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Rituximab plus Ifosfamide, Carboplatin and Etoposide for T-Cell/Histiocyte-Rich B-Cell Lymphoma Arising in Nodular Lymphocyte-Predominant Hodgkin's Lymphoma

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Key Words

Transformation · Nodular lymphocyte-predominant Hodgkin's lymphoma · T-cell/histiocyte-rich B-cell lymphoma · Chemotherapy

Abstract

A small subset of patients with nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHLs) develop a non-Hodgkin lymphoma either concurrently or subsequently, usually T-cell/histiocyte-rich B-cell lymphomas (T/HRBCL), which are subtypes of diffuse large B-cell lymphomas (DLBCL). The standard treatment of DLBCL patients is rituximab-based chemotherapy with cyclophosphamide, adriamycin, vincristine and prednisolone. However, the administration of this chemotherapy regimen to patients with DLBCL arising in NLPHL brings concern about the cardiac toxicity of anthracycline because the majority of these patients had already received anthracycline-based chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine at the time of NLPHL. Herein, we report 2 patients with sequential transformation of NLPHL to T/HRBCL. They initially presented with limited-stage NLPHL and subsequently developed T/HRBCL after 16 and 8 months, respectively. At the time of T/HRBCL, they were treated with rituximab, ifosfamide, carboplatin and etoposide, and complete responses were obtained.

Introduction

Nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) is a rare, distinctive disease characterized by the neoplastic proliferation of abnormal large B cells, so-called lymphocytic and histiocytic cells, in a germinal center-like microenvironment [1, 2]. The disease generally has an indolent clinical course marked by frequent relapses, but with a long overall survival [3].

Despite this favorable outcome, there is an inherent tendency of NLPHL patients to develop secondary non-Hodgkin lymphoma (NHL), usually T-cell/histiocyte-rich B-cell lymphoma (T/HRBCL), either concurrently or subsequently, which is associated with a worsening of the prognosis [4]. The incidence has been reported to range from 3 to 10% [5, 6]. Previous studies have reported that patients with transformed lymphoma were more likely to have advanced-stage disease and splenic involvement at the time of NLPHL diagnosis [7]. However, it is unclear which clinical characteristics are significantly associated with histological transformation. In general, the standard regimen for patients with diffuse large B-cell lymphoma (DLBCL) is rituximab-based chemotherapy with cyclophosphamide, adriamycin, vincristine and prednisolone (R-CHOP). However, the administration of R-CHOP chemotherapy to patients with DLBCL arising in NLPHL brings concerns about the cardiac toxicity of anthracycline due to the cumulative dose of doxorubicin the patients have already received with the chemotherapy regimen doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) at the time of NLPHL. Therefore, it is necessary to establish an effective chemotherapy regimen in patients with T/HRBCL arising in NLPHL.

We describe 2 patients with transformation of limited-stage NLPHL to T/HRBCL, in whom a complete response (CR) after rituximab-based chemotherapy with ifosfamide, carboplatin and etoposide (R-ICE) had been achieved.

Case Reports

Case 1

The patient, a 48-year-old man, was admitted in September 2010 with right inguinal lymph node enlargement. A computed tomography (CT) scan revealed an enlarged right common iliac, external iliac and inguinal lymph node. A biopsy of the inguinal lymphadenopathy was performed, and a histological diagnosis of NLPHL with areas consistent with a diffuse B cell-rich pattern was obtained (fig. 1). A complete staging including blood count and other analyses such as β_2 -microglobulin and lactate dehydrogenase level, neck, thorax and abdominal CT and positron emission tomography, together with bone marrow aspirate and biopsy, revealed no evidence of advanced-stage disease, and the patient was staged as IIA according to the Ann Arbor staging. The patient was treated with six courses of chemotherapy (ABVD), and CR was achieved. Seven months after the end of the treatment, a relapse was observed in the right inguinal lymph node and an excisional biopsy was done. Histology showed a diffuse pattern with a polymorphous background rich in lymphocytes and histiocytes with intermingled isolated blast cells; accordingly, a histopathological diagnosis of T/HRBCL was made (fig. 2). A bone marrow biopsy was negative for secondary involvement. The patient was treated with two courses of chemotherapy (R-CHOP), and he achieved partial response (PR). Because the patient had been treated for angina pectoris and had a cumulative dose of 400 mg/m² doxorubicin, we changed the regimen to R-ICE. CR was obtained after three courses of R-ICE chemotherapy.

Case 2

A 35-year-old man was admitted in October 2010 with left cervical lymph node enlargement. A CT scan revealed lymphomatous involvement in the left lateral neck and right upper jugular chain. A biopsy of the cervical lymphadenopathy was performed, and a histopathological diagnosis of NLPHL

was made (fig. 3). Staging workup revealed no evidence of advanced-stage disease, and the patient was staged as IA according to the Ann Arbor staging. The patient was treated with six courses of ABVD chemotherapy, which resulted only in PR. Neck CT and positron emission tomography scans for restaging workup still showed lymphomatous involvement in the left lateral neck. Therefore, we performed an excisional biopsy in the left cervical lymph node. Histologically, the lymph node revealed a diffuse pattern of tumor infiltration with small-sized lymphoid cells and few interspersed large atypical cells (fig. 4). A histopathological diagnosis of T/HRBCL was made. A bone marrow biopsy revealed no evidence of secondary involvement. Because of concerns about doxorubicin-induced cardiotoxicity, the patient was treated with six courses of R-ICE chemotherapy after two courses of R-CHOP chemotherapy, and CR was obtained after two courses of R-ICE.

Discussion

NLPHL is characterized by a nodular architecture with a proliferation of large neoplastic B cells (lymphocytic and histiocytic cells) exhibiting CD45, CD20 and CD79a immunoreactivity [8, 9]. Usually, immunoreactivity is positive for epithelial membrane antigen but negative for CD15 and CD30 [8–10]. Within the nodules, the background population is composed of follicular dendritic cells, numerous small B cells and follicular CD57+ T lymphocytes, which form rosettes around the lymphocytic and histiocytic cells [8–10].

In contrast, in T/HRBCL, there is a complete effacement of the architecture with a predominant diffuse pattern. Neoplastic B cells account for less than 10% of the diffuse infiltrate [11] and exhibit a morphologic and immunophenotypical appearance of lymphocytic and histiocytic cells, which sometimes mimic centroblastic cells, immunoblastic cells or Reed Sternberg-like cells [9, 10]. The cellular background is composed of small CD57– T lymphocytes accompanied by abundant histiocytes.

More and more reports have shown that NLPHL will eventually transform into DLBCL, even 15–20 years after the initial diagnosis [4, 12]. T/HRBCL is one of the most common subtypes of large B-cell transformation from NLPHL [4, 13]. Our patients both showed subsequent transformation of NLPHL to T/HRBCL. These cases support a close biological relationship between the distinct clinicopathological entities of NLPHL and T/HRBCL. However, it is unknown whether secondary T/HRBCL represents a clonal progression of NLPHL or whether a common germinal center precursor exists. In one study, the transcription factor PU.1 was found to be expressed in all patients with NLPHL but was reduced or absent in T/HRBCL patients [14]. However, genomic imbalances are more frequent in NLPHL than T/HRBCL, which argues against a direct evolution.

Al-Mansour et al. [7] evaluated the frequency of transformation in 95 patients diagnosed with NLPHL between 1965 and 2006 at the British Columbia Cancer Agency. With a median follow-up time for living patients of 6.5 years (range 2.5–33), 13 patients (14%) experienced a transformation to aggressive lymphoma (median time to transformation 8.1 years; range 0.35–20.3). The actuarial risk of transformation to aggressive lymphoma was 7 and 30% at 10 and 20 years, respectively. Transformation was more likely in patients with advanced-stage disease ($p = 0.057$) and initial splenic involvement ($p = 0.006$) at the time of NLPHL diagnosis. The 10-year progression-free and overall survival rates in patients with transformed lymphoma were 52 and 62%, respectively. In our cases, although both patients initially presented with limited-stage

NLPHL and no splenic involvement, transformation to T/HRBCL occurred after 16 and 8 months, respectively.

It is unclear what the appropriate therapy is at the time of transformation. In Hodgkin's lymphoma patients treated with an ABVD regimen, there are concerns about the problem of cardiotoxicity. In one study, echocardiographic evaluation revealed that the treatment of Hodgkin's lymphoma with the standard ABVD regimens was accompanied with mild early and chronic asymptomatic changes of the left ventricular function [15]. In our cases, the patients received a cumulative dose of 300 mg/m² doxorubicin for the treatment of NLPHL and received an additional dose of 100 mg/m² doxorubicin with two courses of R-CHOP chemotherapy at the time of transformation. Although the patients showed PR after two courses of R-CHOP chemotherapy, we changed the regimen from R-CHOP to R-ICE chemotherapy because of concerns about the cardiotoxicity of doxorubicin. In both patients, CR was achieved after two or three courses of R-ICE chemotherapy.

Patients with NLPHL have a substantial risk of future transformation to an aggressive lymphoma, such as T/HRBCL, which can occur at any time after the primary diagnosis of NLPHL with no apparent plateau in risk, but this possibility is underappreciated. Therefore, repeated biopsies of any clinically suspicious lymphadenopathy through surveillance are essential, and we consider R-ICE salvage chemotherapy to be an appropriate regimen at the time of transformation.

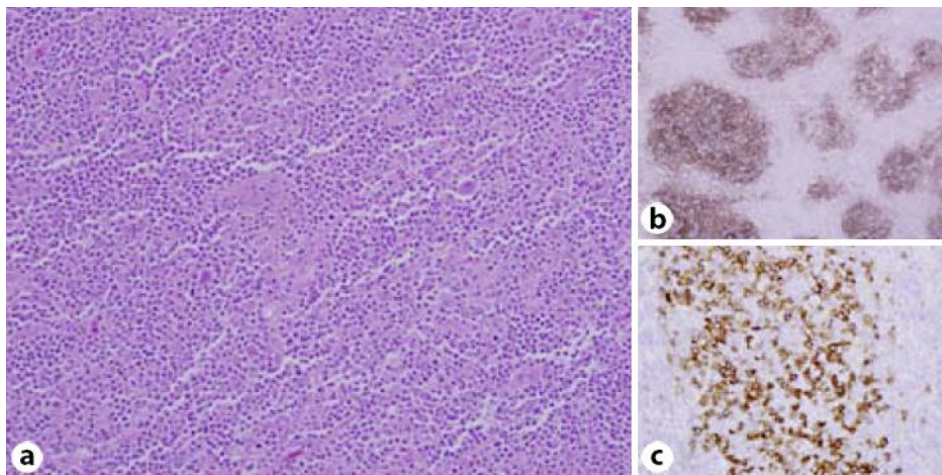


Fig. 1. Case 1: NLPHL. HE staining showed vague nodules with large atypical lymphocytic and histiocytic cells in a background of reactive small lymphocytes (a). Immunohistochemical staining showed networks of follicular CD21+ dendritic cells in the reactive cells (b) and rosettes of CD57+ T lymphocytes (c).

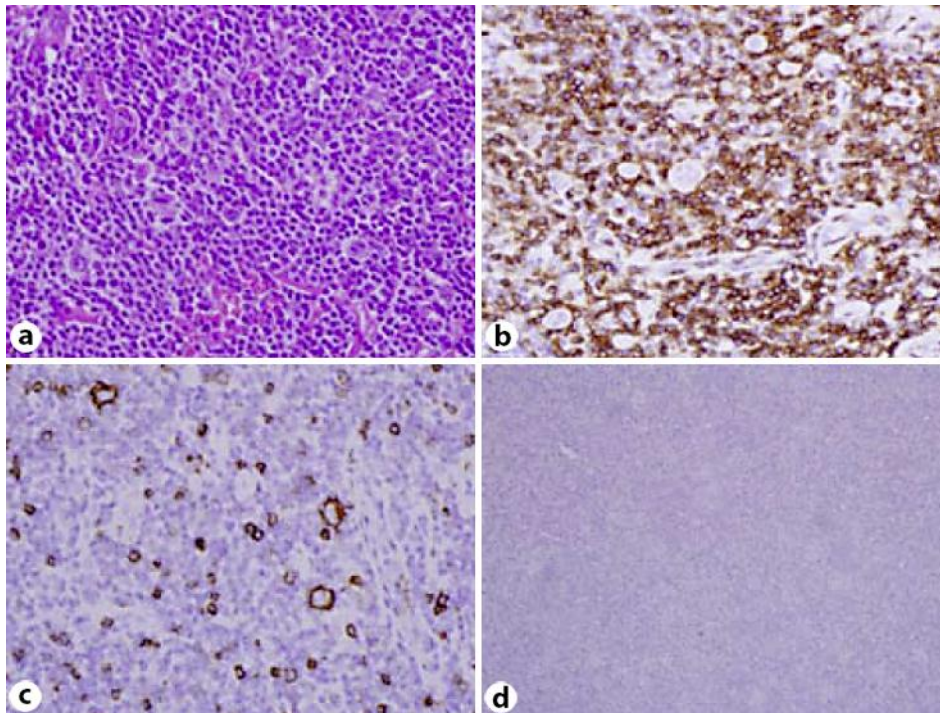


Fig. 2. Case 1: T/HRBCL. HE staining showed a diffuse pattern with a polymorphous background rich in lymphocytes and histiocytes with intermingled isolated blast cells (**a**). Immunohistochemical analysis showed that blastic cells were CD3 negative (**b**) and CD20 positive (**c**), which was consistent with a B-lymphocyte phenotype. Most of the small non-neoplastic lymphocytes were CD3 positive and CD20 negative, consistent with T lymphocytes. Networks of follicular CD21 dendritic cells were absent (**d**).

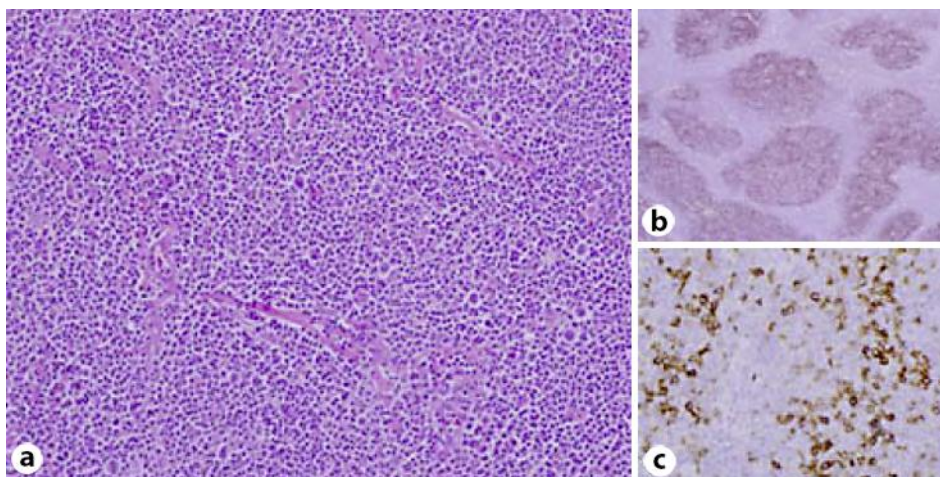


Fig. 3. Case 2: NLPHL. HE staining showed vague nodules with large atypical lymphocytic and histiocytic cells on a background of reactive small lymphocytes (**a**). Immunohistochemical staining showed networks of follicular CD21+ dendritic cells in the reactive cells (**b**) and rosettes of CD57+ T lymphocytes (**c**).

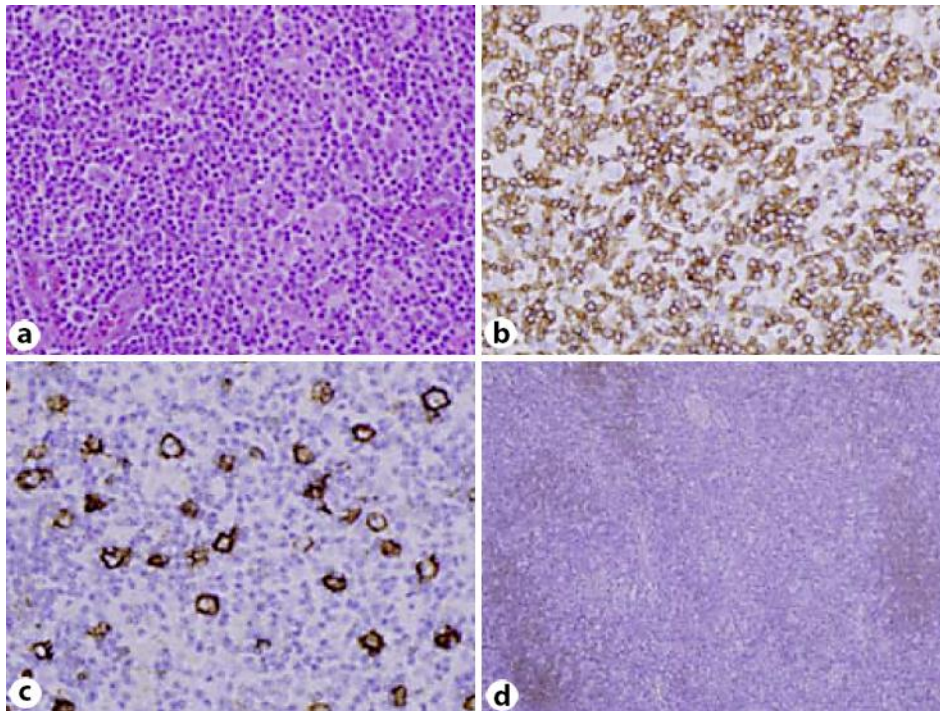


Fig. 4. Case 2: T/HRBCL. HE staining showed a diffuse pattern with a polymorphous background rich in lymphocytes and histiocytes with intermingled isolated blast cells (a). The immunohistochemical analysis showed that blastic cells were CD3 negative (b) and CD20 positive (c), which was consistent with a B-lymphocyte phenotype. Most of the small non-neoplastic lymphocytes were CD3 positive and CD 20 negative, consistent with T lymphocytes. Networks of CD21 follicular dendritic cells were weak (d).

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