

Case Study

Classical Hodgkin Lymphoma Occurring in Association with Progressive Transformation of Germinal Center

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Progressive transformation of germinal center (PTGC) represents an asymptomatic persistent form of lymphadenopathy. We present a case of classical Hodgkin lymphoma occurring in association with PTGC. The patient was a 60-year-old woman who had noted swelling of the submandibular lymph nodes. Histopathologically, the enlarged lymph nodes appeared as multiple nodules with ill-defined and irregularly expanded germinal centers. Immunohistochemical studies indicated that the germinal center cells comprised B cells that were positive for CD10 and CD20, and negative for bcl-2. Enlarged vascular endothelial cells were present in the interfollicular areas. CD30-positive Hodgkin & Reed-Sternberg cells were seen between the interfollicular area and the mantle zone, and were surrounded by CD3-positive T-cells. *In situ* hybridization studies demonstrated no expression of Epstein-Barr virus-encoded small RNA in the Hodgkin & Reed-Sternberg cells. A diagnosis of classical Hodgkin lymphoma complicated by PTGC was made from the lymph node specimen. [*J Clin Exp Hematop* 54(3) : 205-209, 2014]

Keywords: progressive transformation of germinal center, classical Hodgkin lymphoma, follicular lysis

INTRODUCTION

Progressive transformation of germinal center (PTGC) was first described by Müller-Hermelink, and further studies were later reported by Müller-Hermelink and Lennert.¹ PTGC is a morphological feature of reactive lymphoid hyperplasia.^{1,2} It is characterized histologically by expansion of mantle zone lymphocytes into both the adjacent sinusoids and germinal centers.²⁻⁴ The mantle zone is obscured, and the interfollicular areas usually contain small lymphocytes and a few immunoblasts. PTGC is usually found in the lymph nodes of patients with reactive follicular hyperplasia. Overall, 2-10% of reactive lymph nodes with chronic nonspecific lymphadenitis contain one or more areas of PTGC.³ The mantle zone lymphocytes destroying the germinal centers are predominantly B cells, with a minor population of T cells.⁵ PTGC is thought to result from variation in the morphogenesis of follicles over time, as follicles become hyperplastic in

response to antigenic stimuli.^{1,4}

Morphologically, it can be confused with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) because of its nodular pattern and the presence of large cells that may be incorrectly identified as lymphocytic and histiocytic cells.³⁻⁵ PTGC has also been described in association with classical Hodgkin lymphoma (CHL). It has been reported that 22-35% of cases of PTGC are associated with Hodgkin lymphoma, mostly NLPHL.^{2,6-8} However, PTGC rarely occurs in association with CHL.

Another problem is the differential diagnosis between PTGC and the floral variant of follicular lymphoma (FVFL)⁹⁻¹¹ and marginal zone B-cell lymphoma (NMZL).¹²

Here, we report a case of CHL associated with PTGC, with reference to the differential diagnosis.

CASE REPORT

The present case involved a 60-year-old female patient, who had undergone surgery for thyroid cancer at the age of 48 years. She had noted swelling of the submandibular lymph nodes at the age of 59 years, although no relapse of the thyroid cancer had occurred for 11 years. She visited a clinic because of lymphadenopathy, and an enlarged submandibular lymph node was biopsied for further evaluation. Thoracic computed tomography indicated enlarged deep cervical and right axillary lymph nodes. The patient had no symptoms such as fever or weight loss. The biopsied lymph node was diagnosed as Hodgkin lymphoma occurring in PTGC. The

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patient received three cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy. Nine months later, a positron emission tomography scan revealed relapse in an enlarged right axillary lymph node. After a further three cycles of ABVD chemotherapy, complete remission was obtained and the patient remained in a good general condition.

The biopsied lymph node was fixed in formalin and embedded in paraffin. In addition to H&E staining, immunohistochemical study was performed on paraffin-embedded sections using a Dako automated stainer in accordance with the manufacturer's directions. Antibodies against the following antigens were used: CD3 (clone PS-1, Nichirei, Tokyo, Japan), CD4 (clone 4B12, Leica Microsystems GmbH, Wetzlar, Germany), CD10 (clone 56C6, Leica Microsystems GmbH), CD15 (clone C3D-1, Dako, Glostrup, Denmark), CD20 (clone L26, Dako), CD21 (clone 2G9, Leica Microsystems GmbH), CD30 (clone Ber-H2, Dako), CD79a (JCB117, Dako), bcl-2 (clone 124, Dako), bcl-6 (clone PG-B6p, Dako), BSAP (clone sc-1974, Santa Cruz Biotechnology, Santa Cruz, CA, USA), BOB-1 (clone 14, Novocastra, Newcastle-upon-Tyne, United Kingdom), Oct-2 (clone Oct-207, Novocastra), EMA (clone E29, Dako), LMP-1 (clone CS. 1-4, Dako), kappa (clone L1C1, Nichirei), lambda

(clone HP6054, Nichirei), and Ki-67 (clone MIB-1, Dako). *In situ* hybridization with Epstein-Barr virus (EBV)-encoded small RNA oligonucleotides was performed to test for the presence of EBV small RNA in the formalin-fixed paraffin-embedded sections, in accordance with the manufacturer's instructions (Dako).

Under low magnification, the lymph node showed numerous areas of PTGC, characterized by enlarged follicles without clear demarcation of germinal centers and mantle zones, which contained a predominance of small lymphocytes and scattered residual follicle center cells (Fig. 1a). A proportion of the germinal centers showed follicular lysis and distortion due to clusters of dark blue mantle cells (Fig. 1a). High-power views disclosed marked proliferation of venules in which the endothelial cells had enlarged nuclei, and thickening of the basement membrane in the interfollicular area (Fig. 1b). Hodgkin and Reed-Sternberg (HRS) cells were scattered in the mantle zone and interfollicular area (Fig. 1c, 1d). Immunohistochemically, CD21 staining revealed disruption of the meshwork of follicular dendritic cells by infiltrating small lymphocytes (Fig. 2a). Irregular aggregates of small lymphocytes disrupted the germinal centers. The majority of small germinal lymphocytes were positive for CD10, CD20

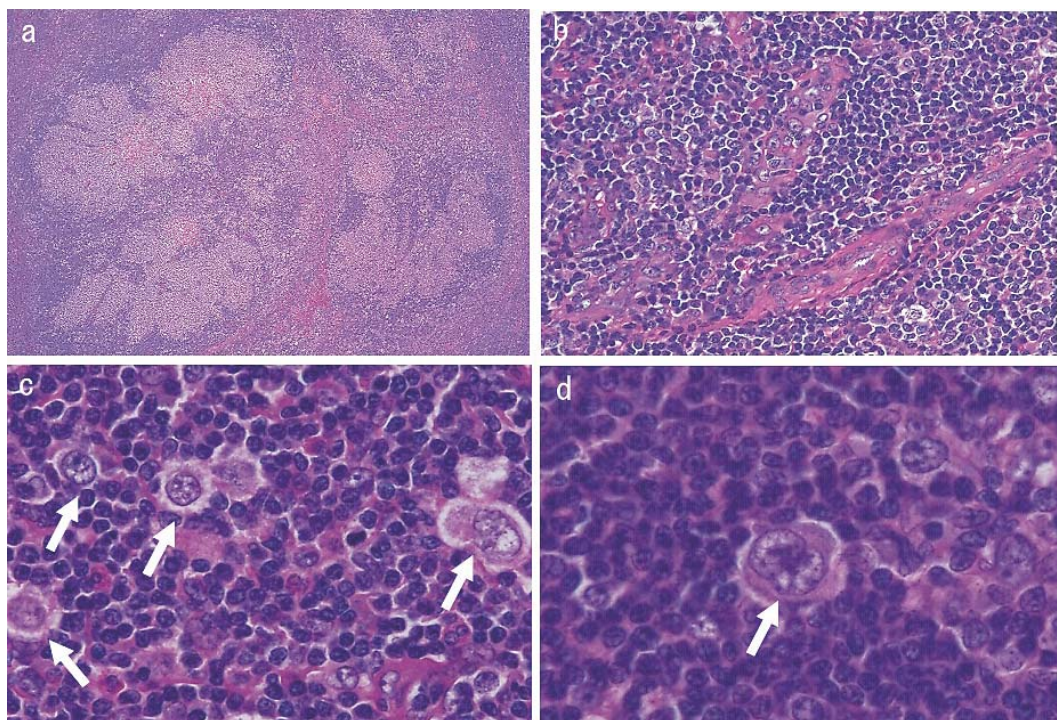


Fig. 1. Histological features of the submandibular lymph node. (1a) Low-power view shows some large progressive transformation of germinal center nodules with an irregular germinal center showing an ill-defined border. (1b) High-power view shows marked proliferation of venules with enlarged nuclei and thickening of the basement membrane in the interfollicular area. (1c) & (1d) HRS cells (arrows) were scattered in the mantle zone and interfollicular area.

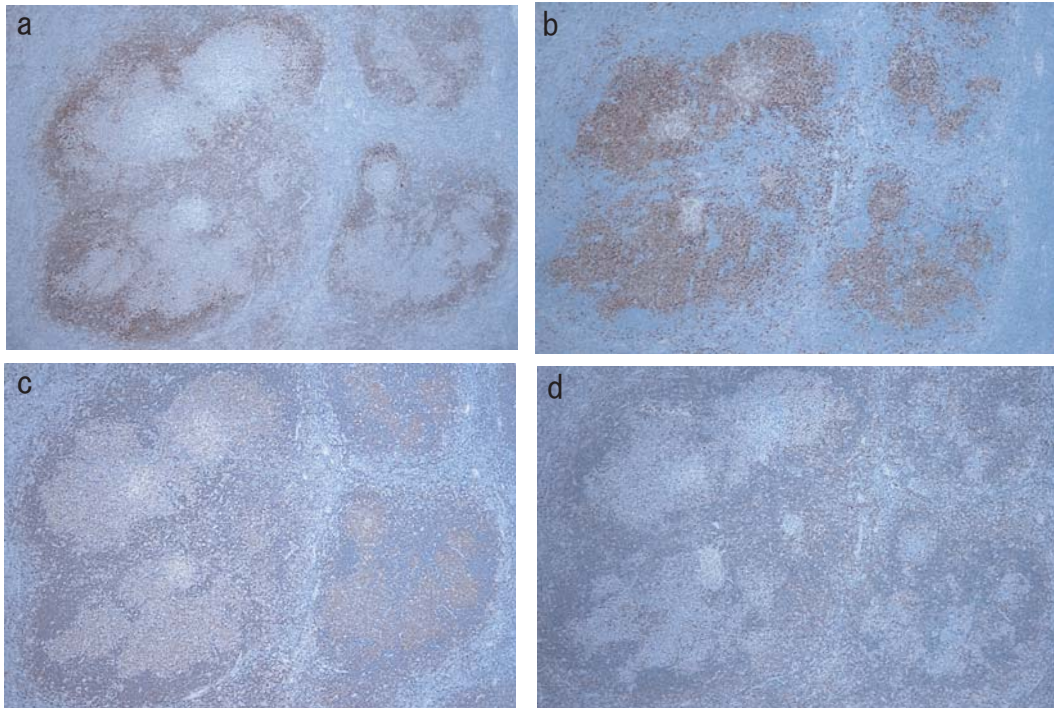


Fig. 2. Immunohistochemistry of CD21 (2a), CD10 (2b), CD20 (2c), and bcl-2 (2d). Immunostaining of CD21 reveals areas of disrupted follicular dendritic cell networks. Irregular aggregates of small lymphocytes disrupt the germinal center. The majority of small germinal lymphocytes are positive for CD10 and CD20, and negative for bcl-2. Small mantle zone lymphocytes are positive for CD20 and bcl-2, and negative for CD10.

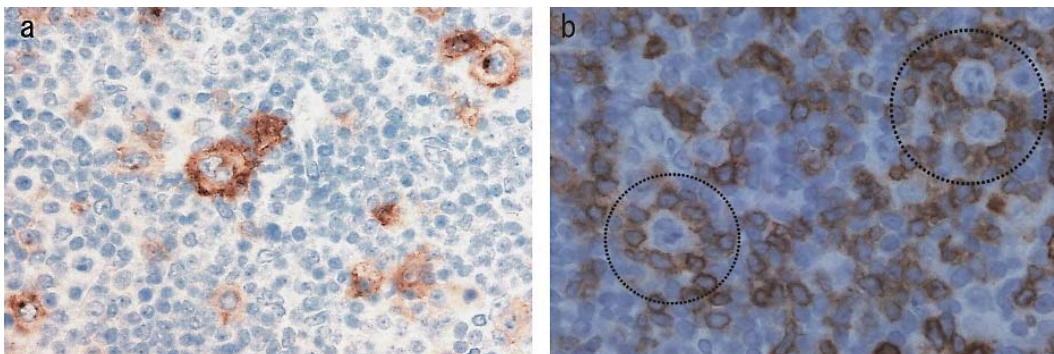


Fig. 3. Immunohistochemistry for CD30 (3a) and CD5 (3b). HRS cells are positive for CD30. T-cell rosettes can be identified around the HRS cells (dotted circles).

and CD79a, and negative for bcl-2 (Fig. 2b-2d). CD10 immunostaining demonstrated a floral pattern of macrofollicular germinal centers (Fig. 2b). Small mantle zone lymphocytes were positive for CD20 and bcl-2, and negative for CD10.

HRS cells among the mantle zone and interfollicular area were positive for CD30 (Fig. 3a) and focally positive for CD20. Some CD3-positive T-cell rosettes were identified around the HRS cells (Fig. 3b). HRS cells were negative for CD15, EMA, BSAP, bcl-6, BOB-1, and Oct-2 (Fig. 4a, 4b).

No clusters of epithelioid histiocytes were observed in this case, and no EBV was detected by *in situ* hybridization.

DISCUSSION

PTGC is a morphological feature of reactive hyperplasia and occurs in approximately 4% of patients with chronic nonspecific lymphadenitis.⁶ In the present case of PTGC, HRS cells were observed in the mantle zone and interfollicu-

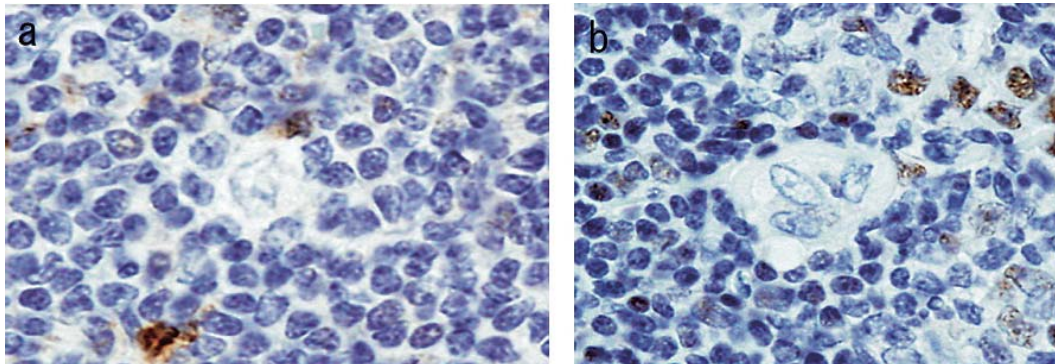


Fig. 4. Immunohistochemistry for BOB-1 (4a) and Oct-2 (4b). HRS cells are negative for BOB-1 and Oct-2.

lar area. Although PTGC is not considered to be a premalignant condition,² it has sometimes been described in association with Hodgkin lymphoma; 22-35% of adult cases of PTGC are associated with Hodgkin lymphoma, mostly NLPHL.^{2,6-8} Poppema *et al.* suggested an association between PTGC and NLPHL on the basis of their similar morphologic features and the presence of both entities in the same lymph node.¹⁴ NLPHL is a monoclonal B-cell neoplasm characterized by nodular, or nodular and diffuse, polymorphous proliferation of scattered neoplastic cells known as “popcorn” or L&H cells (lymphocytic and/or histiocytic Reed-Sternberg cell variants).^{13,14} In NLPHL, the L&H cells are positive for the mature B-cell marker CD20, negative for CD15, and usually negative for CD30.¹⁴ Nguyen *et al.* suggested that most cases of NLPHL could be distinguished from florid PTGC by their irregular “broken-up” pattern with staining for CD20 and the presence of many T-cell rosettes in all of the nodules.³ In the present case, the nodules were composed of small lymphocytes, and many of their harboring germinal centers were eccentrically located and relatively small or regressed. There were scattered HRS cells in the mantle zone and interfollicular area, and T-cell rosettes were identified around them. The HRS cells were positive for CD30, and focally positive for CD20, but negative for CD15, EMA, BSAP, bcl-6, BOB-1, and Oct-2. Although the present case was pathologically similar to NLPHL, a large number of HRS cells were CD30-positive, and BOB-1- and OCT-2-negative, and easily confused with reactive cells. CD30 antigen is expressed strongly on HRS cells in almost all cases of CHL.^{15,16} However, CD30 is an activation antigen that is also expressed by benign cells that are responding to a stimulus (e.g., in cells transformed by EBV infection).¹³ It is also expressed in non-Hodgkin lymphoma, including ALK-positive anaplastic large cell lymphomas and in some aggressive diffuse large B-cell lymphomas. In CHL, HRS cells are usually positive for CD15, an antigen normally expressed in granulocytes and monocytes, but not in lymphocytes. Expression of

CD15 is variable and present in 75-85% of cases, and in some of these, the staining pattern is focal and sometimes evident in only a few cells.¹⁷ Therefore, negativity for CD15 does not rule out Hodgkin lymphoma.¹³ The overall immunohistochemical findings confirmed that the present case was CHL (lymphocyte-rich) complicated by PTGC. Kojima *et al.* reported a case of CHL occurring in clusters of nodal marginal zone B-lymphocytes in association with PTGC.¹⁸ On the basis of a histopathological analysis of 66 cases of PTGC and sequential biopsies from 213 patients with Hodgkin lymphoma, Hansmann *et al.* concluded that PTGC is a result of different processes that may not only be occasionally related to NLPHL, but also rarely associated with CHL.⁶ Although the pathogenetic relationship between PTGC and CHL has not been clarified, the present case suggests that PTGC may rarely be associated with CHL.

The present case should also be differentiated from the macrogerminal center type of FVFL.⁹⁻¹¹ The neoplastic follicles of the FVFL are quite similar to those of PTGC. Moreover, CD23-positive follicular dendritic cell networks are irregularly shaped in FVFL, as well as in PTGC.¹⁹ Since the lymphoid follicles of FVFL are usually neoplastic, bcl-2 immunostaining can be helpful for the diagnosis of FVFL.⁹⁻¹¹ Molecular studies have confirmed that the bcl-2-positive follicles are clonal and frequently exhibit *BCL-2* rearrangement, whereas the bcl-2-negative follicles are polyclonal.^{10,20,21}

The floral variant of NMZL is another entity that has to be included in the differential diagnosis. Karube *et al.* have mentioned the histological similarity between the floral variant of NMZL and PTGC.¹² However, in contrast to PTGC, the peripheral rims of the follicles in NMZL are relatively irregular and often disrupted, and the mantle zone is disrupted and surrounded by a clear-cell zone. Furthermore, monotonous medium-sized cells with relatively abundant cytoplasm are present in the clear-cell zone. The proliferation of these atypical cells in NMZL differed morphologically from that in PTGC. Clinically, the floral variant of NMZL usually shows

localized disease, a good general patient status, and a favorable prognosis.¹²

In conclusion, the differential diagnosis of PTGC from NLPHL and non-Hodgkin lymphoma, including FVFL and the floral variant of NMZL, may be histopathologically problematic. The present case indicates that CHL should be added to the list of differential diagnoses for PTGC.

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DISCLOSURE/CONFLICT OF INTEREST

The authors state that they have no financial interest in the products mentioned in this article.

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