CASE REPORT

Stepwise development of classical Hodgkin lymphoma from diffuse large B-cell lymphoma

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Abstract: Classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma rarely develop in the same patient synchronously or metachronously. Through a series of biopsies, we report a unique case of diffuse large B-cell lymphoma (DLBCL) with stepwise development of classical Hodgkin lymphoma. An intermediate stage of transformation was identified with scattered Reed-Sternberg/Hodgkin cells present in a background of DLBCL cells. These Reed-Sternberg/Hodgkin cells showed typical immunophenotype of cHL cells and were associated with limited inflammatory cells. While Reed-Sternberg/Hodgkin-like cells are not uncommonly seen in a variety of non-Hodgkin lymphomas, the subsequent development of cHL in this patient indicated that the scattered Reed-Sternberg/Hodgkin cells among DLBCL cells truly represented a precursor of cHL, which would be extremely challenging, if not impossible, for pathologists to diagnose. We also highlight the importance of clinicopathological correlation and the crucial role of additional biopsies.

Keywords: diffuse large B-cell lymphoma; classical Hodgkin lymphoma; Reed-Sternberg


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Introduction

Classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL) are both B-cell-derived malignant neoplasms but have different clinical presentations, morphologic features, and optimal chemotherapy regimens. cHL is characterized by the presence of small numbers of Reed-Sternberg/Hodgkin cells admixed in a background of reactive inflammatory cells. The Reed-Sternberg/Hodgkin cells are typically positive for CD30 and CD15, and show defective B-cell differentiation with the loss of B-cell markers such as CD20, CD79a, and OCT2, as well as leukocyte common antigen CD45. The only B-cell antigen that is consistently but characteristically weakly expressed by Reed-Sternberg/Hodgkin cells is PAX5. Meanwhile, DLBCL is a heterogeneous group of malignant B-cell lymphoma that is histologically characterized by sheets of large atypical lymphoid cells with features of centroblasts, immunoblasts, or anaplastic cells. DLBCL cells are positive for most B-cell markers and CD45. Mixed inflammatory cells such as neutrophils and eosinophils are only occasionally seen in DLBCL. CD30 expression has been reported in approximately 14%–25% of DLBCL cases,[1-3] while CD15 is rarely expressed in DLBCL.

Reed-Sternberg/Hodgkin-like cells can be seen in a variety of non-Hodgkin lymphomas, but the diagnosis of cHL requires the presence of expansile lesion with a characteristic mixed inflammatory background associated with Reed-Sternberg/Hodgkin cells. cHL and DLBCL have been reported to rarely occur in the same patient synchronously or metachronously, and may or may not be clonally related.[4-12] In this case report, we describe a unique case of DLBCL with stepwise transfor-
mation into cHL, and for the first time, an intermediate stage of a precursor lesion of cHL was identified in a background of DLBCL cells.

Case report

Clinical presentation

The patient was a 66-year-old male with a history of stage IV DLBCL with diffuse cutaneous, subcutaneous, soft tissue pulmonary, and skeletal involvement status, and had undergone 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone) chemotherapy. He had a persistent disease and received 7 cycles of brentuximab salvage therapy, followed by an autologous bone marrow transplant. Approximately six months later, he was found to have relapsed disease on the left forearm, with his biopsy revealing DLBCL of the anaplastic variant. A positron emission tomography (PET) scan showed metabolically active left supraclavicular and left axillary lymph nodes, as well as numerous sites of tracer activity in the left upper extremity, which are all compatible with lymphoma involvement. He was otherwise clinically stable without fevers, chills, night sweats, headaches, nausea, chest pain, shortness of breath, change in bowel movement, melena, or episodes of spontaneous bleeding. A biopsy of the left axillary lymph node revealed cHL nodular sclerosis subtype.

Pathologic findings

The first specimens were skin biopsies from the left arm and upper back at initial presentation. Results showed diffuse atypical lymphoid infiltrate in the upper and lower dermis associated with extensive coagulation necrosis (Figure 1A). The epidermis was spared. Atypical lymphoid cells were large with round-to-irregular nuclei, mature chromatin, and small nucleoli, and were associated with mitotic figures (Figure 1B). Apoptotic bodies were abundant. The large atypical lymphoid cells were positive for CD20 (strong) (Figure 1C), CD79a (subset), PAX-5, MUM1, CD30 (Figure 1D), Bcl-2, and fascin; and negative for CD5, CD10, Bcl-6, OCT2, CD15, CD45,

![Figure 1](image.png)

**Figure 1.** The first skin biopsy. The skin showed sheets of large lymphoid cells: (A) hematoxylin and eosin (25X) and (B) hematoxylin and eosin (600X). The large lymphoma cells were positive for: (C) CD20 (200X) and (D) CD30 (200X).
ALK1, and CD138. Moreover, Epstein-Barr virus-encoded small RNAs (EBER) was negative. Meanwhile, fluorescence in situ hybridization (FISH) studies identified gains of BCL-2, IgH, and BCL-6 (without rearrangement), along with the gain of TCL-1, clonal rearrangement of IgH, and no c-MYC gene rearrangement. These findings were consistent with diffuse large B-cell lymphoma, non-germinal center (GCB) subtype.

The second specimens were skin biopsies of the left proximal and distal arm six months after the autologous bone marrow transplant. The skin biopsies showed extensive dermal infiltrate by diffuse large atypical lymphoid cells associated with marked necrosis (Figure 2A). The large atypical lymphoid cells showed similar cytology with that of the previous biopsy, but scattered large pleomorphic cells with morphologic features of Reed-Sternberg/Hodgkin cells were identified and present in the sheets of large atypical lymphoid cells

**Figure 2.** The second skin biopsy. (A) The skin showed sheets of large lymphoid cells (hematoxylin and eosin, 25X). (B) Reed-Sternberg/Hodgkin-like cells were present among the large lymphoid cells (hematoxylin and eosin, 200X). The Reed-Sternberg/Hodgkin cells were positive for (C) CD20 (200X), (D) CD79a (200X), (E) CD30 (200X), and (F) CD15 (200X). The diffuse large B-cell lymphoma cells were positive for (C) CD20 (200X), (D) CD79a (200X), (E) CD30 (200X), and partially for (F) CD15 (200X).
There were a small number of neutrophils present but the Reed-Sternberg/Hodgkin-like cells did not seem to elicit a mixed inflammatory reaction and form a discrete mass lesion within the large lymphoid cells. The diffuse large atypical lymphoid cells were positive for CD20 (Figure 2C), CD30 (Figure 2E), Bcl-2, CD79a (Figure 2D), PAX5, MUM1, fascin, and CD15 (subset) (Figure 2F). The Reed-Sternberg/Hodgkin-like cells were positive for CD20 (Figure 2C), CD79a (Figure 2D), CD30 (Figure 2E), PAX5 (weak), MUM1, fascin, and CD15 (Figure 2F). FISH studies were negative for IgH/BCL-2, BCL-6, and c-MYC gene rearrangements. These findings were consistent with DLBCL of the anaplastic variant. While the Reed-Sternberg/Hodgkin-like cells showed some features of cHL, including the expression of both CD30 and CD15, the lack of expansile mass lesion associated with Reed-Sternberg/Hodgkin-like cells, the general lack of mixed inflammatory background, and the expression of other B-cell markers (CD79a in particular) made the diagnosis of cHL very challenging during this time.

The last specimen was an excisional biopsy of the left axillary lymph node three months later. The lymph node architecture was effaced by a nodular lymphoid infiltrate separated by bands of sclerosing fibrosis (Figure 3A). Within the nodules, there were many scattered clusters of

Figure 3. (A) The lymph node biopsy showed nodular lymphoid infiltrate (hematoxylin and eosin, 25X). (B) Reed-Sternberg/Hodgkin cells were present with mixed inflammatory cells (hematoxylin and eosin, 200X). The Reed-Sternberg/Hodgkin cells were negative for (C) CD20 (200X), and positive for (D) CD30 (200X) and partially for (E) CD15 (200X).
Reed-Sternberg/Hodgkin cells with prominent cherry-red nucleoli in a background of small mature lymphocytes and granulocytes, which are associated with areas of necrosis (Figure 3B). The Reed-Sternberg/Hodgkin cells were positive for PAX-5 (weak), CD30 (Figure 3D), CD15 (small subset) (Figure 3E), fascin, CD21, MUM1, and BCL-6; and negative for CD20 (Figure 3C), ALK-1, OCT-2, BOB.1, EMA, and CD3. The findings were diagnostic of cHL (nodular sclerosis subtype), and there was no evidence of DLBCL. Polymerase chain reaction (PCR) studies attempted on both the second and third specimens failed to reveal clonal IgH and IgK gene rearrangements. As a result, the clonal relationship between DLBCL and cHL could not be determined.

Discussion

The development of cHL and DLBCL in the same patient is rare. Based on limited studies on the clonal relationship between the two entities, cHL and DLBCL are derived from the same clone when they occur synchronously at the same anatomic site as composite lymphoma [2,6,10,13], and are clonally unrelated when developing metachronously [9,11,12]. DLBCL and cHL in this case report developed metachronously at the same sites, notably on the skin. While a clonal relationship between DLBCL and cHL cannot be established owing to the failed PCR study of B-cell receptor gene rearrangements, the identification of a hybrid intermediate stage suggested that they were clonally related.

The distinction between DLBCL and cHL is clinically important as they respond differently to chemotherapeutic regimens. Diagnosis relies on careful morphologic and phenotypic evaluation of lymphoma cells. The distinction of cHL from DLBCL is based on the expression of CD30, CD15, and weak PAX5. cHL cells may occasionally express CD20, but the expression level is usually weak and variable. cHL is characteristically negative for CD45 and other pan B-cell markers: CD79a, OCT2, and BOB.1. Fascin is typically positive in cHL cells but it is also expressed in approximately 15% of DLBCL cases [14]. Large lymphoma cells with hybrid morphologic and phenotypic features are characteristically seen in mediastinal gray-zone lymphoma, which is a clinically and pathologically distinct entity. Our case showed prominent skin involvement and no mediastinal mass, and therefore mediastinal gray-zone lymphoma was not in the differential diagnosis.

To the best of our knowledge, this is the first report of an intermediate stage of transformation from DLBCL into cHL. Large atypical lymphoid cells morphologically indistinguishable from Reed-Sternberg/Hodgkin cells in cHL – the so-called Reed-Sternberg/Hodgkin-like cells, are commonly seen in high-grade B-cell lymphoma such as DLBCL (especially the anaplastic variant), EBV-positive DLBCL, and mediastinal gray-zone lymphoma. These Reed-Sternberg/Hodgkin-like cells in DLBCL are often positive for CD30, but are usually negative for CD15. They otherwise show the same phenotype as other DLBCL cells, with the expression of pan B-cell markers CD20, CD79a, PAX5, OCT2, and BOB.1. They are not associated with significant mixed inflammatory cells (neutrophils or eosinophils) and do not progress to cHL.

Our case was unique in which a stepwise transformation from DLBCL into cHL was demonstrated through a series of biopsies. The first biopsy of our patient showed the involvement of skin by a typical DLBCL (non-GCB subtype) based on the expression of MUM1, and negative CD10, and BCL6. There were no Reed-Sternberg/Hodgkin-like cells in this initial biopsy. The DLBCL cells were positive for CD30 but negative for CD15. They also showed aberrant loss of CD45 and a B-cell marker OCT2.

In the second biopsy where the hybrid intermediate stage was demonstrated, there were sheets of DLBCL cells in the skin but scattered Reed-Sternberg/Hodgkin-like cells were admixed with the DLBCL cells. Not only did the Reed-Sternberg/Hodgkin-like cells show typical immunophenotype of cHL cells with the expression of CD30, CD15, and weak PAX5, the DLBCL cells also gained partial expression of CD15. Although there were a small number of neutrophils, the Reed-Sternberg/Hodgkin-like cells did not form a discrete lesion, and showed strong and uniform expression of pan B-cell markers CD20 and CD79a. Therefore, it was not possible to morphologically diagnose cHL at this stage; the overall findings were consistent with DLBCL (anaplastic variant).

While the Reed-Sternberg/Hodgkin-like cells in the second biopsy still retained B-cell program as evidenced by the expression of strong CD20 and CD79a, the Reed-Sternberg/Hodgkin cells in the final biopsy showed a typical loss of B-cell marker CD20. Therefore, after the diagnosis of cHL was established in the final lymph node biopsy, the Reed-Sternberg/Hodgkin-like cells in the intermediate stage were decided to represent a precursor lesion of cHL. Laser capture microdissection of individual Reed-Sternberg/Hodgkin-like cells in this precursor lesion, along with the later cHL cells, and subsequent molecular studies such as next generation sequencing may provide valuable information regarding genetic changes that are important for the progression to cHL. This case also highlighted the importance of repeated biopsies in diagnostically-challenging cases. Presur-
sor or early lesions that could not be initially established diagnostically would eventually manifest themselves in later biopsies.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**Reference**


