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Original contribution

Immunoarchitectural patterns of progressive transformation of germinal centers with and without nodular lymphocyte-predominant Hodgkin lymphoma☆,☆☆

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Abstract Progressive transformation of germinal centers (PTGC) has been frequently described in association with Hodgkin lymphoma, particularly nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). The aim of this study was to evaluate morphologic features of PTGC for better delineation of PTGC from early involvement by NLPHL. A total of 160 cases of PTGC were evaluated and included in the following 3 groups: 93 patients with PTGC who never developed a lymphoma, 23 patients with synchronous PTGC and NLPHL, and 44 patients with PTGC with antecedent or subsequent history of lymphoma. By histopathologic evaluation, 5 patterns of PTGC that reflected progressive dismantling of germinal centers were identified. There was no difference in the distribution of patterns 1 to 4 among the 3 groups of PTGC; however, in patients showing synchronous involvement of PTGC and NLPHL, pattern 5, which resembles a naïve B-cell follicle, was significantly more frequently observed (14/23) when compared with patients with PTGC who never developed a lymphoma (30/93; $P = .0161$). Furthermore, recognition of the spectrum of immunoarchitectural patterns of PTGC, including architectural and cytologic features, was helpful to better differentiate nodules involved by PTGC from NLPHL.
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1. Introduction

Progressive transformation of germinal centers (PTGC) has been reported to develop before or after the occurrence of Hodgkin lymphoma (HL), but also in healthy individuals [1,2]. Morphologically, PTGC shares several features with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL): both show large nodules composed of small IgD-positive

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polyclonal naïve B cells [3,4], expressing the glucose transporter 1 [5]. However, PTGC lacks lymphocyte-predominant (LP) cells, the clonally related tumor cells of NLPHL [3,6]. Therefore, in some cases with only a few or small LP cells, PTGC can be difficult to distinguish from NLPHL. By cytogenetics, chromosomal aberrations were observed in NLPHL but not in PTGC, which substantiates the reactive nature of PTGC [7]. PTGC was also described to occur in different settings of immune dysregulation such as autoimmune lymphoproliferative syndrome [8] or IgG4-related disease [9]. PTGC usually does not require any treatment; however, in a recent study, patients with PTGC and a history of HL showed more frequent relapses of HL if they were not treated with rituximab [10]. PTGC may therefore represent a precancerous lesion with a potentially increased risk of lymphoma development or recurrence. The aim of the present study was therefore to characterize the morphologic features of PTGC with and without associated NLPHL in order to recognize potential features that may be helpful to separate PTGC from NLPHL, particularly in cases of early involvement by NLPHL.

2. Materials and methods

All available cases of PTGC were selected from the archives of the Department of Pathology, Stanford University, CA (n = 63, 1996-present) and the Dr Senckenberg Institute of Pathology, Goethe University Frankfurt, Germany (n = 97, 1997-present). The PTGC cases were categorized into 3 clinical groups: patients who never developed a lymphoma (de novo PTGC; group A); patients with synchronous involvement of PTGC and lymphoma, which was NLPHL in all cases (group B); and patients with metachronous (either antecedent or subsequent) involvement of PTGC and lymphoma (group C). All cases with NLPHL showed a typical nodular pattern (pattern A according to Fan et al [11]). Cases with synchronous PTGC and NLPHL showed a few typical nodules of NLPHL in one area of the node, whereas other areas showed typical PTGC nodules and residual germinal center (GC) cells with no LP cells. All cases of synchronous PTGC and NLPHL available at both institutions were included in this study, and further selection of the patterns or degree of involvement by NLPHL was not undertaken. The ethics committees of Stanford University and Goethe University Hospital Frankfurt (No. 11974, August 31, 2014–August 31, 2015 [Stanford], and No. 39/14, July 7, 2014 [Frankfurt]) approved this study.

In cases with available paraffin blocks, immunostainings for BCL2 and/or IgD, CD21 and/or CD23 and PD1 were completed, so that immunostainings for mantle zone B cells (BCL2 or IgD), follicular dendritic cells (FDCs; CD21 and/or CD23), and follicular T helper cells (PD1) were available for review in most cases (see Supplementary Table). All cases were reviewed in a panel session at a multiheaded microscope (including M. L. H., S. H., Y. N., and R. W.) without prior knowledge of the patients' history.

Twenty PTGC cases including the full spectrum of PTGC patterns were selected for size measurements of PTGC. Because PTGC can morphologically resemble NLPHL and reactive follicular hyperplasia (RFH), control cases of 10 NLPHLs and 10 RFHs were used for comparison. All slides were scanned on an Aperio ScanScope XT Scanner (Leica Biosystems, Wetzlar, Germany) with a resolution of ×40 and the diameters of reactive follicles in RFH, PTGC nodules, and NLPHL nodules were measured on sections stained with IgD using the Aperio ImageScope software.

The Shapiro-Wilk test was used for testing normality of continuous covariates. If present, groups were compared using the unpaired *t* test; otherwise, the Mann-Whitney test was applied. Pairwise comparisons were performed using the Fisher exact test.

3. Results

3.1. Patient characteristics

The 3 clinical groups reviewed consisted of 93 cases of PTGC without any antecedent or subsequent lymphoma (group A), 23 cases with synchronous involvement of the lymph node by PTGC and NLPHL (group B), and 44 cases of PTGC with antecedent (n = 42) or subsequent (n = 2) lymphoma development (group C). Twenty of these 44 patients had a history of NLPHL, 14 patients had a previous (n = 12) or subsequent (n = 2) diagnosis of classical HL, and 10 patients had other lymphoma types in the past (follicular lymphoma or cutaneous T-cell lymphoma). Although 2 patients with PTGC had a history of classical HL, all 23 group B cases showed synchronous lymph node involvement by PTGC and NLPHL, but not classical HL. The time interval between initial occurrence of lymphoma and development of PTGC ranged from 1 to 16 years (median, 5 years) in group C. The median age did not significantly differ between the groups (Table). Interestingly, in all groups, a predominance of male patients was observed with the highest number of men in the group with synchronous NLPHL (Table).

3.2. PTGC exhibits particular immunoarchitectural patterns

Five distinct immunoarchitectural patterns were apparent on review of the 93 cases that contained PTGC only (group A). Common to all patterns were the general enlargement of GCs, thickening of mantle zones, and a dissection of the borders between disrupted GC and thickened mantle zones. A spectrum of more subtle and progressive changes were observed and were used to define distinct patterns of PTGC as follows: scalloped mantle zones with pseudopapillary protrusions or budding of GC into the mantle zones (pattern 1); an incomplete septum-like infiltration of mantle zone cells into residual GC (pattern 2; Fig. 1); GCs that were completely dissected by septal invasion of mantle zone B cells of variable

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