

Post-Transplant Lymphoproliferative Disorder Manifesting as Lymphoplasmacytic Lymphoma Accompanying With Hemophagocytic Lymphohistiocytosis

Anna Armatys^{a, b} , Krzysztof Wozniczka^a, Anna Koclega^a, Adrianna Spalek^a,
Martyna Włodarczyk^a, Grzegorz Helbig^a

Abstract

Post-transplant lymphoproliferative disorder (PTLD) is a potentially life-threatening complication, often associated with Epstein-Barr virus (EBV) in the early period after hematopoietic stem cell transplantation (HSCT). Clinical manifestations range from localized to disseminated disease. The cornerstone of therapy is the reduction of immunosuppression and/or immunochemotherapy. We report a 39-year-old female who developed PTLD presenting as lymphoplasmacytic lymphoma (LPL) associated with hemophagocytic lymphohistiocytosis (HLH). Diagnostic evaluation was blurred by features of severe hepatic acute graft-versus-host disease (GVHD). An initial treatment consisted of high-dose steroids, but it failed. As second-line treatment, ruxolitinib and mycophenolate mofetil were administered, but they were ineffective, and the patient's condition worsened. Further detailed evaluation revealed the presence of monoclonal protein immunoglobulin G (IgG) lambda and bone marrow infiltration by clonal plasmacytoid B lymphocytes. The HLH criteria were also met. Immunosuppression was discontinued, and dexamethasone with rituximab was initiated, but no response was observed. The patient eventually died from multiple organ failure. The learning points from this case emphasize that HLH in the context of PTLD remains underreported, with few cases documented in the literature. Studies indicate that EBV plays a central role in pathogenesis, often presenting with systemic inflammation and immune dysregulation. Diagnostic challenges arise due to overlapping clinical features with other post-transplant complications. Treatment strategies vary but often involve balancing immunosuppression reduction and chemotherapy, with rituximab being a cornerstone for EBV-driven cases. This case underscores the necessity of early recognition to mitigate severe outcomes.

Keywords: Post-transplant lymphoproliferative disorder; Hemophago-

cytic lymphohistiocytosis; Plasmacytic dyscrasia; Acute lymphoblastic leukemia

Introduction

Post-transplant lymphoproliferative disorder (PTLD) represents a heterogeneous spectrum of lymphoproliferative conditions arising as complications of solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT) [1, 2]. The clinical presentation of PTLD varies widely, ranging from localized lesions to disseminated systemic disease, reflecting its histopathological diversity. The 2016 World Health Organization (WHO) classification delineates PTLD into four categories: non-destructive PTLD, polymorphic PTLD, monomorphic PTLD and classic Hodgkin lymphoma-type PTLD. Among these, lymphoplasmacytic lymphoma (LPL) is a particularly rare subtype, especially within the context of PTLD [2].

The pathogenesis of PTLD is closely associated with Epstein-Barr virus (EBV), particularly in the post-HSCT setting, where immunosuppressive therapy facilitates viral reactivation [1, 2]. Detection of EBV-DNA in blood frequently signals reactivation, especially in patients with prior EBV exposure [1, 2]. Early-onset PTLD, typically observed within the first year following transplantation, is often EBV-positive, whereas late-onset PTLD may lack such an association [3]. The risk of PTLD is significantly higher in SOT recipients (about 20%) compared to HSCT recipients (< 5%), with an additional risk in cases involving EBV-seronegative donors and seropositive recipients due to immune dysregulation [4].

Therapeutic strategies for PTLD are highly individualized, guided by the patient's clinical condition and the disease's histopathological characteristics. Initial management often involves reducing or discontinuing immunosuppressive therapy to restore immune surveillance. However, this approach requires careful consideration to mitigate the risk of graft-versus-host disease (GVHD) [3, 4]. For cases where immunosuppression adjustment proves inadequate or contraindicated, systemic immunochemotherapy, radiotherapy, or adoptive immunotherapy using EBV-specific cytotoxic T lymphocytes may be employed [2-4]. These modalities are particularly criti-

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^aDepartment of Hematology and Bone Marrow Transplantation, University of Silesia, Katowice, Poland

^bCorresponding Author: Anna Armatys, Department of Hematology and Bone Marrow Transplantation, University of Silesia, Katowice, Poland.
Email: aarmatys@op.pl

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cal for refractory or disseminated disease.

Despite advancements in diagnostic and therapeutic modalities, PTLTD continues to pose significant challenges, including diagnostic delays, overlapping clinical features with other post-transplant complications, and resistance to conventional therapies. Early recognition and tailored management strategies remain paramount to improving patient outcomes [4].

PTLTD manifesting as LPL is exceedingly rare, particularly when accompanied by hemophagocytic lymphohistiocytosis (HLH). This combination introduces unique diagnostic and therapeutic complexities, as HLH's hyperinflammatory state exacerbates disease management. The scarcity of such cases underscores the need for heightened clinical vigilance and a multidisciplinary approach to treatment [5]. Novel insights into the interplay between EBV-driven lymphoproliferation and HLH may pave the way for more effective management paradigms.

Case Report

Investigations

A 39-year-old female, 3 months following HSCT from 9/10 human leukocyte antigens (HLA) matched unrelated donor for *BCR-ABL*-positive acute lymphoblastic leukemia (ALL) was admitted to our institution on day +88 post-transplant, with a presumptive diagnosis of hepatic acute graft-versus-host disease (aGVHD), following a month-long clinical course marked by progressive hyperbilirubinemia, refractory to extensive diagnostic evaluation. On admission, the patient presented with systemic manifestations, including febrile episodes, persistent nausea, abdominal pain and a non-productive cough. Physical examination was notable for jaundice, bruises and petechiae localized to the forearms, cervical lymphadenopathy and splenomegaly.

Comprehensive laboratory evaluation demonstrated moderate normocytic anemia (hemoglobin 10.4 g/dL) and severe thrombocytopenia (platelet count $21 \times 10^9/L$), whereas the leukocyte count was normal (white blood cells = $7.16 \times 10^9/L$). Hypercreatinemia was observed, with a creatinine level of 269 $\mu\text{mol/L}$ and marked hyperbilirubinemia exceeding 250 $\mu\text{mol/L}$. Inflammatory markers were not significantly elevated, with a modest increase observed (C-reactive protein (CRP) = 31 mg/L, procalcitonin (PCT) = 0.09 ng/mL), which could have been attributed to the patient's clinical condition. The results of bacteriological cultures, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) swab testing and fungal antigen assays were all negative. Liver function tests revealed elevated transaminases: aspartate transaminase (AST) = 84 IU/L, alanine transaminase (ALT) = 80 IU/L; alkaline phosphatase (ALP) = 259 IU/L; and significantly elevated gamma-glutamyl transferase (GGT) = 703 IU/L. The patient had previously undergone antiviral therapy with ganciclovir and foscarnet for cytomegalovirus (CMV) reactivation, which had resolved prior to admission, as confirmed by CMV polymerase chain reaction (PCR) clearance. However, despite antiviral treatment, hepatic dysfunction persisted and

progressively worsened. The patient did not give her consent for a liver biopsy. Further evaluation revealed profound hypergammaglobulinemia (serum immunoglobulin G (IgG) = 53 g/L), with a distinct monoclonal IgG lambda peak (21 g/L) on serum protein electrophoresis. Serum free light chain (FLC) analysis demonstrated a markedly elevated lambda FLC level (1,060 mg/L) and a severely reduced FLC kappa-to-lambda ratio (0.0003). Trephine and bone marrow biopsies were performed on day +93 following transplantation. Cytological analysis of the bone marrow aspirate revealed that plasmacytoid lymphocytes constituted 21% of the total lymphocyte population, with plasma cells accounting for 14%. Immunophenotypic analysis by flow cytometry revealed an aberrant clonal B cell population expressing CD19, CD20, CD23, CD43, CD38, CD200 and CD138dim, with distinct subpopulations displaying variable CD20 and CD138 expression. The number of bone marrow samples obtained was insufficient to perform additional tests, such as the detection of EBV in the marrow or additional genetic analyses (e.g., MYD88^{L265P}). Bone marrow trephine biopsy corroborated the presence of 40% plasmacytoid lymphocytes characterized by CD38 and CD138 positivity with partial CD25 expression, while phagocytic activity was not confirmed. The patient's clinical condition, including a low platelet count and the inability to achieve the required threshold for the procedure despite transfusion attempts, did not permit additional diagnostic procedures, such as a lumbar puncture.

The constellation of laboratory findings, however, strongly suggested secondary HLH, characterized by profound hypoferritinemia (25,029 ng/mL), hypofibrinogenemia (< 1.5 g/L), and hypertriglyceridemia (> 2.5 mmol/L). EBV-PCR positivity (474,613,485 copies/mL on day +91) in peripheral blood further implicated an EBV-driven lymphoproliferative process consistent with PTLTD.

Diagnosis

The diagnostic workup culminated in the identification of EBV-positive PTLTD manifesting as LPL with secondary HLH with HScore = 223. Serological analysis prior to transplantation demonstrated the presence of EBV-specific IgG antibodies, the absence of IgM antibodies, and the positivity of the nuclear antigen. On day +28 post-HSCT, EBV-PCR was negative. Although hepatic aGVHD was initially suspected and treated with high-dose methylprednisolone (2 mg/kg intravenous (IV)), subsequent therapeutic escalation to ruxolitinib (20 mg/day) and mycophenolate mofetil (2 g/day IV) failed to elicit clinical improvement.

Treatment

Management was intensified with dexamethasone (10 mg IV twice daily) targeting HLH, yet the patient's clinical status remained refractory. Various therapeutic options were considered, including etoposide, which is frequently used in HLH. However, its administration was contraindicated in this case due to the patient's severe hepatic dysfunction (bilirubin > 250

$\mu\text{mol/L}$, elevated transaminases) and renal impairment (creatinine = $269 \mu\text{mol/L}$), which posed a high risk of toxicity. Given the EBV-driven PTLD, we prioritized rituximab as first-line therapy. Rituximab (700 mg IV) was administered in an attempt to control EBV-driven clonal proliferation on day +95. Despite these efforts, the patient's condition continued to deteriorate, culminating in septic shock. The patient ultimately died with multiple organ failure on day +97.

Follow-up and outcomes

The patient succumbed to multiple organ failure within days of treatment escalation. This case underscores the formidable diagnostic and therapeutic challenges posed by PTLD complicated by HLH in the post-HSCT context. It highlights the dismal prognosis of such cases despite the application of aggressive multimodal therapeutic strategies.

Discussion

Viral infections remain a critical concern in the post-transplant period, standing as the leading cause of mortality in this vulnerable population. Mortality rates associated with viral infections post-transplant are reported to range from 20-30% [2]. Among these, EBV plays a pivotal role as an oncogenic, lymphotropic gamma herpesvirus, significantly contributing to the pathogenesis of lymphoid malignancies [6]. EBV is known for its ability to establish latency in B cells and reactivate in immunocompromised individuals, such as those undergoing SOT or HSCT. Despite extensive research, the exact oncogenic mechanisms of EBV remain incompletely understood [6]. However, the virus's ability to evade immune surveillance and alter host cellular machinery is thought to underlie its pathogenicity.

PTLD is a severe complication of transplantation that is frequently linked to EBV reactivation. Interestingly, non-EBV-associated PTLD typically occurs later in the post-transplant course and is associated with worse clinical outcomes than EBV-positive lymphomas. This observation, while widely accepted, has been challenged by more recent data, suggesting that further research is required to fully delineate the prognostic differences between EBV-positive and EBV-negative PTLD [3, 7]. Diagnosis of EBV-associated PTLD requires both the identification of clinical symptoms consistent with PTLD and the detection of EBV in tissue samples, emphasizing the need for comprehensive histological and molecular evaluation [4].

PTLD encompasses a wide spectrum of histological subtypes, with diffuse large B-cell lymphoma (DLBCL) being the most common manifestation. However, rarer subtypes, such as LPL, have been documented. In a study by Karuturi et al, only nine out of 210 PTLD patients exhibited histological features consistent with plasma cell disorders, underlining the rarity of this presentation [8]. None of these cases were associated with HLH, further highlighting the exceptional nature of the co-occurrence of these two entities.

The treatment of PTLD requires a nuanced approach that considers both the patient's clinical condition and the under-

lying pathology. Initial strategies often involve reducing or discontinuing immunosuppressive therapy to restore immune function [2, 3, 9]. However, in patients with concurrent GVHD, this approach may not be feasible, as immunosuppression plays a critical role in managing GVHD-related complications.

Antiviral therapies, such as acyclovir, ganciclovir, and valganciclovir, are typically ineffective against EBV-transformed latency type II cells. These cells evade conventional antiviral agents due to their integration into the host genome and altered viral gene expression patterns. Emerging therapies, including ruxolitinib, ibrutinib, and imatinib, have shown promise in managing GVHD, but their role in PTLD remains unproven and requires further investigation [3]. As a result, recommended first-line treatments for PTLD include systemic immunochemotherapy, which may involve intrathecal injections for cases with central nervous system involvement [10]. Radiotherapy is an option for patients with localized disease. For some patients, donor lymphocyte infusion (DLI) or unmanipulated donor T cells can be considered as part of an adoptive immunotherapy strategy [2-4, 9, 11].

Rituximab, a monoclonal antibody targeting CD20, remains the cornerstone of treatment for CD20-positive EBV-associated PTLD due to its proven efficacy in reducing disease burden and achieving remission [2-4, 11]. However, its therapeutic applicability is restricted to cases with CD20 expression, highlighting a critical gap in options for CD20-negative PTLD. In the context of PTLD complicated by HLH, where EBV often plays a central role in pathophysiology, rituximab has demonstrated potential by depleting EBV-infected B cells and mitigating the resulting inflammatory cascade [12]. Although specific data on rituximab's efficacy in PTLD-associated HLH are limited, its established role in managing EBV-driven lymphoproliferative disorders supports its use in these complex cases.

PTLD with HLH is exceedingly rare in adults, with most reported cases occurring in pediatric patients or adults following SOT [4, 12, 13]. The prognosis of PTLD complicated by HLH is universally poor, reflecting the aggressive nature of both conditions and the challenges in managing their coexistence [4]. Current evidence suggests that EBV-driven HLH in the context of PTLD is more commonly observed in pediatric populations due to their immunological immaturity and the high prevalence of EBV seronegativity prior to transplantation. In adults, the rarity of this condition underscores the need for heightened clinical vigilance and a multidisciplinary approach to management [13].

The diagnostic and therapeutic challenges associated with PTLD and HLH highlight the importance of individualized care plans. Diagnostic criteria for HLH, including the HLH-2004 guidelines, may serve as a framework for identifying patients at risk. However, the heterogeneity of PTLD and its various clinical presentations necessitate a high index of suspicion and tailored diagnostic strategies.

Therapeutically, the management of PTLD with HLH requires a delicate balance between controlling the inflammatory storm of HLH and addressing the underlying lymphoproliferative disorder. Emerging therapies targeting specific cytokine pathways implicated in HLH, such as interferon-gamma and interleukin-1 inhibitors, hold promise for improving outcomes

in this challenging patient population. Additionally, further research into the pathophysiology of EBV-driven lymphoproliferative disorders and HLH may yield novel therapeutic targets, offering hope for better prognoses in the future.

In conclusion, PTLD and HLH represent rare but devastating complications of transplantation. Their co-occurrence poses unique diagnostic and therapeutic challenges, emphasizing the need for early recognition, rapid intervention, and a multidisciplinary approach to optimize patient outcomes. The integration of emerging therapies and personalized treatment strategies holds the potential to address the unmet needs in this complex clinical scenario.

Learning points

HLH in the context of PTLD is a rare and underreported clinical entity, with only a few cases documented in the literature. PTLD associated with HLH is an exceptionally rare and complex condition that warrants further research to enhance diagnostic tools and therapeutic strategies, particularly for patients with overlapping clinical features. The combination of these conditions presents unique challenges, primarily due to shared manifestations such as fever, pancytopenia, and organomegaly, which may mimic other post-transplant complications and complicate timely diagnosis. EBV often plays a central role in pathogenesis, driving immune dysregulation and systemic inflammation. Treatment strategies must be individualized, frequently requiring a delicate balance between reducing immunosuppression and initiating chemotherapy. Rituximab remains the cornerstone therapy in EBV-driven PTLD cases, offering targeted intervention. This case underscores the importance of a multidisciplinary approach to optimize management, improve survival, and address the gaps in understanding this rare and challenging clinical presentation.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

The data supporting the findings of this case report pertain to a

patient who is deceased. While the patient was unable to provide informed consent prior to their death, all data have been fully anonymized to ensure the privacy and confidentiality of the patient. No identifiable information was included in this report.

Author Contributions

Anna Armatys contributed to the conceptualization, data analysis, writing - original draft preparation and the review of the final manuscript. Krzysztof Wozniczka was responsible for data acquisition, clinical case management, and the critical revision of the manuscript for intellectual content. Anna Koclega conducted the literature review, drafted specific sections, and contributed to the interpretation of clinical findings. Adrianna Spalek assisted with data analysis, and edited the manuscript. Martyna Włodarczyk coordinated the research process, managed patient follow-up, and proofread the manuscript. Grzegorz Helbig supervised the project, provided critical input into the study design, and approved the final manuscript version.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

PTLD: post-transplant lymphoproliferative disorder; HSCT: hematopoietic stem cell transplantation; SOT: solid organ transplantation; GVHD: graft-versus-host disease; EBV: Epstein-Barr virus; HLH: hemophagocytic lymphohistiocytosis; CRP: C-reactive protein; PCT: procalcitonin; CMV: cytomegalovirus; aGVHD: acute graft-versus-host disease; FLC: free light chains; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; AST: aspartate transaminase; ALT: alanine transaminase; PCR: polymerase chain reaction; LPL: lymphoplasmacytic lymphoma; DLBCL: diffuse large B-cell lymphoma; DLI: donor lymphocyte infusion; IV: intravenous

References

1. Dharnidharka VR. Comprehensive review of post-organ transplant hematologic cancers. *Am J Transplant.* 2018;18(3):537-549. [doi pubmed](#)
2. Carreras E, Dufour C, Mohty M, Kroger N. eds. *The EBMT Handbook: hematopoietic stem cell transplantation and cellular therapies*, 7th ed. Springer, Cham. 2019.
3. Clerico M, Dogliotti I, Aroldi A, Consoli C, Giaccone L, Bruno B, Cavallo F. Post-transplant lymphoproliferative disease (PTLD) after allogeneic hematopoietic stem cell transplantation: biology and treatment options. *J Clin Med.* 2022;11(24):7542. [doi pubmed](#)
4. Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorder.

- phoproliferative disorders in adults. *N Engl J Med*. 2018;378(6):549-562. [doi pubmed](#)
5. Weber T, Wickenhauser C, Monecke A, Glaser C, Stadler M, Desole M, Ligeti K, et al. Treatment of rare co-occurrence of Epstein-Barr virus-driven post-transplant lymphoproliferative disorder and hemophagocytic lymphohistiocytosis after allogeneic stem cell transplantation. *Transpl Infect Dis*. 2014;16(6):988-992. [doi pubmed](#)
 6. Ayee R, Ofori MEO, Wright E, Quaye O. Epstein barr virus associated lymphomas and epithelia cancers in humans. *J Cancer*. 2020;11(7):1737-1750. [doi pubmed](#)
 7. Ford M, Orlando E, Jin Z, et al. Prevalence and characterization of EBV-negative post-transplant lymphoproliferative disorder. *Blood*. 2022;140:3777-3778.
 8. Karuturi M, Shah N, Frank D, Fasan O, Reshef R, Ahya VN, Bromberg M, et al. Plasmacytic post-transplant lymphoproliferative disorder: a case series of nine patients. *Transpl Int*. 2013;26(6):616-622. [doi pubmed](#)
 9. Compagno F, Basso S, Panigari A, Bagnarino J, Stoppini L, Maiello A, Mina T, et al. Management of PTLT after hematopoietic stem cell transplantation: immunological perspectives. *Front Immunol*. 2020;11:567020. [doi pubmed](#)
 10. Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, Neuhaus R, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLT-1 trial. *Lancet Oncol*. 2012;13(2):196-206. [doi pubmed](#)
 11. Heslop HE. How I treat EBV lymphoproliferation. *Blood*. 2009;114(19):4002-4008. [doi pubmed](#)
 12. La Rosee P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, Birndt S, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019;133(23):2465-2477. [doi pubmed](#)
 13. Mazzola Poli de Figueiredo S, Johnson JC, Lyapichev KA, Stevenson HL, Lea A, Hussain S, Kulkarni RD, et al. Fatal case of EBV-negative posttransplant lymphoproliferative disorder with hemophagocytic lymphohistiocytosis in an adult kidney transplant recipient. *Transplant Direct*. 2022;8(9):e1368. [doi pubmed](#)