

Transformation of Mixed Cellularity Classical Hodgkin Lymphoma to Diffuse Large B-cell Lymphoma: A Case Report and Literature Review

Review began 07/04/2026

Review ended 10/07/2026

Published 10/18/2026

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DOI: 10.7759/cureus.118134

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Abstract

The development of diffuse large B-cell lymphoma (DLBCL) in patients with a history of classical Hodgkin lymphoma (cHL) is a well-established but rarely documented event, particularly when it originates from the mixed cellularity subtype, an occurrence that has been minimally reported and documented. We present the case of a 47-year-old woman with mixed cellularity classical Hodgkin lymphoma (MC-cHL), Lugano stage IV, who underwent hematopoietic cell transplantation, subsequently relapsed, and later developed DLBCL, raising the possibility of histologic transformation. She was treated with polatuzumab vedotin, rituximab, and ibrutinib.

Categories: Hematology, Pathology

Keywords: chronic immunosuppression, classic hodgkin lymphoma mixed cellularity, diffuse large b-cell lymphoma, immunotherapy and hematological malignancies, neoplastic transformation

Introduction

Classical Hodgkin lymphoma (cHL) is a lymphoid neoplasm characterized by Hodgkin and Reed-Sternberg (HRS) cells within a prominent inflammatory microenvironment. Histologically, cHL comprises several subtypes, including mixed cellularity classical Hodgkin lymphoma (MC-cHL). The subsequent development of non-Hodgkin lymphoma (NHL) after cHL is uncommon. In a population-based cohort of 26,826 patients with cHL, the cumulative incidence of secondary NHL was 0.41% at five years, 1.34% at 10 years, and 2.50% at 15 years; among the reported secondary NHLs, diffuse large B-cell lymphoma (DLBCL) and its variants represented the most frequent histologic category [1]. However, these epidemiological estimates describe the occurrence of a subsequent NHL after cHL and should not be interpreted as the incidence of molecularly confirmed clonal transformation.

The development of DLBCL following cHL represents a complex diagnostic and biological scenario that has been infrequently described in the literature [2,3]. Although sequential histologic and immunophenotypic changes may support the possibility of transformation, the development of DLBCL after cHL does not by itself establish a shared clonal origin. Molecular assessment of clonality is required to distinguish true clonal transformation from a metachronous de novo B-cell lymphoma [2]. Histologic transformation in lymphoid neoplasms involves the emergence of a morphologically and biologically more aggressive lymphoma; however, establishing a direct evolutionary relationship requires the integration of histopathologic, immunophenotypic, and, when available, molecular findings [4]. This distinction is particularly relevant in heavily pretreated and post-transplant patients, in whom alternative mechanisms, including post-transplant lymphoproliferative disorders (PTLDs), Epstein-Barr virus (EBV)-driven lymphoproliferation, and secondary lymphoid neoplasms, should be considered. Chronic immunosuppression and impaired immune surveillance following hematopoietic cell transplantation may provide a permissive environment for B-cell proliferation, particularly in the setting of EBV infection [2,3].

Here, we report the case of a 47-year-old woman with EBV-positive, Lugano stage IV MC-cHL who underwent multiple lines of systemic therapy followed by hematopoietic cell transplantation and subsequently developed DLBCL with strong CD20 expression, MUM1 positivity, and a Ki-67 proliferation index of 50-60%. Molecular clonality studies comparing the MC-cHL and DLBCL components were not performed; therefore, although the sequential clinicopathological findings support the possibility of histologic transformation, a shared clonal origin cannot be confirmed, and a metachronous de novo DLBCL cannot be completely excluded. The patient was subsequently treated with polatuzumab vedotin, rituximab, and ibrutinib, achieving a clinical response. This case highlights the rare development of DLBCL following

How to cite this article

Lopez Navarro O, García-Méndez J O, Santana Cruz L, et al. (October 18, 2026) Transformation of Mixed Cellularity Classical Hodgkin Lymphoma to Diffuse Large B-cell Lymphoma: A Case Report and Literature Review. Cureus 18(10): e118134. DOI 10.7759/cureus.118134

MC-cHL in the post-transplant setting, the diagnostic challenge of establishing a biological relationship between the two lymphomas, and the potential role of targeted therapeutic strategies in heavily pretreated disease.

Case Presentation

A 47-year-old woman with a history of hypothyroidism initially presented in June 2020 with nontender cervical adenomegaly and inguinal lymphadenopathy. An excisional lymph node biopsy performed in September 2020 established the diagnosis of MC-cHL, Lugano stage IV, with CD30, CD15, EBV, and LMP-1 positivity. PAX5 and CD20 expression in the HRS cells was not documented in the available initial pathology report (Figure 1). Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) performed in October 2020 demonstrated bilateral axillary lymph node involvement (Figure 2). The patient began treatment with brentuximab-based multiagent chemotherapy in October 2020 and completed six cycles in February 2021. Subsequent FDG PET/CT demonstrated a complete metabolic response with a Deauville score of 2, and maintenance brentuximab was initiated.

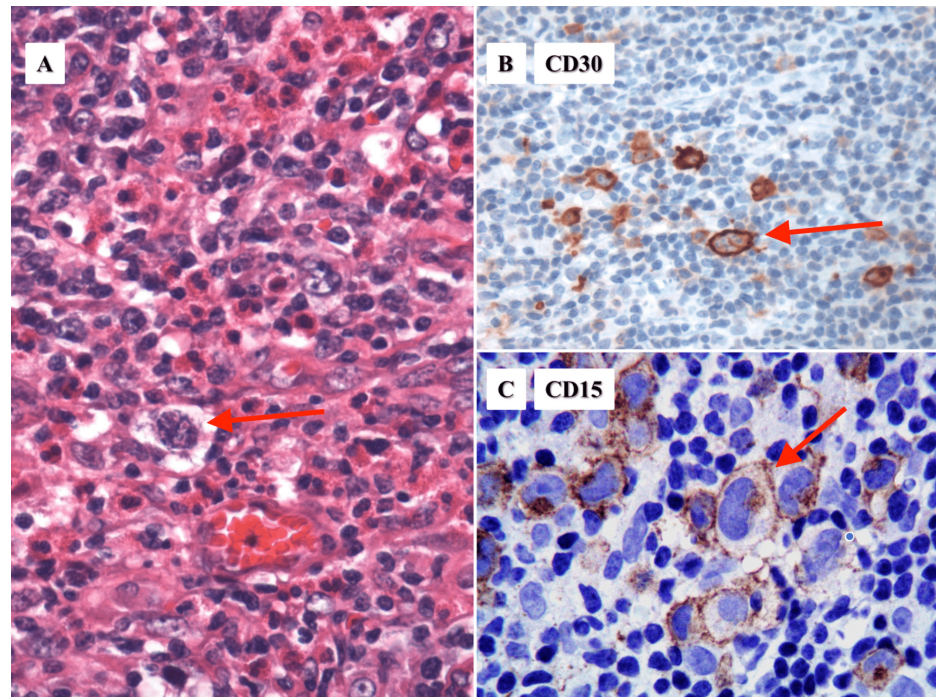


FIGURE 1: Histopathology and immunohistochemistry of MC-cHL at initial diagnosis

Histopathology and immunohistochemistry of MC-cHL at initial diagnosis.

(A) H&E, 40×: Mixed inflammatory background composed predominantly of lymphocytes and eosinophils, with scattered large HRS cells (red arrow). (B) CD30 immunohistochemistry, 40×: Membranous and Golgi-pattern CD30 positivity in HRS cells (red arrow). (C) CD15 immunohistochemistry, 40×: CD15 positivity in HRS cells (red arrow). The original pathology report additionally documented EBV and LMP-1 positivity; corresponding images were not available for inclusion. PAX5 and CD20 expression in HRS cells was not documented in the available initial pathology material.

H&E, hematoxylin and eosin; HRS, Hodgkin/Reed-Sternberg; CD, cluster of differentiation; EBV, Epstein-Barr virus; MC-cHL, mixed-cellularity classical Hodgkin lymphoma

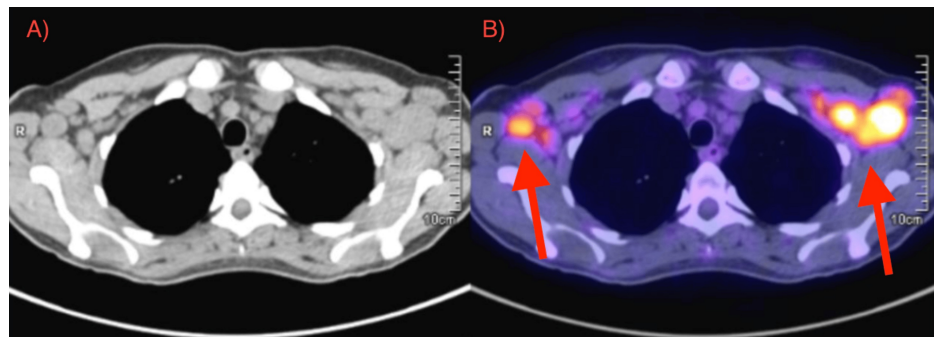


FIGURE 2: First FDG PET/CT performed in October 2020

(A) Axial CT image demonstrating bilateral axillary lymphadenopathy. (B) Fused FDG PET/CT image demonstrating increased metabolic activity in bilateral axillary lymph nodes (red arrows), consistent with metabolically active lymphomatous involvement. Quantitative SUV values and a formal Deauville score were not available for this examination.

FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; CT, computed tomography; SUV, standardized uptake value

During follow-up, the patient developed recurrent lymphadenopathy. FDG PET/CT performed in January 2022 demonstrated increased supradiaphragmatic and infradiaphragmatic lymphadenopathy and findings consistent with recurrent disease, with a Deauville score of 5. Salvage therapy consisting of etoposide (days 1-3), carboplatin (day 3), ifosfamide (day 1), and brentuximab (day 2) was initiated, and six cycles were completed. The patient subsequently underwent autologous hematopoietic cell transplantation in September 2022. The available medical records did not provide sufficient information regarding the conditioning regimen or other transplant-specific characteristics for inclusion in the present report.

In March 2023, she presented with lymphadenopathy in both axillary regions, as well as in the internal mammary chain and splenic hilum. A second biopsy reported positivity for CD3, CD20, and PAX5, with Reed-Sternberg cells positive for CD30, confirming relapse of MC-cHL (Figure 3). The available pathology report did not clearly specify the cellular distribution of all immunohistochemical markers; therefore, CD20 expression in the HRS cells could not be established. In May 2023, immunotherapy with nivolumab was started; however, she developed Stevens-Johnson syndrome (SJS) secondary to treatment in June 2023, characterized by disseminated dermatitis. She was treated empirically for seven days, and nivolumab was discontinued.

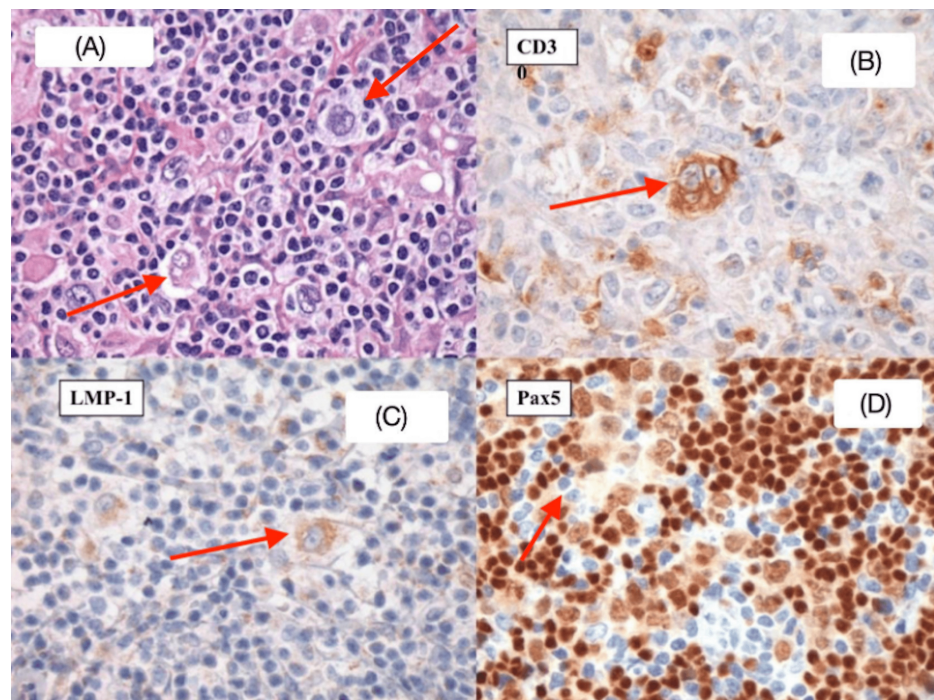


FIGURE 3: Histopathology and immunohistochemistry of recurrent MC-cHL

(A) H&E, 40×: Mixed-cellularity pattern with numerous HRS cells (highlighted with red arrows). (B) CD3 immunohistochemistry, 40×: CD3-positive lymphocytes are present in the inflammatory background; the available pathology documentation does not establish CD3 expression in HRS cells. (C) LMP-1 immunohistochemistry, 40×: LMP-1 positivity in HRS cells (red arrow). (D) PAX5 immunohistochemistry, 40×: Weak nuclear PAX5 positivity in HRS cells (red arrow), supporting the diagnosis of recurrent cHL. CD30 positivity in Reed-Sternberg cells was documented in the pathology report but is not shown as a separate panel in this figure.

H&E, hematoxylin and eosin; HRS, Hodgkin/Reed-Sternberg cells; CD, cluster of differentiation; cHL, classical Hodgkin lymphoma

In August 2023, a new treatment regimen with brentuximab and bendamustine was initiated. After administration of the second cycle, the patient developed bacteremia, and the catheter was removed because of a catheter-associated infection. Bendamustine was subsequently discontinued because of grade 3 anemia and thrombocytopenia, while brentuximab therapy was continued for a total of 15 cycles. FDG PET/CT in August 2024 showed an increased number of cervical and mediastinal lymph nodes with increased metabolic activity, along with newly appearing retroperitoneal nodes (Figure 4). Therefore, second-line therapy consisting of pembrolizumab, gemcitabine, vinorelbine, and liposomal doxorubicin was initiated, with pembrolizumab continued for five cycles.

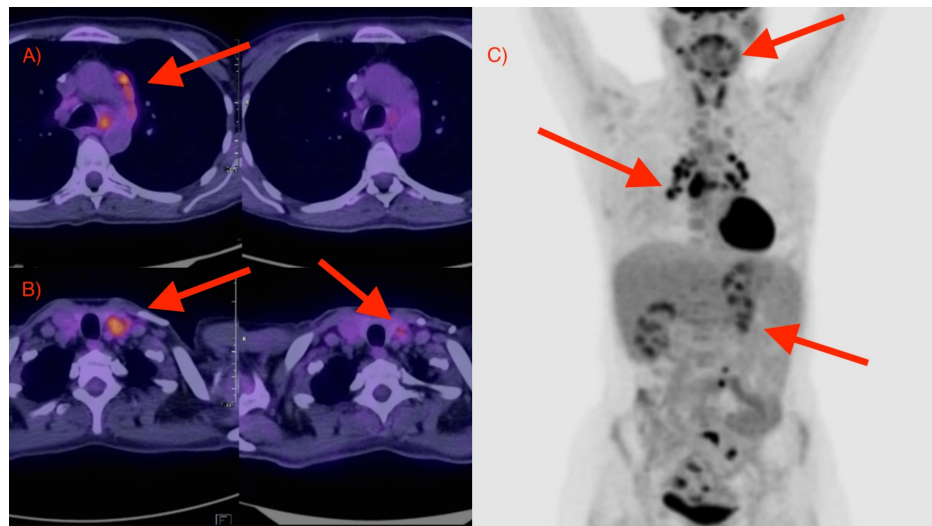


FIGURE 4: Second FDG PET/CT performed in August 2024

(A) Axial fused FDG PET/CT image demonstrating metabolically active mediastinal lymphadenopathy (red arrow). (B) Axial fused FDG PET/CT images demonstrating metabolically active cervical/supraclavicular lymphadenopathy (red arrows). (C) Maximum intensity projection PET image demonstrating multiple metabolically active lymph node sites involving the cervical and thoracic regions, with newly identified retroperitoneal lymphadenopathy (red arrows), consistent with disease progression. Quantitative SUV values and a formal Deauville score were not available for this examination.

FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; SUV, standardized uptake value

In June 2025, the patient developed DLBCL. She presented with lymphadenopathy involving both axillary regions, the internal mammary chain, and the splenic hilum. A third biopsy demonstrated strong CD20 expression, MUM1 positivity, and a Ki-67 proliferation index of approximately 50-60%, supporting the diagnosis of DLBCL (Figure 5). Cell-of-origin classification could not be established using the Hans immunohistochemical algorithm because CD10 and BCL6 results were unavailable. Additional immunohistochemical markers, including BCL2, MYC, and CD45, as well as Epstein-Barr virus-encoded RNA (EBER) in situ hybridization, were not documented as having been performed. Molecular clonality studies comparing the previous MC-cHL and subsequent DLBCL were also not performed. Therefore, although the sequential histopathological and immunophenotypic findings were clinically interpreted as compatible with transformation, a shared clonal origin could not be established, and a metachronous de novo DLBCL could not be completely excluded.

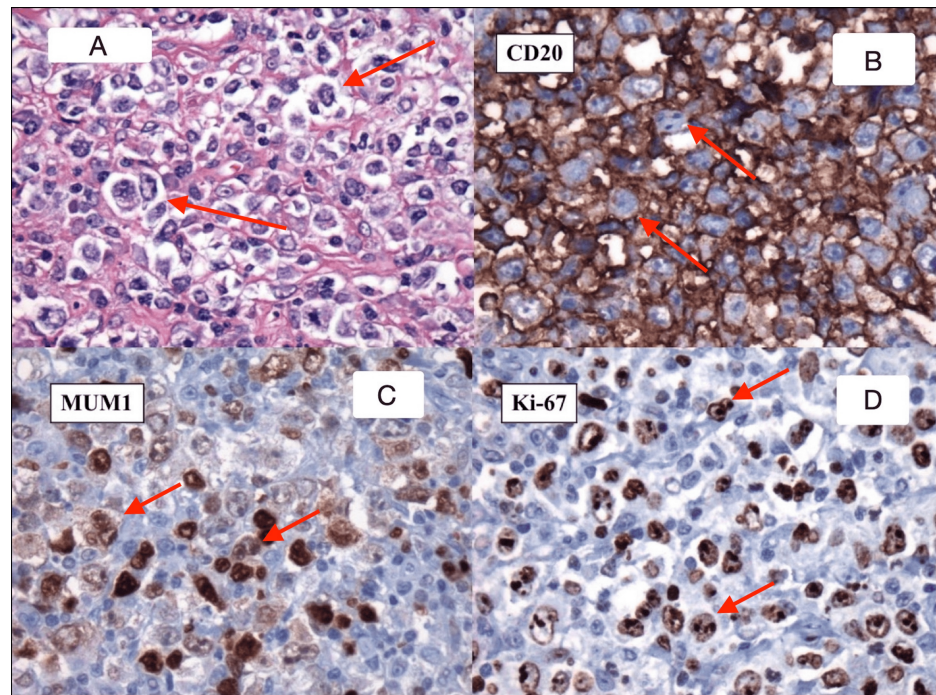


FIGURE 5: Histopathology and immunohistochemistry of DLBCL

(A) H&E, 40×: diffuse infiltrate of large atypical lymphoid cells with prominent nucleoli (red arrows). (B) CD20 immunohistochemistry, 40×: strong membranous CD20 positivity in the large neoplastic B cells (red arrows). (C) MUM1 immunohistochemistry, 40×: nuclear MUM1 positivity in the neoplastic cells (red arrows). (D) Ki-67 immunohistochemistry, 40×: proliferative index of approximately 50–60% in the neoplastic cell population (red arrows). The morphological and immunophenotypic findings supported the diagnosis of DLBCL. Additional immunohistochemical markers, including CD10, BCL6, BCL2, MYC, and CD45, as well as EBER in situ hybridization, were not available in the documented diagnostic evaluation.

H&E, hematoxylin and eosin; DLBCL, diffuse large B-cell lymphoma; CD, cluster of differentiation; EBER, Epstein-Barr virus-encoded RNA

An FDG PET/CT scan in July 2025 demonstrated disease progression (Figure 6), which prompted initiation of a new treatment regimen consisting of polatuzumab 85 mg (D1), rituximab 555 mg (D1), and ibrutinib 420 mg (D1-21), cycle 2, day 1 (C2D1). The patient demonstrated a clinical response following treatment; however, confirmatory response-assessment PET/CT was pending at the time of manuscript preparation; therefore, a complete metabolic response could not yet be established.

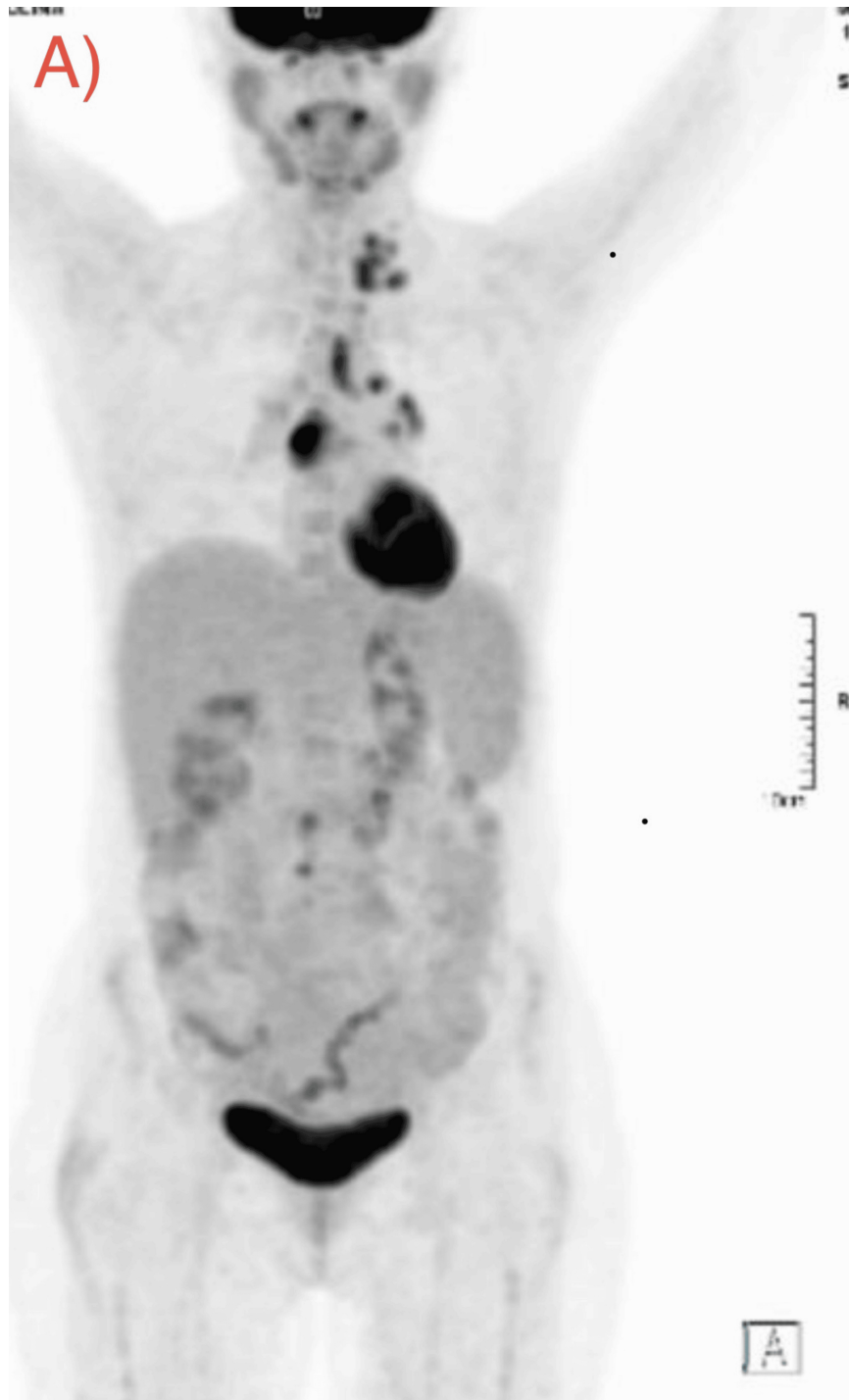


FIGURE 6: Third FDG PET/CT performed in July 2025

(A) Maximum intensity projection PET image demonstrating multiple metabolically active lymph node sites, consistent with progressive disease. At this stage, the documented disease distribution included axillary, internal mammary, and splenic hilar lymphadenopathy. Quantitative SUV values and a formal Deauville score were not available for this examination.

FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; SUV, standardized uptake value

A clinical timeline summarizing all relevant events, including diagnosis, therapeutic interventions, complications, remission, and transformation, is shown in Figure 7.

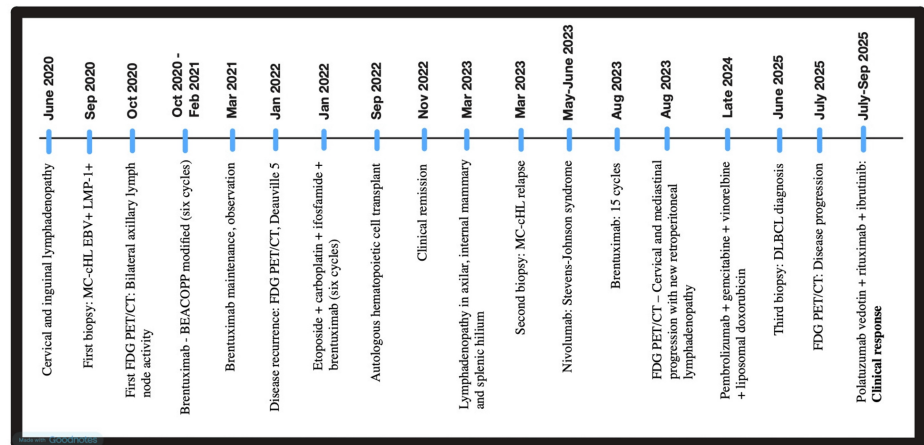


FIGURE 7: Clinical timeline summarizing all relevant events

The timeline summarizes the initial presentation and diagnosis of MC-cHL in 2020, subsequent systemic therapies, disease recurrence, autologous hematopoietic cell transplantation in September 2022, histologically confirmed MC-cHL relapse in 2023, subsequent treatment lines and complications, and the diagnosis of DLBCL in June 2025. Following disease progression documented by FDG PET/CT in July 2025, treatment with polatuzumab vedotin, rituximab, and ibrutinib was initiated, resulting in a clinical response; confirmatory response-assessment PET/CT was pending at the time of manuscript preparation.

MC-cHL, mixed-cellularity classical Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography

Discussion

Transformation of MC-cHL to DLBCL has been described in the literature, although the distinction between true clonal transformation and the sequential development of a second lymphoma remains important [3,5]. Molecularly confirmed transformation requires evidence of a shared clonal origin between the preceding lymphoma and the subsequent aggressive neoplasm. However, sequential histopathological diagnoses alone cannot establish this relationship [5,6].

Molecular biology of transformation to DLBCL

The development of DLBCL following MC-cHL may involve molecular alterations associated with aggressive clinical behavior, including increased proliferation, resistance to apoptosis, and changes in signaling and immune escape mechanisms [7,8]. In the present case, the subsequent lymphoma expressed CD20 and MUM1, with a Ki-67 proliferation index of approximately 50-60%, supporting the diagnosis of DLBCL. These findings are compatible with an aggressive B-cell lymphoma but do not independently demonstrate clonal transformation from the preceding MC-cHL.

Cell of origin shifts

DLBCL constitutes a heterogeneous group of tumors classified by gene expression profiling into germinal center B-cell-like (GCB) and activated B-cell-like (ABC) molecular subtypes, among other recognized entities. GCB-DLBCL exhibits features associated with GCBs, whereas ABC-DLBCL is associated with ABC differentiation and signaling pathways such as NF- κ B. Cell-of-origin classification provides prognostic information and may inform therapeutic decisions [7].

The ABC phenotype has been associated with adverse outcomes in some DLBCL populations. Its molecular characteristics include transcriptional reprogramming, activation of prosurvival signaling pathways, and alterations in immune regulation [7-9]. However, MUM1 expression alone does not establish an ABC phenotype. The Hans immunohistochemical algorithm requires evaluation of CD10, BCL6, and MUM1 to distinguish GCB from non-GCB DLBCL [8]. In the present case, CD10 and BCL6 results were not available; therefore, cell of origin could not be formally assigned using this algorithm.

Genetic drivers

Genetic mutations that perturb regulatory networks serve as key drivers of lymphoma progression. TP53 mutations promote genomic instability, unchecked proliferation, and therapeutic resistance. Aberrations in MYC, including translocations and amplifications, accelerate cell cycle progression and induce metabolic reprogramming. Alterations in BCL2 provide an antiapoptotic advantage, preventing programmed cell death even under cytotoxic stress. Mutations in CREBBP and EZH2 remodel the epigenetic landscape, while

deletions of CDKN2A/B and mutations involving CCND3 deregulate cell-cycle control. Defects involving B2M and loss of MHC class I or II expression may impair antigen presentation and facilitate immune evasion. Certain aggressive B-cell lymphomas harbor rearrangements involving MYC and BCL2, with or without BCL6, which have important diagnostic and prognostic implications [7,10].

These molecular mechanisms have been described in the literature but were not demonstrated in the present patient, as comparative molecular profiling, cytogenetic studies, and fluorescence in situ hybridization were not available.

Microenvironmental remodeling

Lymphoma progression may involve significant alterations in the tumor microenvironment. Malignant B cells can acquire mechanisms of autonomous growth and survival, while changes in PD-L1 and PD-L2 expression, antigen presentation, and cytokine signaling may contribute to immune escape. Remodeling of cytokine and chemokine networks may establish a microenvironment that promotes tumor expansion and dissemination [8]. Although these mechanisms provide a potential biological framework for lymphoma progression, their contribution to the present case was not directly evaluated.

Signaling pathways

Aggressive B-cell lymphomas may exhibit activation of oncogenic signaling cascades. NF- κ B signaling, potentially influenced by alterations involving CARD11, MYD88, or TNFAIP3, contributes to tumor-cell survival and inflammatory responses. The PI3K/AKT/mTOR pathway supports cellular growth and resistance to apoptosis, while JAK/STAT signaling may promote proliferation and immune evasion. B-cell receptor signaling also contributes to the survival of certain DLBCL subtypes [7]. These pathways represent mechanisms described in DLBCL biology and should not be interpreted as molecular findings established in our patient.

Histology

Histopathological evaluation is essential for distinguishing recurrent cHL from a subsequent aggressive B-cell lymphoma. cHL is characterized by Hodgkin/Reed-Sternberg (HRS) cells within a characteristic inflammatory background, whereas DLBCL generally exhibits a diffuse infiltrate of large atypical B cells with prominent nucleoli and variable proliferative activity [11,12]. Although Ki-67 may be elevated in aggressive lymphomas, no single Ki-67 threshold establishes histologic transformation.

In our patient, the initial and recurrent biopsies supported MC-cHL, whereas the subsequent biopsy demonstrated a diffuse infiltrate of large atypical CD20-positive B cells, with MUM1 positivity and a Ki-67 index of approximately 50-60%. This proliferative index is compatible with DLBCL but does not independently establish its biological relationship to the preceding lymphoma. The histological and immunophenotypic differences support the diagnosis of a subsequent aggressive B-cell lymphoma; however, they do not establish whether it arose through clonal transformation or as a distinct neoplasm.

Immunophenotype

The immunophenotypic distinction between cHL and DLBCL is important when evaluating sequential lymphoma diagnoses. Classical HRS cells typically express CD30 and may express CD15, with weak PAX5 expression, whereas DLBCL generally demonstrates a mature B-cell immunophenotype, including CD20 expression. MUM1 expression may occur in DLBCL but does not independently establish ABC cell of origin or prove transformation [9,11,12].

In the present case, the initial MC-cHL demonstrated CD30 and CD15 positivity, with EBV/LMP-1 positivity documented in the original pathology report. The recurrent MC-cHL biopsy demonstrated weak PAX5 expression and LMP-1 positivity in HRS cells. CD3-positive lymphocytes were identified in the inflammatory background; this finding should not be interpreted as CD3 expression by HRS cells. The subsequent DLBCL demonstrated strong membranous CD20 positivity, nuclear MUM1 positivity, and a Ki-67 index of 50-60%.

The immunophenotypic differences support the distinct histopathological diagnoses established at different time points. Nevertheless, comparative immunophenotyping cannot substitute for molecular clonality studies when determining whether the two lymphomas share a common origin.

Risk factors

Immunosuppression and EBV infection have been implicated in the development of certain B-cell lymphoproliferative disorders. EBV may contribute to lymphomagenesis through effects on B-cell survival, proliferation, and immune evasion. Genetic alterations involving TP53, MYC, and BCL6 have also been associated with aggressive lymphoma biology [7,8].

Our patient had a history of EBV-associated MC-cHL, multiple previous systemic therapies, and autologous

hematopoietic cell transplantation in September 2022. However, autologous transplantation should not be equated with the prolonged pharmacological immunosuppression commonly encountered after allogeneic transplantation. Chronic immunosuppressive treatment was not documented in the available clinical information. Furthermore, EBV status was not established in the subsequent DLBCL biopsy. Therefore, neither persistent EBV-driven lymphomagenesis nor chronic post-transplant immunosuppression can be identified as a demonstrated causal mechanism in this patient.

PTLD, including DLBCL-type lymphoproliferation, is an important differential consideration in patients with a transplantation history. In the present case, the autologous transplant history and absence of documented chronic immunosuppressive therapy make the typical immunosuppression-associated PTLD scenario less compelling. Nevertheless, the available pathological and virological studies do not permit definitive exclusion of a transplant-associated lymphoproliferative process.

Clinical features of DLBCL

The most common initial symptoms included weight loss (30%), abdominal and gastrointestinal issues (26%), peripheral lymphadenopathy (22%), mainly in the head and neck region, and B symptoms (13%), including fever and night sweats. Other notable symptoms were craniofacial manifestations (10%), back pain (8%), limb pain or swelling (7%), respiratory symptoms (6%), testicular tumors (4%), chest symptoms (2%), and urologic/gynecological and skin symptoms (1% each) [13].

Diagnosis

The diagnostic approach to DLBCL requires thorough clinical and physical assessment in conjunction with laboratory investigations and imaging studies. Initial laboratory tests include a complete blood count with differential (CBC), comprehensive metabolic profile (CMP), and lactate dehydrogenase (LDH). Additional investigations are selected according to the clinical presentation. CBC may identify cytopenias or abnormal circulating cells, while elevated LDH may reflect disease activity and has prognostic relevance. The presence of B symptoms, including unexplained fever above 38°C, drenching night sweats, and unintentional weight loss greater than 10% over six months, or rapid lymph node enlargement may indicate active lymphoma requiring further investigation [14].

Excisional lymph node biopsy is generally preferred when feasible because it allows evaluation of nodal architecture, morphology, and immunophenotype. The diagnosis of DLBCL requires integration of histopathological findings with appropriate B-cell markers and additional studies when indicated [12,14]. In patients with preceding cHL, comparative evaluation of available biopsy specimens may help distinguish recurrent cHL, composite lymphoma, and subsequent DLBCL. Molecular clonality testing may be particularly informative when a biological relationship between the diagnoses is proposed.

Imaging studies for staging include FDG PET/CT and computed tomography. PET/CT is useful for identifying metabolically active disease, assessing disease extent, and selecting an appropriate biopsy site. Areas of increased FDG uptake may suggest aggressive disease, although imaging findings alone cannot establish histological transformation. PET/CT has also demonstrated utility in evaluating bone marrow involvement and treatment response [14,15].

Management

Standard first-line therapy for many patients with DLBCL has historically been based on R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), combining chemotherapy with an anti-CD20 monoclonal antibody. Treatment selection depends on disease characteristics, prior therapy, patient fitness, and the clinical setting. Relapsed or refractory disease may require alternative systemic regimens, targeted therapies, cellular therapies, or consideration of autologous stem cell transplantation in eligible patients [12,15].

Polatuzumab vedotin, an anti-CD79b antibody-drug conjugate, has demonstrated clinical activity in DLBCL. Trials including GO29365 and POLARIX have evaluated polatuzumab-containing regimens in different treatment settings, providing evidence for their efficacy and safety [16-18]. These findings support the role of polatuzumab-based treatment in DLBCL, although outcomes from these trials cannot be directly extrapolated to the specific combination or biological circumstances of the present case [16,18].

In our patient, polatuzumab vedotin was administered in combination with rituximab and ibrutinib following multiple previous lines of treatment. This combination was associated with a favorable clinical response. However, confirmatory PET/CT was pending at the time of manuscript preparation; therefore, complete metabolic remission and response durability could not be established. Although the combination provides an interesting therapeutic observation, a single case cannot establish its efficacy or safety in patients with suspected transformation of MC-cHL to DLBCL. Further studies are required to evaluate this approach [19].

Prognosis

The prognosis of DLBCL depends on multiple clinical and biological factors, including disease stage, performance status, LDH, treatment response, and specific molecular abnormalities. Aggressive B-cell lymphomas harboring certain MYC and BCL2 rearrangements may have particularly adverse outcomes [10,20]. However, prognostic estimates derived from molecularly confirmed transformation or other lymphoma subtypes should not automatically be applied to patients with sequential MC-cHL and DLBCL when their clonal relationship is unknown.

Current trends in management and future directions

This case highlights the potential clinical relevance of targeted treatment strategies and the need for further research into biomarkers associated with the development of DLBCL following cHL. Multidisciplinary management integrating hematology, oncology, pathology, and transplant medicine is important for accurate diagnosis, treatment selection, and long-term follow-up, particularly in heavily pretreated patients [15,20].

Few cases describing the occurrence of DLBCL following MC-cHL have been reported in the literature [21,22]. However, published cases vary in their presentation, diagnostic evaluation, and degree of molecular evidence supporting a shared clonal origin. Composite lymphomas, sequential lymphomas, and molecularly confirmed transformations should therefore not be considered interchangeable. The clinical response observed in our patient following polatuzumab-based treatment is noteworthy but requires radiological confirmation and longer follow-up before conclusions regarding remission durability can be drawn.

Looking forward, molecular profiling may improve diagnostic classification and risk stratification by identifying clinically relevant alterations involving MYC, BCL2, BCL6, TP53, CREBBP, and EZH2 [7,15]. Cellular therapies, including CAR-T cells, and bispecific antibodies such as glofitamab and epcoritamab have expanded therapeutic options for selected patients with relapsed or refractory DLBCL. Further studies are necessary to determine their applicability to patients with DLBCL occurring after cHL, particularly when prior transplantation and multiple lines of treatment complicate clinical management.

Table 1 summarizes previously reported cases involving cHL and DLBCL, including composite and sequential presentations, while Table 2 focuses on reports describing DLBCL following MC-cHL [5,18,19,21,22]. These comparisons highlight the limited published experience and the heterogeneity of available evidence. Importantly, not all reported cases have molecular confirmation of a shared clonal origin. Our patient’s treatment history included brentuximab, bendamustine, checkpoint inhibitors, and subsequent polatuzumab-based therapy, illustrating the complexity of therapeutic decision-making in this setting.

Reference	Age	Gender	Ethnicity	Histology (CHL+DLBCL)	Molecular/IHC	Chemotherapy and cycles	Treatment response (months)	Disease free survival
[5]	40	Female	Caucasian	NS-CHL+DLBCL	NA	QT+RT (cycles NR)	Progression/death due to lymphoma (48 months)	NA
[5]	44	Male	Caucasian	NS-CHL+DLBCL	EBV+ in both	QT	Progression/death due to lymphoma (6 months)	NA
[5]	66	Male	Caucasian/Latino	NS-CHL+DLBCL	EBV- in both	QT	NA	NA
[5]	43	Male	Caucasian/Latino	NS-CHL+DLBCL	EBV- in both	QT+AuSCT	Progression/death due to lymphoma (26 months)	NA
[21]	63	Male	Caucasian/Latino	MC-CHL+DLBCL	EBV+ in both	Surgery	Progression/death due to lymphoma (2 months)	NA
[5]	62	Female	Caucasian/Latino	NS-CHL+DLBCL	NA	RT	Complete response (27 months)	27 months disease free survival
[21]	22	Male	Caucasian/Latino	MC-CHL+DLBCL	EBV- in both	QT	Progression/death due to lymphoma (6 months)	NA
							Complete	Three months

[21]	25	Male	Caucasian/Latino	MC-CHL+DLBCL	EBV+ in both	QT	response (3 months)	disease free survival
[5]	3	Male	Caucasian/European	NS-CHL+DLBCL	NA	QT	Complete response (24 months)	24 months free survival
[21]	70	Female	Caucasian	CHL(NA)+DLBCL	EBV+ in both	NA	NA	NA
[21]	63	Male	Caucasian	CHL(NA)+DLBCL	EBV- in both	NA	NA	NA
[21]	58	Male	Caucasian	CHL(NA)+DLBCL	EBV+ in both	NA	NA	NA
[21]	29	Female	Caucasian/European	NS-CHL+DLBCL	EBV- in both; partial clonality	QT+AuSCT	Complete response (30 months)	30 months disease free survival
[21]	74	Female	Caucasian/European	MC-CHL+DLBCL	EBV- in both; clonality	QT	Complete response (12 months)	12 months disease free survival
[21]	26	Female	Asian	NS-CHL+DLBCL	NA	QT	NA	NA
[21]	56	Male	Asian	NS-CHL+DLBCL	EBV+CHL+, DLBCL-; clonality	Surgery	Progression/death due to lymphoma (1 month)	NA
[21]	75	Female	Asian	NS-CHL+DLBCL	NA	QT	Death from other causes (no documented)	NA
[21]	58	Male	Asian	NS-CHL+DLBCL	EBV- in both; clonality	Surgery+QT	Complete response	NA
[21]	37	Female	Asian	NS-CHL+DLBCL	EBV- in both	Surgery+QT	Complete response (33 months)	33 months disease free survival
[21]	6	Female	Asian	LD-CHL+BLBCL	EBV+ DLBCL+, CHL NA	QT	Progression/death due to lymphoma (4 months)	NA
[21]	53	Female	Asian	MC-CHL+DLBCL	EBV- in both; clonality	Surgery+QT	Progression/death due to lymphoma (3 months)	NA
[21]	79	Female	Asian	MC-CHL+DLBCL	EBV- in both; clonality	QT	Complete response (12 months)	12 months disease free survival
[21]	65	Female	Asian	MC-CHL+DLBCL	NA	QT	Progression/death due to lymphoma (12 months)	NA
[21]	67	Male	Asian	MC-CHL+DLBCL	EBV:CHL-, DLBCL NA	Surgery	Progression/death due to lymphoma (15 months)	NA
[5]	NA	NA	Caucasian/European	NS-CHL+DLBCL	EBV- in both	QT	Complete response	34 months disease free survival
[5]	NA	NA	Caucasian/European	NS-CHL+DLBCL	EBV- in both	QT	Complete response	34 months disease free survival
[5]	NA	NA	Caucasian/European	NS-CHL+DLBCL	EBV- in both	QT	Complete response	34 months disease free survival
[5]	64	Male	Asian	MCCHL+EBV+DLBCL	CHL:CD30+, CD15 (partial)+, LMP1+, PAX5weak+, CD20partial+, MUM1+, BOB.1+; DLBCL:CD20+, CD79a+,	Six cycles R-CHOP+two cycles Rituximab	Complete response (9 months)	9 months disease free survival

TABLE 1: Reported cases of cHL and DLBCL: composite and sequential presentations

The reported cases describe DLBCL occurring after MC-cHL. The sequential occurrence of these lymphomas does not necessarily establish a shared clonal origin or confirm histologic transformation. In the current case, EBV involvement of the subsequent DLBCL and a causal relationship with post-transplant immunodeficiency were not demonstrated.

NA, not available/not applicable; NS-cHL, nodular sclerosis classical Hodgkin lymphoma; MC-cHL, mixed-cellularity classical Hodgkin lymphoma; LD-cHL, lymphocyte-depleted classical Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; QT, chemotherapy; RT, radiotherapy; AuSCT, autologous stem cell transplantation; EBV+/EBV-, Epstein-Barr virus-positive/negative; in both, Epstein-Barr virus-positive/negative in both cHL and DLBCL; IHC, immunohistochemistry; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; DFS, disease-free survival; cHL, classical Hodgkin lymphoma.

Reference	Age	Gender	Initial treatment	Type of relapse	Proposed etiology
[21]	63	Male	ABVD	Nodal DLBCL	Shared EBV+ clonality
[21]	22	Male	ABVD	Extra-nodal DLBCL (liver)	Latent EBV in both lymphomas
[21]	25	Male	Radiotherapy	Nodal DLBCL	Suspected clonal relationship, not confirmed
[21]	74	Female	ABVD	Nodal DLBCL	EBV persistence in Reed Sternberg and large B cells
[21]	53	Female	ABVD	Extra-nodal DLBCL (stomach)	EBV positivity in both components
[21]	79	Female	ABVD+RT	Nodal DLBCL	Clonal transformation mediated by EBV
[21]	65	Female	ABVD	Nodal DLBCL	EBV associated
[21]	67	Male	ABVD	Extra-nodal DLBCL (lung)	EBV persistence
[21]	64	Male	ABVD	Nodal DLBCL	EBV dependent clonal evolution
[22]	24	Female	NA	Rapid transformation to aggressive B-cell lymphoma	Rare event, clonal evolution suspected
Current reported case	47	Female	Brentuximab+BEACOPP modified+hematopoietic transplantation	Subsequent DLBCL, CD20+, MUM1+, Ki-67 50-60%; cell of origin not established	Possible histological transformation; clonal relationship not confirmed. De novo DLBCL or a treatment-associated lymphoproliferative process cannot be excluded

TABLE 2: Reported cases of mixed-cellularity cHL followed by DLBCL

The cases presented include reported occurrences of DLBCL following mixed-cellularity cHL. Sequential occurrence does not necessarily establish clonal transformation. In the current case, EBV involvement of the subsequent DLBCL and a causal relationship with post-transplant immunodeficiency were not demonstrated.

ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; N/A, not available; cHL, classical Hodgkin lymphoma.

Limitations

Several limitations should be acknowledged. First, comparative molecular clonality studies, including immunoglobulin gene rearrangement analysis or next-generation sequencing, were not performed. Consequently, a shared clonal origin between the preceding MC-cHL and subsequent DLBCL could not be established, and a metachronous second lymphoma remains a possible alternative explanation. Second, the available DLBCL immunophenotypic evaluation did not include the complete CD10, BCL6, and MUM1 panel required for cell-of-origin assignment using the Hans algorithm. Additional studies, including EBER in situ hybridization, MYC and BCL2 immunohistochemistry, and fluorescence in situ hybridization for MYC, BCL2, and BCL6 rearrangements, were not available. Therefore, EBV involvement of the DLBCL, its molecular classification, and relevant genetic abnormalities could not be fully assessed. Third, although the patient

underwent autologous hematopoietic cell transplantation and received extensive prior therapy, a causal relationship between these exposures and the subsequent DLBCL cannot be established.

Finally, the response to polatuzumab vedotin, rituximab, and ibrutinib was assessed clinically, while confirmatory PET/CT was pending; complete metabolic remission could not be confirmed. Taken together, these limitations support interpreting transformation as a plausible clinicopathological hypothesis rather than a molecularly confirmed event.

Conclusions

This case exemplifies the rare possibility of transformation of MC-cHL into DLBCL following multiple lines of treatment and autologous hematopoietic cell transplantation, a phenomenon reported only sporadically in the literature. The subsequent tumor expressed CD20 and MUM1, with a Ki-67 proliferation index of 50–60%, findings consistent with an aggressive B-cell lymphoma. Although the sequential histopathological and immunophenotypic findings are suggestive of transformation, molecular clonality studies were not performed, and a shared clonal origin could not be definitively established. Genetic and epigenetic alterations involving TP53, MYC, BCL2, CREBBP, and EZH2, coupled with changes in immune surveillance and B-cell signaling pathways, have been proposed in the literature as potential mechanisms of lymphoma progression but were not investigated in this patient. Clinically, the development of DLBCL following MC-cHL represents a significant diagnostic and therapeutic challenge, emphasizing the importance of comprehensive pathologic and molecular evaluation.

Conventional chemoimmunotherapy regimens such as R-CHOP remain an established first-line option for DLBCL, although treatment selection in relapsed or refractory cases depends on previous therapies and individual disease characteristics. Novel targeted agents, including polatuzumab vedotin, BTK inhibitors such as ibrutinib, and immune checkpoint inhibitors, have expanded therapeutic options for selected patients with relapsed or refractory disease. In our case, the combination of polatuzumab vedotin, rituximab, and ibrutinib resulted in a favorable clinical response at the last assessment, with confirmatory PET/CT pending. Therefore, complete metabolic remission and long-term response durability could not be established. This case underscores the importance of molecular profiling to clarify the relationship between sequential lymphomas, stratify risk, and guide precision-based treatment strategies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

Given the multidisciplinary approach required for this rare case, several institutions were involved in the patient's care. The initial diagnosis and workup were performed at Medica Sur. ChatGPT (OpenAI, San Francisco, CA, USA) was used to improve the clarity of the abstract and conclusion sections and to organize the references. The authors retain full responsibility for the content of the manuscript and confirm their ownership of the work.

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