

A Rare Case of Post-Transplant Lymphoproliferative Disorder Presenting as Hodgkin Lymphoma After Autologous Hematopoietic Stem Cell Transplantation: A Case Report and Literature Review

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Abstract: Post-transplant lymphoproliferative disorder (PTLD) is a rare complication following hematopoietic stem cell transplantation (HSCT), with its occurrence post-autologous hematopoietic stem cell transplantation (auto-HSCT) being even rarer. Research on PTLD following auto-HSCT is exceedingly scarce. Here, we present a noteworthy instance wherein a patient with diffuse large B-cell lymphoma (DLBCL) developed PTLD, manifesting as classical Hodgkin lymphoma (cHL) two years after auto-HSCT. Additionally, we conducted an extensive review of existing literature, exploring the current research on PTLD following auto-HSCT and illuminating this scarcely examined area.

Keywords: post-transplant lymphoproliferative disorder, Hodgkin's lymphoma, diffuse large B-cell lymphoma, Epstein-Barr virus

Introduction

Post-transplantation lymphoproliferative disorders (PTLD) encompass a diverse spectrum of lymphoid proliferations that manifest following solid organ transplant (SOT) and hematopoietic stem cell transplantation (HSCT). PTLD represents a relatively uncommon complication following transplantation, with incidence rates ranging from 0.5% to 10.0% in SOT cases, depending on the type of transplanted organ. In HSCT, PTLD arises at an approximate rate 3.2%, with nearly all cases occurring after allogeneic hematopoietic stem cell transplantation (allo-HSCT).¹ Despite advancements in treatment strategies, PTLD remains a significant challenge in the management of transplant patients, particularly in terms of prevention and timely diagnosis.² Among PTLD patients, reactivation of the Epstein-Barr virus (EBV) during immunosuppressive therapy is the primary instigator, although EBV-negative cases have also been documented.²

Auto-HSCT has emerged as a therapeutic modality for various medical conditions, including Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, acute leukemia, and related ailments.^{3,4} The immunosuppressive effect and duration following auto-HSCT are perceived to be considerably diminished compared to HSCT, due to the absence of graft-versus-host disease (GVHD).⁵ Reports of PTLD as a complication following auto-HSCT are exceedingly rare. In this context, we present a compelling case study involving a patient afflicted with DLBCL, who subsequently developed PTLD resembling Hodgkin lymphoma following auto-HSCT. Additionally, we have synthesized literature elucidating the current research landscape pertaining to PTLD after auto-HSCT.

Case Presentation

On January 24, 2020, a 65-year-old female was admitted to The First Affiliated Hospital of Ningbo University, presenting with a two-month history of upper abdominal pain. An abdominal CT scan revealed significant thickening of the gastric wall in the antrum, accompanied by ulcers and multiple lymph nodes surrounding the stomach (**Figure 1**). The FDG PET-CT scan showed mucosal thickening in the gastric antrum, and multiple enlarged lymph nodes around the stomach and above the left clavicle, along with increased metabolic activity. Subsequent endoscopic examination unveiled a substantial ulceration in the gastric antrum (**Figure 2**). Based on the morphological characteristics and immunohistochemistry profile, the patient was diagnosed with diffuse large B-cell lymphoma (DLBCL). No abnormal cells were detected in the bone marrow examination. Importantly, the patient had no prior history of exposure to industrial toxins or radioactive substances.

After successfully completing six cycles of R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy and achieving complete remission confirmed by FDG PET-CT (**Figure S1**), the patient underwent autologous hematopoietic stem cell transplantation on October 16, 2020. The conditioning regimen included Rituximab combined with BEAM (carmustine, Etoposide, cytarabine, and melphalan). The transplantation involved a total nucleated cell count of $3.31 \times 10^8/\text{kg}$ and a CD34+ cell count of $0.42 \times 10^6/\text{kg}$. Granulocyte engraftment occurred on Day 10 post-transplantation, followed by megakaryocyte engraftment on Day 12. Post-transplant, the patient continued antiviral therapy with Entecavir and attended regular outpatient follow-ups.

On January 11, 2023, the patient sought medical attention after noticing the enlargement of the left clavicular lymph nodes. An ultrasound examination identified several well-defined hypoechoic areas above the left clavicle, with the largest measuring approximately 23×14 mm (**Figure 3**). The corticomedullary structure was indistinct with a full contour

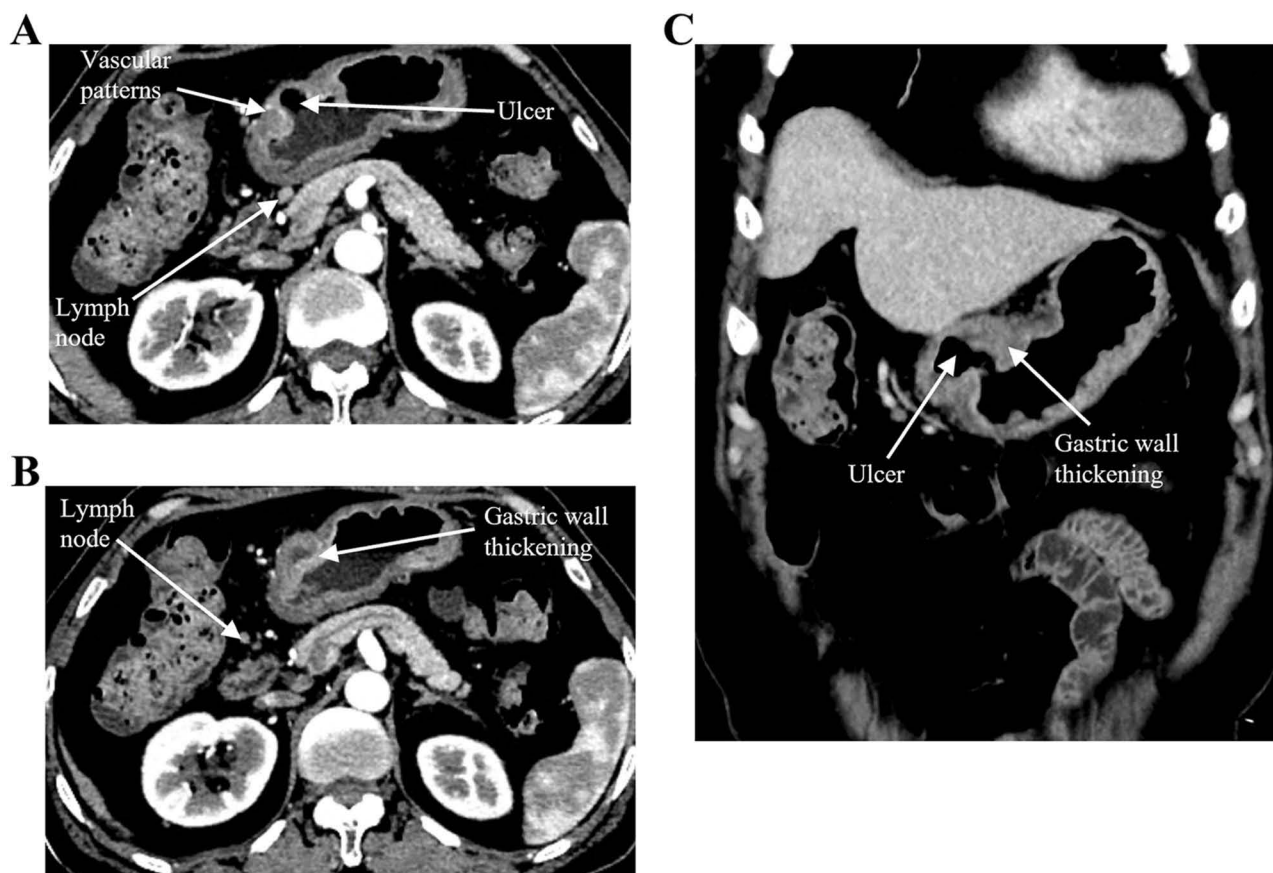


Figure 1 (A) Vascular patterns can be found within the thickened mucosa. Ulcerative lesions present on the lesser curvature and anterior wall of the stomach, with multiple visible lymph node shadows in the vicinity. (B) The abdominal enhanced CT scan indicates a conspicuous thickening of the gastric wall in the gastric antrum region, measuring approximately 12.5 mm at its thickest point. (C) Coronal reconstruction of CT images.

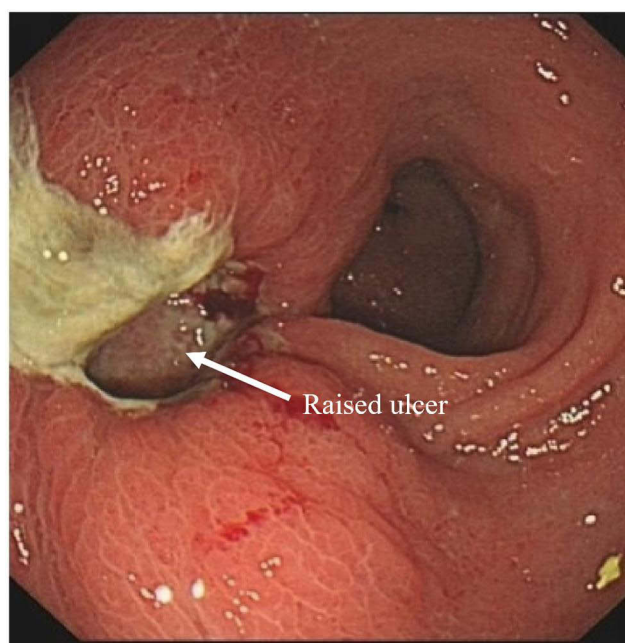


Figure 2 The anterior wall of the stomach and the lesser curvature exhibit a sizable raised ulcer.

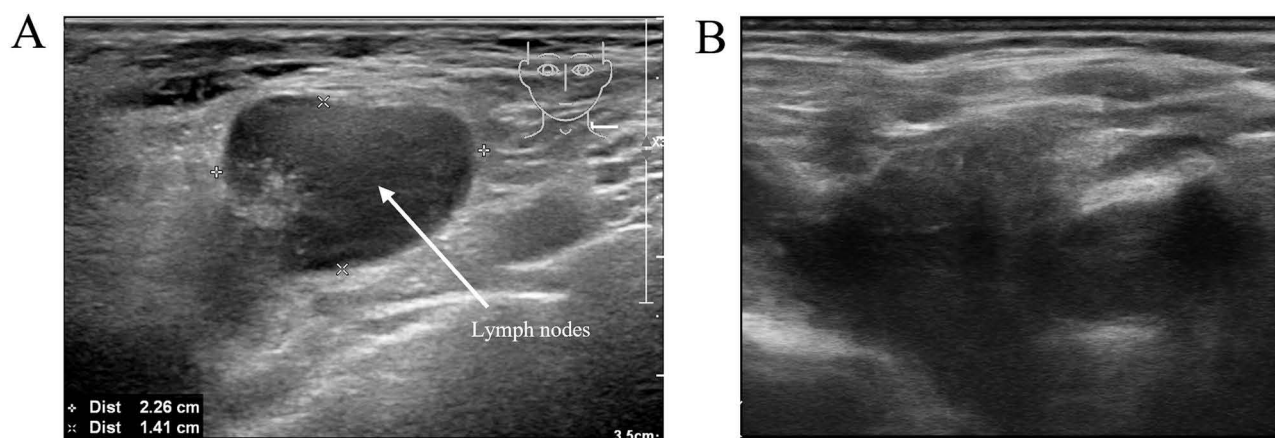


Figure 3 (A) Enlarged lymph nodes are visible in the left supraclavicular area, with the largest measuring approximately 23×14 mm. (B) No significantly enlarged lymph nodes were observed in the supraclavicular region after treatment.

and internal vascularity, showing significant enlargement compared to the previous examination. No significant lymph node enlargement was observed above the right clavicle. Other superficial lymph nodes retained clear structures, with sizes similar to the previous assessments. Additionally, a fine-needle aspiration biopsy of the lymph node was performed, and the morphological characteristics and immunohistochemistry result confirmed classical Hodgkin lymphoma, nodular sclerosis type.

Subsequently, the patient underwent two cycles of ABVD regimen (Epirubicin, Bleomycin, Vindesine and Dacarbazine) followed by two cycles of the BV+AVD regimen (Brentuximab, Vedotin, Epirubicin, Vindesine and Dacarbazine). Post-treatment ultrasound examinations of superficial lymph nodes throughout the body indicated no enlargement above the clavicle, while the lymph nodes in other regions remained structurally unchanged and consistent in size with previous measurements (Figure 3). These findings suggest the changes are likely benign. Additionally, abdominal MRI and chest CT scans revealed no apparent abnormalities. As of the present, the patient remains in good health.

To investigate the molecular similarities between DLBCL and HL in this patient, next-generation sequencing was conducted on the pathological specimens from both the DLBCL and Hodgkin lymphoma. This analysis included sequencing for lymphoma-related gene mutations and the immunoglobulin heavy chain. The results indicated no molecular homology between the two types of lymphoma (Table 1). Moreover, EBV detection showed a transition from negative to positive for EBV-encoded RNA (EBER), suggesting the possible development of post-autologous transplantation PTLD.

Discussion

In the case, the investigation aimed to determine the molecular similarity between tissues from cHL and DLBCL Lymph nodes. Subsequent sequencing of lymphoma-related gene and immunoglobulin heavy chain mutations was performed. The results indicated that the cHL of the patient did not originate from his previous DLBCL. Additionally, the EBV infection status changed from negative to positive, suggesting that the onset of cHL could be regarded as a newly emerged PTLD.

PTLD was first identified in 1968 and formally classified in 1984.⁶ The precise mechanisms underlying PTLD remain elusive. However, it is known that EBV triggers abnormal lymphocyte proliferation in 50–80% of PTLD cases, particularly in the early stages.² Current PTLD research primarily focuses on cases following allo-HSCT. Evidence suggests that compromised immunity, especially impaired T-cell immunity, is crucial in facilitating EBV infection in transplant recipients.

Immunosuppression following HSCT can reactivate latent EBV infection or impair responses to new infections, thereby increasing the risk of developing PTLD. For instance, anti-thymocyte globulin, used to prevent graft rejection by depleting T cells, is associated with a higher risk of PTLD. Similarly, agents like fludarabine and azathioprine, which profoundly suppress T cells or have mutagenic properties, have been implicated in PTLD pathogenesis.^{7,8} Other factors, such as advanced age, compromised baseline immune status, a history of splenectomy, monoclonal gammopathy of undetermined significance, and CMV infection, can also contribute to an elevated risk of developing PTLD. Allo-HSCT presents additional complexities compared to auto-HSCT, including donor type, graft compatibility, and the immunosuppressive therapy required for managing GVHD.^{1,9} Discontinuing immunosuppression to restore host immunity has led to disease remission in a many PTLD cases.⁶ It is worth noting that, due to the absence of issues such as GVHD, the immunosuppression during auto-HSCT is often relatively mild, making PTLD extremely rare following auto-HSCT.

In recent years, extensive research on PTLD following SOT and allo-HSCT, coupled with the application of rituximab, has gradually improved the prognosis of PTLD, with a median survival now reaching 6.6 years.¹⁰ However, studies on PTLD following auto-HSCT are still limited to case reports, and further research is needed to evaluate prognosis and develop strategies to enhance outcomes. Reports have indeed indicated that auto-HSCT can lead to PTLD and hemophagocytic syndrome.^{11,12} We have compiled several instances of PTLD resulting from auto-HSCT (Table 2).^{13–22} From the table, we can discern that it's evident that PTLD following auto-HSCT is often associated with a poor prognosis, typically resulting in a survival period not exceeding one year, which is significantly shorter compared to PTLD following SOT and allo-HSCT. Currently, there is no comprehensive prognostic assessment system for PTLD, regardless of whether it involves allo-HSCT, auto-HSCT, or SOT. A study based on a registry of 500 PTLD cases post-

Table 1 The Result of Next-Generation Sequencing

DLBCL		HL	
Gene Mutation	Ig Sequence	Gene Mutation	Ig Sequence
BRAF NFKBIE KLHL6 MGAM	IGHD3-9/IGHJ6 IGKV1-33/IGKJ5 IGKV2D-30/IGKJ3 Intron/KDE IGLVI-40/IGLJ2	Germline Mutation	None

Table 2 PTLDs After Auto-HSCT

Study	Year of Publication	Disease	Source of Stem Cells	Graft Manipulation	Time of PTLD Onset After HSCT	PTLD	OS
Briz M, et al ¹³	1997	T-ALL	Marrow	T-cell depletion	60d	DLBCL	107d
Yufu Y, et al ¹⁴	2000	HL	Marrow	None	30m	peripheral T-cell lymphoma	9m
Heath JA, et al ¹⁵	2002	RB	PBSC	None	3w	DLBCL	>5y
Zambelli A, et al ¹⁶	2005	cAA	PBSC	None	105d	HL	2m
Takahashi S, et al ¹⁷	2007	MM	PBSC	CD34 selected	128d	large cell type B-cell lymphoma.	155d
Feuillet S, et al ¹⁸	2009	DLBCL	PBSC	None	2y	FL	<1m
Viola GM, et al ¹⁹	2011	NHL	PBSC	None	3y	diffuse atypical/clonal plasma cell hyperplasia	<1y
Ishikawa T, et al ²⁰	2016	MM	PBSC	None	9m	peripheral T-cell lymphoma,	>5y
Kajimoto Y, et al ²¹	2020	DLBCL	PBSC	None	4y	peripheral T-cell lymphoma	8m
Khalid SN, et al ²²	2022	MM	PBSC	None	3y	HL	4m

Abbreviations: cAA, Cerebral Anaplastic Astrocytoma; DLBCL, Diffuse Large B-cell Lymphoma; FL, Follicular Lymphoma; HL, Hodgkin's Lymphoma; MM, Multiple Myeloma; NB, Neuroblastoma; OS, Overall Survival; PBSC, Peripheral Blood Stem Cell; RB, Retinoblastoma; T-ALL, T-cell Acute Lymphocytic Leukemia.

kidney transplantation in France proposed a prognostic scoring system encompassing five variables: age, serum creatinine levels, lactate dehydrogenase levels, PTLD localization, and histological characteristics.²³ Although this system has been validated in smaller single-center studies, there is no evidence to suggest it outperforms the classic International Prognostic Index (IPI) for lymphoma.²⁴

The most recent WHO classification of lymphoid neoplasms suggests that these rarely reported PTLD lesions following auto-HSCT are more likely to be iatrogenic, related to the therapy rather than the transplant itself.²¹ Consequently, management strategies before and after transplantation, as well as treatment methods employed following the occurrence of PTLD, may significantly influence the prognosis of PTLD after auto-HSCT.

Assessing prognosis and risk stratification in PTLD is complicated by factors such as small sample sizes, diverse patient characteristics, varied treatment approaches, and the lack of definitive efficacy data. Current research indicates that reducing immunosuppression and administering rituximab following PTLD occurrences may enhance therapeutic outcomes. Restoring immune function, particularly T-cell recovery, and eliminating EBV-infected B cells may indeed be pivotal in improving prognosis. Response rates to reduced immunosuppression and rituximab therapy range from 44% to 79%, with complete remission rates of 20% to 55%.¹ Therefore, personalized transplant management plans for recipients are essential. Pre-transplant assessments should include the recipient's age, baseline immune function, and EBV infection status. High-risk patients might benefit from less aggressive immunosuppressive regimens. Individualized EBV monitoring can aid in the early detection and diagnosis of PTLD. The Sixth European Conference on Infections in Leukemia (ECIL-6) recommends starting EBV DNA monitoring in the first month following HSCT, with weekly tests until four months post-transplant.²⁵ PTLD occurrences in EBV-positive recipients are typically concentrated within the first year post-transplant.¹ Our patient developed PTLD more than two years after auto-HSCT, which is significantly longer than previously reported cases. This suggests that extending EBV monitoring beyond the first year, particularly post-auto-HSCT, and tailoring surveillance plans for different patients are critical. Monitoring frequency could be adjusted based on EBV-DNA levels, with prophylactic rituximab treatment initiated once EBV-DNA reaches a certain threshold.²⁶ Compared to the PTLD outcomes listed in Table 2, our patient's prognosis is notably better, likely owing to pre-transplant rituximab administration and the subsequent incorporation of brentuximab in the treatment regimen after PTLD diagnosis. Although the patient has survived and maintained a favorable condition over a year following the PTLD diagnosis, ongoing observation is necessary to determine the long-term prognosis. In the future, it is essential to collect more such rare cases and conduct prolonged follow-up to facilitate further investigation.

Conclusion

In conclusion, we have presented a rare case of PTLD manifesting as cHL following auto-HSCT. This case developed EBV-positive PTLD over two years post-transplant, while most PTLD cases typically occur within the first year. This

highlights the importance of extended and personalized EBV monitoring. Currently, it is suggested that improving PTLD treatment may involve reducing immunosuppression and using rituximab. Notably, our case has maintained a positive clinical status thus far, which is unusual compared to other PTLD cases. This may relate to specific pre-transplant conditioning methods and post-PTLD treatment strategies. Consequently, it is crucial to develop personalized pre- and post-transplant management plans tailored to individual patients.

Data Sharing Statement

In order to protect patient privacy and respect the patient's personal wishes, the raw NGS data are not publicly available. All other data generated or analyzed in this study are included in this published article.

Ethics Approval and Consent to Participate

Institutional approval was not required to publish the case details. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Ningbo University (2024RS040). Written informed consent was obtained from the patient.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Patient Consent for Publication

Written informed consent was obtained from the patient for publication of the data and images in this case report.

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Disclosure

No potential conflict of interest was reported by the authors.

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