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Case study

Immunoblastic follicular lymphoma: a very unusual transformation of low-grade follicular lymphoma☆

Shereen Gheith MD, PhD[a,*], Dennis Cornfield MD[a], Weiyi Chen PhD[b], Pal Singh-Kahlon PhD[c], Basil Ahmed MD[d]

[a]*Hematopathology Section, Department of Pathology, Health Network Laboratories/Lehigh Valley Health Network, Allentown, PA, 18103*
[b]*Molecular Diagnostics Section, Cancer Genetics, Rutherford, NJ, 07070*
[c]*Cytogenetics Section, Cancer Genetics, Rutherford, NJ, 07070*
[d]*Hematology/Medical Oncology Section, Department of Medicine, Lehigh Valley Health Network, Allentown, PA, 18103*

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Summary A 73-year-old man, in clinical remission 17 years after radiation therapy for a localized low-grade follicular lymphoma (FL), developed extensive lymphadenopathy, ascites, and splenomegaly with splenic masses. Axillary lymph node biopsy showed FL composed of nodules of centrocytes side by side with nodules of immunoblasts rather than centroblasts. Immunophenotyping revealed conventional FL markers (BCL-2, BCL-6, and CD10) as well as MUM-1 in the immunoblastic component, suggesting postgerminal center differentiation. Fluorescence in situ hybridization showed t(14;18) in both centrocytic and immunoblastic components and a copy gain of *BCL-6* predominantly in the immunoblastic component. Areas of centrocytic and of immunoblastic nodules were macrodissected separately and underwent molecular evaluation for immunoglobulin heavy chain gene rearrangement. Identical base-pair peaks were found, attesting to their clonal identity. This case represents a very unusual example of transformation of a low-grade FL to a nodular immunoblastic FL.

1. Introduction

Follicular lymphoma (FL) is described in reviews and in the World Health Organization (WHO) classification of lymphoid tumors as a neoplasm of centrocytes and centroblasts and is graded according to the relative proportion of these 2 elements [1]. Immunoblasts are not ordinarily present in significant numbers in FL, unless there is evidence for transformation to a diffuse large B-cell lymphoma (DLBCL), in which case they form part or all of the diffuse large cell component. The present report describes a case of FL with a completely follicular architecture and with the unusual finding of nodules of pure immunoblasts alongside nodules of centrocytes, that is, FL, follicular, grade 1 to 2, 60%; and FL, follicular, grade 3B, 40%. Molecular evaluation of both types of neoplastic

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* Corresponding author. Department of Pathology, Lehigh Valley Health Network, 1200 S Cedar Crest Blvd, Allentown, PA 18103.
E-mail address: Shereen_M.Gheith@lvhn.org (S. Gheith).

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nodules for *immunoglobulin heavy chain* (*IGH*) gene rearrangement demonstrated their clonal identity.

2. Case report

A 73-year-old man presented to the hospital with abdominal discomfort, anorexia, weight loss, and increasing abdominal girth. Seventeen years earlier, he had been diagnosed with a localized cervical FL, mixed small and large cell (corresponding to a grade 2 FL in the 2008 WHO classification of lymphomas) [1], and treated with radiation therapy alone, with resolution of lymphadenopathy. Radiologic evaluation during the present hospitalization showed extensive lymphadenopathy, ascites, and splenomegaly with several splenic masses. Excision biopsy of an axillary lymph node revealed the FL described below.

3. Materials and methods

3.1. Immunohistochemistry

Immunohistochemistry (IHC) was performed on deparaffinized, formalin-fixed tissue sections using a panel of antibodies routinely used to evaluate lymphomas. These include the following: CD20 (1:20; Biocare, Tempe, AZ), CD3 (undiluted; Dako North America, Carpinteria, CA), BCL-2 (1:200; Dako), BCL-6 (undiluted; Dako), CD10 (undiluted; Dako), MUM-1 (undiluted; Dako), BCL-1 (1:50; Dako), MIB-1/Ki-67 (undiluted; Dako), CD138 (1:50; Dako), κ (1:8, Dako), and λ light chain (1:8; Dako).

3.2. Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) analysis was performed using the *BCL-2* 18q21/*IGH* 14q32 and the *MYC* 8q24/*IGH* 14q32 dual-fusion, dual-color probes and *BCL-6* 3q27 DNA single probe (Abbott Molecular, Des Plaines, IL) on paraffin-embedded sections using methods described in the Vysis Paraffin Pretreatment kit (Abbott Molecular). Results were interpreted as positive for *IGH/BCL-2* translocation or *BCL-6* copy gain if a fusion signal or additional signal was observed in more than 1% of nuclei, respectively. Two hundred cells were scored per probe.

Digital acquisition of FISH images was done using an Olympus fluorescent microscope Boston, MA and Isis Fluorescence Imaging System (MetaSystems, Boston, MA) imaging software.

3.3. *IGH* gene rearrangement by polymerase chain reaction

High- and low-grade nodules were identified on the hematoxylin and eosin (H&E)–stained slides. Manual macrodissection of the fragments of interest were performed as previously reported [2] and submitted separately for molecular analysis. IGH clonality assay was performed using a kit from InVivoScribe Technologies (San Diego, CA) and following manufacturer's methodology. Three panels were used in the study: tubes A, B, and C with 6VH-FR1, 7VH-FR2, and 7VH-FR3 primers with associated Joining segment (JH) consensus primers in each tube. The polymerase chain reactions (PCRs) were performed and analyzed using the ABI 3100 sequencer (Life Technologies, Grand Island, NY).

A result was considered positive when the amplified product size was within the base pair size range assigned for each tube, with an unequivocal peak having a signal/noise ratio of 3 or greater and an equivocal peak a signal/noise ratio of 2 to 3 above the polyclonal background.

3.4. Flow cytometry

Flow cytometry was performed according to standard procedures and manufacturers' protocols, using a panel of 19 antibodies routinely used to evaluate lymphomas. Data acquisition and analysis were performed on a 5-color Cytomics FC-500 (Beckman Coulter, Brea, CA) flow cytometry instrument.

4. Results

H&E stain of the excision biopsy demonstrated fragments of lymphoid tissue with a nodular architecture (Fig. 1A). Approximately half of the nodules are composed of small centrocytes with cleaved nuclei and rare large transformed forms, recapitulating the classic cytologic features of low-grade (grade 1) FL (Fig. 1B). Other nodules are composed almost exclusively of immunoblasts (Fig. 1C) (grade 3B) with prominent single nucleoli and ample basophilic cytoplasm, as opposed to centroblasts, which are typically seen in high-grade FL.

Flow cytometry showed a κ light chain–restricted CD19(+), CD10(+), and CD20(+) B-cell population. Interestingly, a subset of this B-cell population, mostly within the large cell gate, demonstrated loss of CD20 expression (data not shown), although this finding was not reproduced by paraffin IHC.

CD20 expression by IHC was evident in all nodules (Fig. 2A), with coexpression of BCL-2 (Fig. 2B), BCL-6, and CD10. The nodular pattern of the FL was confirmed by the CD21 stain, which highlights low- and high-grade nodules (Fig. 2C) and therefore argues against a diffuse (immunoblastic) large B-cell lymphoma. High-grade nodules were positive for MUM-1 (Fig. 2D) and BCL-6 (Fig. 2E); low-grade nodules were positive for BCL-6 and negative for MUM-1.

Molecular studies for *IGH* gene rearrangement, performed on macrodisssected low-grade (centrocytic) and high-grade