Transformation of Follicular Lymphoma to Plasmablastic Lymphoma With c-myc Gene Rearrangement

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Abstract

Follicular lymphoma (FL) is an indolent lymphoma that transforms to high-grade lymphoma, mostly diffuse large B-cell lymphoma, in about a third of patients. We present the first report of a case of FL that transformed to plasmablastic lymphoma (PBL). Clonal transformation of the FL to PBL was evidenced by identical IGH/BCL2 gene rearrangements and VDJ gene usage in rearranged IGH genes. IGH/BCL2 translocation was retained in the PBL, which also acquired c-myc gene rearrangement. Genealogic analysis based on somatic hypermutation of the rearranged IGH genes of both FL and PBL suggests that transformation of the FL to PBL occurred most likely by divergent evolution from a common progenitor cell rather than direct evolution from the FL clone. Our study of this unusual case expands the histologic spectrum of FL transformation and increases our understanding of the pathogenetic mechanisms of transformation of indolent lymphomas to aggressive lymphomas.

Follicular lymphoma (FL) is a neoplasm of centrocytes and centroblasts with a follicle center B-cell immunophenotype, characterized in most cases by the presence of the reciprocal chromosomal translocation t(14;18)(q32;q21) that results in juxtaposition of the BCL2 gene to the immunoglobulin heavy chain (IGH) gene. Although FL is often clinically indolent with a median survival of more than 7 or 8 years, it is an incurable malignancy. The natural history of FL has been well documented, with 25% to 35% of cases progressing to a high-grade lymphoma,1 usually diffuse large B-cell lymphoma (DLBCL). In these cases, the most common morphologic pattern is one of sheets of large transformed cells with centroblastic morphologic features and a germinal center immunophenotype.2,3 However, cases of transformation to other lymphoma subtypes have been documented, including B-cell lymphoma with features intermediate between DLBCL and Burkitt lymphoma (BL),4-7 CD30+ large cell lymphoma with anaplastic cytologic features,8 prolymphocytoid transformation,9 and blastic/blastoid transformation.10

Transformation of FL to B-lymphoblastic lymphoma/leukemia has been documented11; some of the older B-lymphoblastic lymphoma/leukemia reported cases show an additional c-myc translocation12,13 and are now better classified as B-cell lymphoma with features intermediate between DLBCL and BL.6 Morphologic transformation is usually characterized by an aggressive course, poor response to chemotherapy, and short survival. Because of the clinical implications, it is important for pathologists to recognize the variety of histologic features of transformed FL to avoid misinterpreting the noncentroblastic forms of transformation as de novo lymphomas. The clonal relationship between the original low-grade FL and the transformed higher grade lymphoma
Case Report

A 69-year-old man with a recent history of prostate adenocarcinoma treated with radiation therapy seeds sought care because of newly developed inguinal lymphadenopathy. A right inguinal lymph node excisional biopsy resulted in a diagnosis of FL, grade 1 of 3. A staging bone marrow biopsy was negative for lymphoma. The patient was not treated but was closely followed up.

A computed tomography scan performed about 6 months after the lymphoma diagnosis showed abdominal lymphadenopathy. The patient subsequently received 4 cycles of rituximab and showed a good response.

A few months later, he had hematuria. A bladder biopsy was diagnosed as involved by PBL. Chest and abdominal computed tomography did not show osseous lesions. Creatinine and blood urea nitrogen levels were both unremarkable. Serum and urine protein electrophoresis were not performed. The patient began chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone and received a total of 6 cycles. During the course of treatment, the patient had a 1.2-cm right cystic neck mass. A fine-needle aspiration of the mass was positive for malignant cells, consistent with a poorly differentiated malignant neoplasm. The neck mass was resected, and a diagnosis of PBL was made.

The patient sought care 1 month later because of an extratesticular scrotal mass. Core biopsies again showed PBL. The patient received 2 cycles of dexamethasone, ifosfamide, cisplatin, and etoposide infusional chemotherapy and was being evaluated for stem cell transplantation. The patient died of disease less than 6 months after the diagnosis of PBL.

Materials and Methods

Morphologic and Immunophenotypic Studies

Case material was retrieved from Weill Cornell Medical Center, New York, NY. The FL and PBL were diagnosed according to the current diagnostic criteria published by the World Health Organization (WHO) in 2008. The inguinal lymph node, the bladder biopsy specimen, and the cystic neck mass specimen were fixed in 10% neutral buffered formalin, and the bone marrow biopsy specimen was fixed in Bouin. All samples were embedded in paraffin, and 4-μm sections were cut and stained with H&E for histologic evaluation.

For immunohistochemical studies, paraffin-embedded tissue sections were stained using a Leica autostainer (Leica Microsystems, Bannockburn, IL) following the standard immunoperoxidase staining protocol for each antibody. An external positive control was run against each antibody and a negative control run with each case. The antibodies used to immunophenotype the PBL are listed in Table II. Four-color flow cytometry of the lymph node showing FL was performed using a Becton Dickinson FACSCalibur (BD Biosciences, San Jose, CA) for acquisition and analysis. Becton Dickinson monoclonal antibodies (BD Biosciences) were used and conjugated to the fluorochromes peridinin chlorophyll protein, fluorescein isothiocyanate, phycoerythrin, and allophycocyanin. Direct smears of the fine-needle aspirate of the neck mass were stained with rapid Romanowsky (air-dried) and Papanicolaou (alcohol-fixed) stains.

Immunoglobulin Heavy Chain and BCL2 Gene Rearrangement Analysis by Polymerase Chain Reaction and Sequencing

Molecular studies were performed on DNA extracted from formalin-fixed, paraffin-embedded tissues from the inguinal lymph node involved with FL and the cystic neck mass involved with PBL. Polymerase chain reaction (PCR) to assess the presence of IGH gene rearrangements was performed using the IGH Somatic Hypermutation Assay kit (InVivoScribe Technologies, San Diego, CA) with primers that target the framework 1 (FR1) and joining regions of the IGH gene. The amplified products were visualized in 10% polyacrylamide gel. PCR using primers corresponding to the leader sequence, which is capable of analyzing the entire VH region in conjunction with the J<sub>H</sub> primers, were also attempted. However, an amplicon of this size could not be obtained from the DNA material extracted from formalin-fixed tissues. A multiplex PCR for the presence of BCL2 gene rearrangements was performed to detect the common breakpoints in the major breakpoint region and the minor cluster region of the BCL2 gene. PCR products were analyzed by agarose gel electrophoresis, extracted, and cloned for sequencing.

FISH Analysis

Fluorescence in situ hybridization (FISH) was performed on paraffin section slides of the PBL and FL according to the manufacturer’s instructions (Vysis/Abbott Molecular, Des Plaines, IL) with minor modifications. Commercially available LSI IGH/BCL2 dual-color dual fusion probes and the LSI M cycl-dual-color break-apart probe (Abbott Molecular, Abbott Park, IL) were used to look for t(14;18)(q32;q21) (IGH/BCL2) and c-myc gene rearrangements, respectively. About 200 interphase nuclei were screened for each probe.
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Somatic Hypermutation Analysis

A DNA fragment obtained from IGH gene rearrangement analysis with the FR1 and IJ primers was extracted from the gel and cloned for sequencing. About 30 clones were analyzed. The sequences were compared with the IGH-VDJ germline sequence using IMGT/V-QUEST (http://imgt.cines.fr/IMGT_vquest/share/textes/15) and were aligned by ClustalW2 (http://www.ebi.ac.uk/Tools/clustalw2/index.html). Genealogic trees were constructed based on analysis of these aligned sequences.

Results

Histologic and Immunophenotypic Studies

Histologic examination of the inguinal lymph node revealed complete architectural effacement by an abnormal lymphoid proliferation displaying a nodular growth pattern, composed mainly of small atypical lymphoid cells with cleaved nuclei (centrocytes), consistent with FL, grade 1 of 3. The atypical lymphoid cells were positive for CD20, PAX5, BCL6, and BCL2 by immunohistochemical analysis. Flow cytometry demonstrated a monoclonal κ-restricted B-cell population that was positive for CD10 and negative for CD5. There was no morphologic evidence of metastatic carcinoma. A staging bone marrow biopsy showed no morphologic evidence of involvement by lymphoma or myeloma.

Fine-needle aspirates of the neck mass were hypercellular with many singly dispersed, highly atypical, large to intermediate tumor cells. Nuclei were round and eccentrically located with 1 or 2 prominent nucleoli. Some cells were binucleated or multinucleated. The cytoplasm was densely basophilic with occasional fine vacuoles and varied from scant to moderate. The background showed mitoses and few lymphoglandular bodies. Histologic examination of the neck mass showed diffuse, cohesive sheets of large abnormal tumor cells with round nuclei, prominent eosinophilic nucleoli, and abundant amphophilic cytoplasm. Numerous mitoses were noted. The cytomorphic features of these tumor cells were consistent with immunoblasts and plasmablasts. Results of the immunohistochemical stains are summarized in Table 1. The tumor cells lacked CD45 and did not exhibit a B-cell phenotype, being negative for CD20, PAX5, CD79a, and BCL6. They were, however, immuno-reactive for plasma cell markers such as CD138, MUM1, and PRDM1/Blimp-1 but were negative for cytoplasmic immunoglobulins. Epstein-Barr virus (EBV)-encoded small RNA in situ hybridization and human herpesvirus 8 (HHV-8)–associated latent protein LANA immunostain were both negative. The Ki-67 proliferation index was 90%. These findings are diagnostic of PBL.

Histologic examination of the bladder biopsy and scrotal mass specimens showed similar histologic and immunophenotypic findings (data not shown).

Table 1
Antibodies Used to Immunophenotype Plasmablastic Lymphoma and the Immunohistochemical Results

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Company</th>
<th>Clone Number</th>
<th>Results</th>
</tr>
</thead>
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<tr>
<td>CD138</td>
<td>AbD Serotec, Raleigh, NC</td>
<td>B-A38</td>
<td>Positive</td>
</tr>
<tr>
<td>MUM1</td>
<td>DAKO, Carpinteria, CA</td>
<td>MUM1p</td>
<td>Positive</td>
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<td>Ki-67</td>
<td>DAKO</td>
<td>MIB-1</td>
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<tr>
<td>PRDM1/BLIMP-1</td>
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<td>3H2E8</td>
<td>Positive</td>
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<td>EMA</td>
<td>DAKO</td>
<td>E29</td>
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</tr>
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<td>L26</td>
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</tr>
<tr>
<td>PAX5</td>
<td>BD Biosciences, San Jose, CA</td>
<td>24/Pax-5</td>
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<td>CD79a</td>
<td>DAKO</td>
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<td>NeoMarkers, Fremont, CA</td>
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<td>CD6</td>
<td>Vector, Burlingame, CA</td>
<td>4C7</td>
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<td>CD10</td>
<td>Novocastra, Newcastle upon Tyne, England</td>
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<td>DAKO</td>
<td>2B11+PD7/26</td>
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<td>ps3</td>
<td>BioGenex, San Ramon, CA</td>
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<td>CD22</td>
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<td>DAKO</td>
<td>PG-B8p</td>
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<td>AE1/AE3</td>
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<td>CK7</td>
<td>DAKO</td>
<td>OV-TL 12/30</td>
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<tr>
<td>v-100</td>
<td>DAKO</td>
<td>—</td>
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<tr>
<td>AS.100</td>
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<tr>
<td>Synaptophysin</td>
<td>Thermo Scientific, Pittsburgh, PA</td>
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<tr>
<td>Chromogranin</td>
<td>BioGenex</td>
<td>LK2H10</td>
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</table>

ALK, anaplastic lymphoma kinase; clg, cytoplasmic immunoglobulin; CK, cytokeratin; EMA, epithelial membrane antigen.
Image 1 Histologic and immunophenotypic findings of follicular lymphoma. **A**, Sections of inguinal lymph node showing neoplastic follicles with attenuated mantle zones (H&E, ×40). **B**, The nodules are composed predominantly of atypical small cleaved lymphoid cells and a few (<15 per high-power field) atypical large noncleaved lymphoid cells (H&E, ×400). **C-F**, Immunohistochemical staining showed that the tumor cells express CD20 (**C**, ×40), PAX5 (**D**, ×40), BCL2 (**E**, ×40), and BCL6 (**F**, ×40).
Cytologic, histologic, and immunophenotypic findings of plasmablastic lymphoma. 

A. Fine-needle aspiration of the cystic mass showing large atypical cells composed of abundant cytoplasm and eccentrically located round nuclei with prominent nucleoli (rapid Romanowsky, ×600). 

B. Sections of the neck mass showing diffuse proliferation of immunoblast-like cells with prominent nucleoli (H&E, ×400). 

C-G. Immunohistochemical staining showed that the tumor cells express CD138 (C, ×400) and MUM1 (D, ×400) and lack CD45 (E, ×400), CD20 (F, ×400), and PAX5 (G, ×400).
Gene Rearrangement Analysis

PCR to assess the presence of IGH gene rearrangements showed distinct monoclonal bands that were similar in the FL (lymph node) and the PBL (cystic neck mass), suggesting that these 2 neoplasms were clonally related. PCR analysis for t(14;18)(q32;q21) (IGH/BCL2) yielded clonal rearrangements at the major breakpoint region with identical migration patterns in the FL and PBL. Sequencing of the amplicons for IGH/BCL2 rearrangement from the FL and PBL showed an identical junction sequence consisting of BCL2 sequence from the 3' untranslated region in exon 3 and JH6 sequence, confirming that the 2 tumors are clonally related.

FISH Analysis

FISH analyses performed in the neck mass involved by PBL identified the presence of a variant IGH/BCL2 translocation in approximately 100% of the interphase nuclei evaluated. In addition, a c-myc gene rearrangement was identified in the PBL in almost all nuclei. FISH did not detect a c-Myc gene rearrangement in the FL.
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Somatic Hypermutation Analysis

We tried to determine whether the PBL in this case was transformed from the FL through direct evolution from an FL clone or by divergent evolution from a common progenitor cell (CPC) by analysis of the somatic hypermutation (SHM) pattern of the rearranged IGH genes in these 2 tumors. Sequence analysis demonstrated V3-23/D1-26/34 usage in both tumors, further confirming that they were clonally related. The FL showed a high SHM rate, with homology to the germline sequence ranging from 77.3% to 79.2% and high intraclonal diversity. The PBL demonstrated a similar mutation rate, with 78.6% to 79.8% homology. However, it exhibited a much lower intraclonal diversity compared with the FL. Genealogic trees generated from analysis of multiple sequence clones in both tumors revealed a pattern compatible with divergent evolution from a CPC. Figure 1A. A hypothetical model of transformation of FL to PBL for this case is presented Figure 1B.

Discussion

The clinical course of FL has been well described, including transformation to DLBCL, most commonly with centroblastic morphologic features and germinal center immunophenotype.2,3 Maeshima et al,3 in a retrospective study of patients with DLBCL with preexisting or coexisting FL, showed that 95% (41/43) of DLBCLs were of the centroblastic type with only 5% (2/43) showing anaplastic morphologic features. It is important to note that not all DLBCLs were CD20+ and CD138−. Rare cases with an immunoblastic appearance have been described,16,17 but a detailed immunophenotype was not included. Changes in terminology and definitions make interpretation of these previous reports difficult.

Transformation of FL to PBL is highly unusual and has not been previously reported. PBL represents a group of neoplasms that have immunoblastic or plasmablastic morphologic features and an immunophenotype of terminally differentiated B cells, ie, absence of CD20 and PAX5 with positive CD38 and CD138.18 PBL was first described in 199719 and was initially classified in the WHO 200120 as a rare variant of DLBCL that manifests in the oral cavity in the setting of HIV infection. In the more recent WHO 2008, PBL is recognized as a separate entity that can arise outside the oral cavity and can occasionally be seen in non-HIV patients, mostly iatrogenic immunosuppressed patients (eg, in posttransplantation settings) or immunocompetent elderly patients.21

The differential diagnoses of PBL include several other neoplasms characterized by a proliferation of atypical cells with plasmablastic/immunoblastic morphologic features. Plasmablastic multiple myeloma (MM) must be distinguished from PBL because of the different clinical management pathways. Typically, the presence of serum paraprotein and/or lytic bone lesions in older patients favors MM. However, widely disseminated bone disease and monoclonal serum immunoglobulin have been described in PBL and could lead to major confusion with MM.22,23 Although PBL and MM have nearly identical immunophenotypic profiles,24 CD56 positivity, occasionally cyclin D1 positivity, and a relatively lower Ki-67 can help identify secondary extramedullary plasmablastic MM.17 Extramedulocalization, a history of immune deficiency, the occasional absence of cytoplasmic immunoglobulins, and the presence of EBV by in situ hybridization are also useful for the diagnosis of PBL.21

Immunoblastic variants of DLBCL and BL with plasmablastic differentiation are also part of the differential diagnosis and can be distinguished immunophenotypically from PBL by their strong positivity for B-cell markers, even though CD138 can be occasionally positive. Anaplastic lymphoma kinase–positive DLBCL can show plasmablastic differentiation and is differentiated from PBL by anaplastic lymphoma kinase expression.

Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease, also called HHV-8+ PBL, also needs to be distinguished from PBL. The former entity originates from a CD20+ naive B cell that expresses IgM without IGH gene somatic hypermutation and consistently shows stippled nuclear staining for HHV-8–associated latent protein LANA-1, while PBL is not related to HHV-8 infection and arises from a B cell that has switched its phenotype to the plasma cell gene expression program with class-switch and hypermutated immunoglobulin genes. Primary effusion lymphomas and their recently described solid counterparts are also composed of a proliferation of large immunoblastic or plasmablastic cells and are associated with HHV-8 with EBV coinfection. The diagnosis of PBL can be challenging, and it is important for surgical pathologists and hematopathologists to recognize this entity and differentiate it from its numerous mimickers and also be aware that PBL can represent a form of high-grade transformation of a lower grade B-cell lymphoma because of the clinical and therapeutic implications.

It may be argued that rituximab therapy may have accounted for the absence of CD20 in the aggressive lymphoma. Several studies have shown that B-cell non-Hodgkin lymphomas show CD20− relapse after rituximab therapy. Maeshima et al25 studied 59 B-cell non-Hodgkin lymphomas, including 34 FLs, treated with chemotherapeutic regimens including rituximab and observed postrituximab CD20 loss in relapsed lymphomas in 27% of the cases. However, CD20− DLBCL after rituximab treatment in FL remains positive for CD79a.26 The absence of all pan–B-cell markers together with the uniform strong expression of plasma cell–associated markers in this case cannot be accounted for by rituximab treatment and supports the diagnosis of PBL.
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We definitively demonstrated that this PBL represented a transformed FL by identifying a clonal relationship between these 2 neoplasms using PCR analysis of IGH and BCL2 gene rearrangements and IGH/BCL2 FISH studies. A recent study based on analysis of the IGH-VH regions of FL and paired samples of DLBCL transformed from FL indicates that the DLBCL may arise from a CPC by divergent evolution or may derive from direct evolution from the FL subclone.27 To investigate these 2 possibilities, we analyzed the SHM patterns of the IGH-VDJ regions of the FL and PBL and...
concluded that the transformation of FL to PBL in this case occurred most likely by a divergent evolution from a CPC rather than a direct evolution. Based on the number of SHMs, we postulate that this CPC is derived from a germinal center B cell. However, the exact identity and genetic constituents of this CPC are unknown.

Our findings pointing to the existence of a CPC that links the FL and transformed FL are in line with those previously described by Carlotti et al.27 Its putative existence helps explain the clinical features of this case. The CPC may have survived the initial FL treatment and subsequently acquired new genomic lesions that promoted FL transformation. The existence of a CPC may also provide a mechanistic explanation to the scenarios in which FL is transformed to a high-grade lymphoma with discordant stage of differentiation, for example, a precursor B lymphoblastic lymphoma/leukemia or, as seen in the current case, a PBL. It is possible that the CPC, unlike the major tumor clone in FL, has a higher plasticity for major transitions along the B-cell differentiation pathway. The molecular events underlying differentiation transition in these unusual forms of FL transformation remain to be found.

FLs undergoing transformation typically retain the IGH/BCL2 translocation, and subsequent secondary genetic abnormalities are believed to be important for the evolution of the disease. The most commonly identified genetic alterations associated with higher grade transformation of FL are TP53 gene mutations, inactivation of CDKN2A and CDKN2B genes, and deregulation of the c-myc gene.28 We identified in our case c-myc rearrangement in association with the IGH/BCL2 translocation. The acquisition of the c-myc gene rearrangement on transformation is consistent with the complementation between c-myc and BCL2 in transgenic systems in which BCL2 is thought to protect against the proapoptotic properties of c-myc, thus allowing for a more robust proliferation signal.28 c-myc gene rearrangement was reported in 8% (3/38) of transformed FLs in 1 series.29 None of the available matched pretransformation FL biopsy specimens from the corresponding cases demonstrated a rearranged c-myc gene.

Only a few cases of PBL harboring a translocation between the c-myc gene and the IGH gene have been reported.22,20,32 Although the actual prevalence of c-myc rearrangement in PBL is unknown, activation of c-myc by gene rearrangement may not be uncommon in PBL. Taddesse-Heath et al23 demonstrated the presence of c-myc rearrangement in 4 of 6 PBLs studied. Bogusz et al30 studied 9 PBLs and detected a c-myc translocation in a third of their cases. All reported PBL cases with a c-myc translocation were de novo lymphoma described in HIV+ patients, and most were positive for EBV. Our case is the only reported case of PBL with c-myc translocation occurring in an HIV− patient with negative EBV. A rearranged c-myc may be important in the pathogenesis of aggressive lymphomas with plasmablastic features, as a de novo lymphoma or a lymphoma transformed from low-grade B-cell lymphoma. It is conceivable that for c-myc expression to be deregulated in this type of lymphomas, translocation of c-myc may be necessary for it to escape from the normal control of its transcription repressor PRDM1/Blimp-1,33 which is present at high levels in lymphomas showing plasma cell differentiation and in plasma cell myelomas.

We presented the first case of FL transforming to PBL containing t(14;18)(q32;q21) (IGH/BCL2) and c-myc rearrangements. This study widens the histologic spectrum of FL transformation and also highlights the need for pathologists to be mindful that FL can transform to other subtypes of aggressive lymphomas besides the “garden-variety” DLBCL. Additional molecular study on this unusual case of FL transformation may provide further insights on the intriguing pathologic process underlying transformation of indolent lymphomas.

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References


