis, obinutuzumab plus CHOP (Obino-CHOP) was initiated on day 15. Obinutuzumab was selected as an alternative anti-CD20 therapy following the hypersensitivity reaction to rituximab. Obinutuzumab was administered at 1000 mg on days 1, 8, and 15 of the first cycle, followed by 1000 mg on day 1 of each subsequent cycle. Subsequent cycles were administered every 21 days, for a total of six cycles. Each cycle consisted of obinutuzumab, cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² (maximum 2 mg) and methylprednisolone 62.5 mg.

Central nervous system prophylaxis with intrathecal methotrexate, cytarabine, and dexamethasone was administered at the beginning of the first cycle because of the high risk of central nervous system involvement. MMF was discontinued, prednisolone 5 mg daily was introduced, and tacrolimus was continued with a target trough concentration of 5-7 ng/mL, with levels preferentially maintained toward the lower end of this range.

Anakinra was discontinued after eight days of treatment (day 19). Table 1 summarises serial laboratory findings in relation to the timing of therapeutic interventions. Fever resolved and inflammatory parameters progressively improved, coinciding with sequential interventions including anakinra, the incomplete rituximab infusion, initiation of Obino-CHOP, and modification of immunosuppression. Kidney allograft function also recovered to baseline, with serum creatinine returning to approximately 1.5 mg/dL.

He was discharged after 19 days of hospitalization and continued follow-up in the Hematology Department. He completed six cycles of Obino-CHOP by month 4 after diagnosis. Bone marrow assessment documented complete remission at month 6. The EBV DNA load progressively declined, reaching 40 IU/mL at month 6 and becoming undetectable by month 10. At this time, he remained in complete remission, with stable kidney allograft function (serum creatinine approximately 1.5 mg/dL), while receiving tacrolimus and prednisolone.

Table 1. Serial laboratory findings in relation to therapeutic interventions and follow-up

Time point	Treatment / clinical event	Ferritin (ng/mL)	Triglycerides (mg/dL)	CRP (mg/L)	EBV DNA (IU/mL)
Day 9	HLH assessment (HScore 231)	6093	391	255.32	>1 000 000
Day 11	Anakinra initiated	6870	407	294.56	-
Day 12	Rituximab infusion attempted	6280	336	169.81	-
Day 15	Obino-CHOP initiated	3797	210	63.65	-
Day 19	Anakinra discontinued	1343	210	21.65	684 268
Month 4	Completion of Obino-CHOP	983	111	4.46	78
Month 6	Complete remission documented by bone marrow assessment	817	110	4.02	40
Month 10	Follow-up	761	108	3.42	Undetectable

CRP, C-reactive protein; EBV, Epstein–Barr virus; HLH, hemophagocytic lymphohistiocytosis; Obino-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine and methylprednisolone.
Note: Dashes indicate unavailable measurements.

DISCUSSION

The diagnosis of HLH in kidney transplant recipients remains particularly challenging because its clinical presentation frequently mimics severe sepsis. Persistent fever despite appropriate antimicrobial therapy, together with cytopenias, hyperferritinemia, hypertriglyceridemia, hepatocellular injury and splenomegaly, should prompt early consideration of HLH, especially when repeated microbiological investigations remain negative.[7,8] Although the HLH-2004 diagnostic criteria continue to be widely used, they were originally developed for pediatric patients and have recognized limitations when applied to adults. In this setting, the HScore has shown good diagnostic performance and has become a valuable tool for evaluating suspected adult HLH.[6,14,15] In the present case, an HScore of 231, corresponding to a model-estimated probability of 98%-99%, together with markedly elevated sCD25 levels, strongly supported the diagnosis. Although not specific for HLH, sCD25 reflects T-cell activation and, when interpreted alongside the overall clinical and laboratory picture, may provide additional diagnostic support.[16,17]

Once HLH is recognized, identifying and treating the underlying cause becomes a priority, as controlling the hyperinflammatory response alone may be insufficient to achieve a favorable outcome. In our patient, the markedly elevated EBV viral load was the key finding guiding the diagnostic work-up. The temporal distribution of PTLD after transplantation is heterogeneous, with both early- and late-onset disease being well recognized. Although the incidence is particularly high during the early post-transplant period, late-onset PTLD may occur many years after transplantation. Therefore, PTLD should remain in the differential diagnosis regardless of the time elapsed since transplantation, particularly in patients with significant EBV viremia.[1-3] Despite the absence of significant lymphadenopathy and abnormal ^{18}F-FDG uptake on PET/CT, the high clinical suspicion warranted further hematological investigation, ultimately leading to the diagnosis of PTLD on bone marrow biopsy.

Management of HLH requires simultaneous control of the hyperinflammatory syndrome and investigation of its underlying cause. Treatment of hyperinflammation should not be delayed while the etiological investigation is ongoing, as postponing therapy may adversely affect prognosis. Anakinra, a recombinant interleukin-1 receptor antagonist, has emerged as a potentially important therapeutic option in adult HLH, with an increasingly described role in controlling systemic hyperinflammation and a favorable safety profile.[6,18,19] In the present case, anakinra was initiated while the etiological investigation was ongoing, with clinical and laboratory improvement occurring alongside sequential therapeutic interventions. Subsequently, marked EBV viremia prompted the introduction of rituximab, which is recommended in EBV-associated HLH because it depletes infected B cells, reducing the viral reservoir and contributing to viral load clearance.[6,20] Once PTLD was confirmed, treatment focused on the lymphoproliferative disorder and included reduced immunosuppression, a cornerstone of initial PTLD management.[1,2] The favorable clinical course, characterized by resolution of HLH, complete hematological remission and preservation of kidney allograft function, highlights the importance of an approach in which management of hyperinflammation and investigation of the underlying disease proceed in parallel, allowing timely initiation of disease-specific treatment.

CONCLUSION

HLH should prompt investigation of its underlying cause rather than being regarded as a final diagnosis. In kidney transplant recipients, HLH associated with significant EBV viraemia should raise suspicion of PTLD, even in the absence of suggestive imaging findings. Early recognition and investigation of the underlying trigger are essential to guide timely disease-specific treatment.

Learning Points/Take-Home Messages

Persistent fever, cytopenias, hyperferritinemia, hypertriglyceridemia and splenomegaly in a kidney transplant recipient should raise suspicion of HLH, particularly in the absence of a response to antimicrobial treatment.
PTLD should remain in the differential diagnosis of transplant recipients with HLH and marked EBV viremia, including many years after transplantation.
Controlling hyperinflammation and identifying its underlying cause should be pursued simultaneously to ensure timely disease-specific treatment.

Contributorship Statement

SP and MBB: Conceptualization, data collection, literature review and writing of the original draft.
ABP: Data collection and manuscript revision.
JS: Critical review and editing of the manuscript.
MLSM: Supervision, critical review and final approval of the manuscript. All authors read and approved the final version. All authors contributed to this work, approved the final version of the manuscript for publication, and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the data presented.

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