

Article

The many rare faces of follicular lymphoma - Part 1

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Abstract: Follicular lymphoma (FL) is the most common well defined malignant lymphoma in the adults. Besides the classical pattern of effaced nodal architecture by back-to-back lymphoid follicles/nodules, it shows many morphological variations. Using actual cases, this article will illustrate the morphological features of these FL variants. In part 1, I will present 6 FL variants: 1) *In situ* FL and "early" interfollicular/partial nodal involvement by FL; 2) FL, floral variant ("cloudy variant"); 3) FL with abundant eosinophilic precipitate; 4) FL with marginal zone differentiation; 5) FL with plasmacytic differentiation; and 6) Pediatric FL. Pathologists should be familiar with these morphological variations to avoid mistakes in diagnosing FLs.

Keywords: Follicular lymphoma, morphologic variants

Introduction

Follicular lymphoma (FL) is the most common low-grade mature B-cell lymphoma in adults. Furthermore, FL is the only B-cell lymphoma that has experienced least changes during the evolving lymphoma classifications in the last century. On morphology, FL generally shows effaced nodal architecture with closely packed, back-to-back lymphoid follicles that lack polarization. Cellular components of the follicles are represented by a monotonous population of small centrocytes (small cleaved cells) with angulated nuclei admixed with a variable number of large centroblasts. Moreover, quite uncommon morphologic variants of FL do exist.

In this article, I describe the "most common" rare morphologic variants of FL encountered during my daily practice. Pathologists with special interests

in lymph node and hematopathologists should be familiar with these rare faces to avoid mistakes in the diagnosis of FL.

Materials and Methods

With approval by the Institutional Review Board of St. Eugenio Hospital, the FL cases were retrieved from the archives of the Department of Pathology, St. Eugenio Hospital. Lymph node specimens were fixed in 10% formalin fixatives and paraffin embedded before 3 micron sections were prepared. Hematoxylin-eosin (H&E) stains were routinely performed on a ST5010 Autostainer XL (Leica, Milano, Italy). Immunohistochemical stains were performed on a Dako Omnis stainer (Dako, Denmark) using monoclonal antibodies against CD3, CD10, CD20, CD23, BCL2, BCL6, Ki-67/MIB-1, MUM-1, etc. (Dako, Denmark). All the stains were performed with appropriate positive and negative controls.

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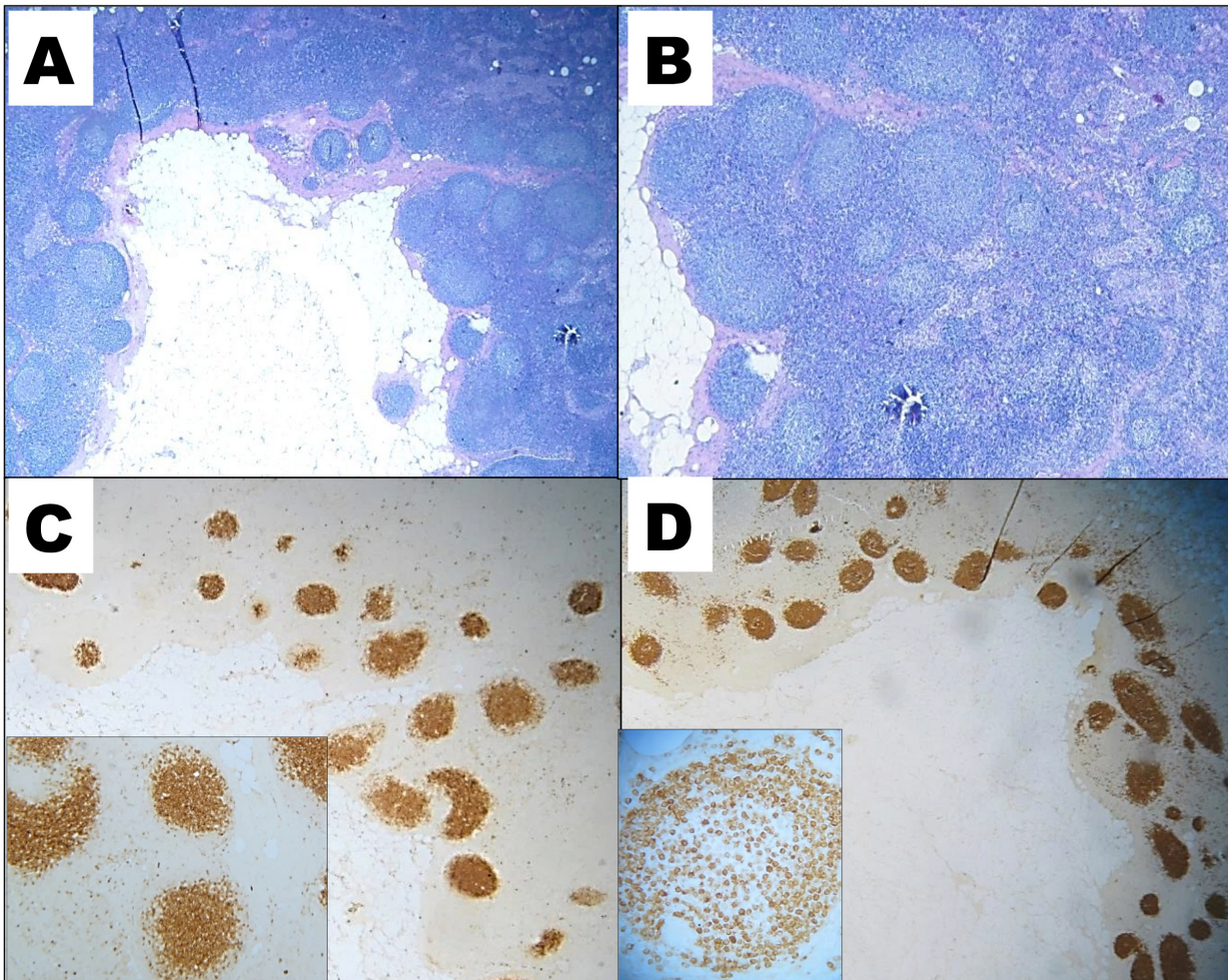


Figure 1: *In situ* Follicular lymphoma and "early" interfollicular /partial nodal involvement by Follicular lymphoma.

(A) Largely preserved nodal architecture with a cluster of large and monomorphous follicles (H&E, low magnification); (B) Loss of polarization in the lymphoid follicles (H&E, medium magnification); (C) Strong CD10 expression by both neoplastic follicles and scattered interfollicular B cells (IHC, low magnification); inset (medium magnification); (D) Strong BCL2 expression by neoplastic centrocytes (IHC, low magnification).

Results and Discussion

In situ follicular lymphoma and "early" interfollicular involvement by follicular lymphoma

A lymph node was resected from a 56-year-old female with left axillary lymphadenopathy. The specimen measured 1.4 cm in diameter. Nodal architecture was largely preserved [Figure 1A]. In the background of reactive follicular hyperplasia, a clus-

ter of large and monomorphic follicles was present. These follicles did not show morphologic "dark and light" zone polarization [Figure 1B] and strongly expressed CD20, CD10 and BCL2 [Figure 1C & 1D]. At first look this finding could represent an "*in situ* FL". However, a few interfollicular CD10+/CD20+ centrocytes were also present (beyond the germinal centers). This feature suggested an "early" interfollicular or partial nodal involvement by a low grade

FL.

To be diagnosed as "intrafollicular neoplasia"/*in situ* FL, it has to fulfill 7 criteria (Table 1). This case is quite interesting because histological sections showed a small cluster of neoplastic follicles which at low magnification were not much different from their surrounding reactive follicles. Even medium and high magnifications only revealed a monotonous population of small cleaved centrocytes with no polarization of the follicles. The presence of scattered CD10+ small lymphocytes in the interfollicular area is consistent with an "early" interfollicular or partial nodal involvement by a systemic FL. This finding suggests that the patient may not have a benign clinical course.

"*In situ* FL" was first reported in 2002 by Cong *et al.* [1] who suggested that some cases of "*in-situ* FL" represented homing to and early colonization of reactive germinal centers (GCs) by FL cells. They could also represent FL at the earliest stage of development or a pre-neoplastic event, requiring a second hit for full-blown neoplastic transformation. Other studies suggested that normal follicles might be colonized by BCL2+ small cleaved centrocytes that represented early intrafollicular involvement by FL [2]. However, whether these intrafollicular neoplastic B-cells represent an early phase of FL or a pre-neoplastic intrafollicular precursor lesion remains controversial. In patients with overt FL at other sites, this finding probably represents colonization of preexisting follicles by neoplastic FL cells. Nevertheless, we should admit that, when an "intrafollicular neoplasia"/*in*

situ FL is found in a patient with a prior documented FL, whether it represents a new or pre-existing neoplastic population or subtle nodal involvement by a covert FL cannot easily be determined.

To differentiate the early partial nodal (interfollicular) involvement by FL from "intrafollicular neoplasia"/*in situ* FL, the most important finding is the presence of atypical small cleaved centrocytes extending beyond the GCs. Immunostains for CD10 and BCL6 are the most useful tools in identifying interfollicular infiltration by FL. In addition, follicles with early interfollicular infiltration by FL may appear larger and crowded than uninvolved follicles. However, there are so far no standardized histopathologic criteria for differentiating "intrafollicular neoplasia"/*in situ* FL from the "early" interfollicular/partial nodal involvement by FL. Thus, the borderlands and overlap between "intrafollicular neoplasia"/*in situ* FL and "early" interfollicular/partial nodal involvement by FL have been ambiguous [3].

Currently, the "intrafollicular neoplasia"/*in situ* FL is recognized as a variant of FL by the WHO Classification [4]. It is defined as a clonal B-cell population in GCs which strongly express BCL2 and CD10, but lack interfollicular infiltration; B-cells strongly positive for BCL2 (and CD10) are exclusively localized in the GCs of an otherwise reactive lymph node. Hence the term "*in situ* FL" is used to designate a condition in which the t(14;18) cells are restricted to the GCs. The case presented here does not meet the strict criteria for "*in situ* FL", but instead it repre-

Table 1: Diagnostic criteria of "intrafollicular neoplasia"/*in situ* follicular lymphoma*

1. Lymph node architecture is intact with prevalent follicular hyperplasia;
2. Monomorphic cell composition of the GC composed mainly by small cleaved centrocytes without tingible-body macrophages and absence of follicular polarization;
3. Strong simultaneous expression of both BCL2 and CD10 in the involved germinal-center;
4. Low proliferation index than normal reactive GCs by Ki67/MIB1 immunostain;
5. These cells have the t(14;18)(IGH/BCL2) translocation;
6. Absence of interfollicular invasion;
7. Immunohistochemistry (BCL2 and CD10 stains) is mandatory for the diagnosis.

*: References [1, 3].

sents an "early" interfollicular or early partial nodal involvement by FL, which at presentation could be more often found in patients with limited diseases.

"Intrafollicular neoplasia"/*in situ* FL is an incidental finding, only diagnosed with the aid of immunostains (BCL2 and CD10) in the setting of reactive follicular hyperplasia. In a series of unselected reactive lymph nodes, Henopp *et al.* reported a prevalence of 2.3% for "intrafollicular neoplasia"/*in situ* FL [5]. The clinical significance of this diagnosis has not yet been fully understood. In their series of 13 *in situ* FL cases, Montes-Moreno *et al.* identified 3 patients with an overt FL, 1 patient that developed a full-blown FL after 15 months from the initial diagnosis of *in situ* FL, and 5 patients associated with lymphoproliferative disorders other than FL [6]. Moreover, specific risk factors for disease progression are currently unknown [7]. The diagnosis and management of these so called "precursor lesions" remain a challenge because diagnostic criteria, appropriate terminology and clinical implications are poorly defined. It is currently recommended that in the absence of an overt lymphoma a "wait-and-see" policy with a follow-up strategy reserving imaging evaluation only in the presence of disease-related symptoms or organ involvement appears to be a reasonable practice [8].

Follicular lymphoma, floral variant ("cloudy variant")

A 1.0 cm cervical lymph node specimen was resected from a 55-year-old male with diffuse lymphadenopathy. Under low magnification, the nodal architecture was completely effaced by a vaguely nodular lymphoid proliferation [Figure 2A]. Irregular multinodular proliferation displayed a cloud like [Figure 2B] or "floral-like" appearance [9]. CD20 immunostain revealed that they were all B-cells [Figure 2C]. Stain for CD10 confirmed a GC B-cell origin [Figure 2D]. Some mantle zone small B lymphocytes infiltrated into the follicles to produce a prominent inward extension inside the neoplastic GCs result-

ing in the "floral-like" follicles [9]. These nodules may also simulate progressive transformation of GCs (PTGC), and the cells may often be CD5+ [10]. In the author's opinion, the appearance of the neoplastic follicles looks more like clouds rather than flowers [Figure 2B].

The so called "floral" variant of FL features a prominent mantle zone surrounding ragged follicles with mantle zone B cells pushing into large GCs to produce the classic "floral" appearance of the follicles. Mantle zone B-cells may totally disrupt the neoplastic follicles producing a pattern of growth similar to nodular lymphocyte predominance Hodgkin lymphoma (NLPHL). Mantle zone B-cells are well defined by IgD immunostain in these cases. Follicular dendritic cell markers such as CD21, CD23, CD35, and Podoplanin D2-40 are helpful for diagnosis by revealing the expanded follicular dendritic cell meshwork. Inside the meshwork, neoplastic GC B-cells express CD10, BCL2 and BCL6, and usually lack IgD, CD43 and cyclin D1. Rarely CD5 may be expressed by neoplastic GC B-cells [11].

Follicular lymphoma with abundant eosinophilic precipitate

A 73-year-old male with supraclavicular lymphadenopathy underwent biopsy of a lymph node measuring 2.5 cm in diameter. Histology showed a portion of lymph node entirely effaced by back-to-back lymphoid follicles composed of large and small cleaved lymphoid cells, admixed with extracellular deposition of amorphous eosinophilic precipitate within the follicles [Figure 3A]. Scattered and diffuse centroblasts were identified in most portions of the specimen [Figure 3B, inlet]. The cleaved lymphoid cells and the amorphous eosinophilic precipitate were positive for CD20 [Figure 3C]. The lymphoma cells were also positive for BCL2 and CD10 [Figure 3D]. A high grade (Grade 3A/3B) follicular lymphoma with abundant amorphous eosinophilic precipitate was diagnosed.

FL with abundant eosinophilic precipitate was

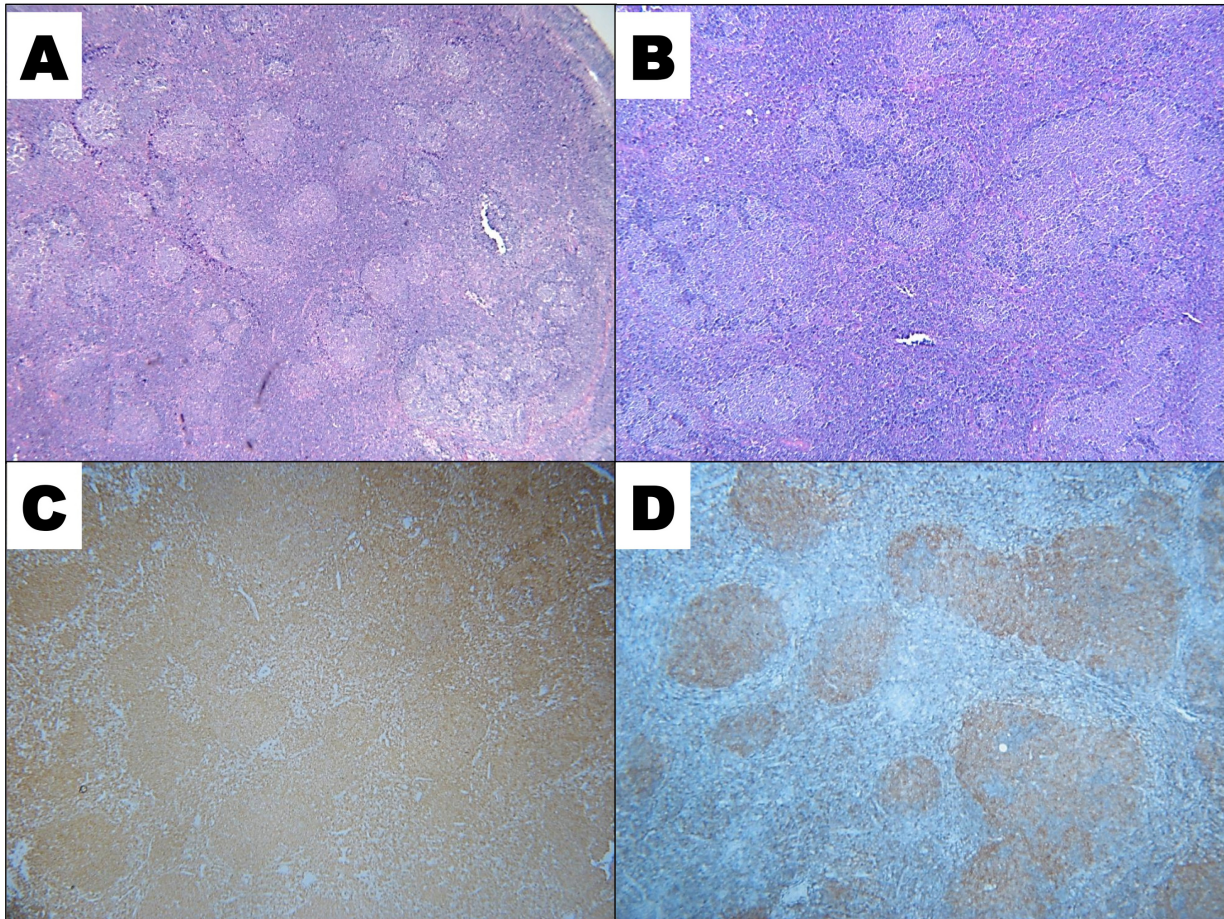


Figure 2: Follicular lymphoma, floral variant ("cloudy variant").

(A) Nodal architecture totally effaced by a vaguely nodular proliferation of lymphocytes (H&E, low magnification); (B) Irregular multinodular pattern of growth with the "cloud-like" appearance (H&E, low magnification); (C) CD20+ lymphoid follicles/nodules (IHC, low magnification); (D) CD10+ neoplastic B-cells (IHC, low magnification).

first reported by Rosas *et al.* in 1973 [12] and later described by various others [13–15]. Accumulation of amorphous, hyaline, non-amyloid substances is an occasional finding in B-cell lymphoproliferative disorders such as reactive follicular hyperplasia, follicular lymphoma, plasma cell dyscrasia, and dysimmune disorders [15]. Nevertheless, abundant extracellular PAS-positive proteinaceous material is quite rare in follicular lymphoma [13]. These deposits must be differentiated from amyloid deposits found in follicular lymphoma, and from stromal reactions variously described as hyalinosis, fibrosis, or sclerosis [16–18].

Furthermore, since a proteinaceous precipitate is often evident within the hyperplastic lymphoid follicles, an erroneous diagnosis of reactive follicular hyperplasia may be made. The differential diagnosis between reactive follicular hyperplasia and follicular lymphoma has in the past been of great concern to pathologists. This problem may be aggravated by the presence of abundant proteinaceous material in the nodules of follicular lymphomas. With well-defined histopathologic criteria, immunohistochemistry, flow cytometry, and molecular studies, this problem can be easily solved. However, when the number of malignant atypical follicular center

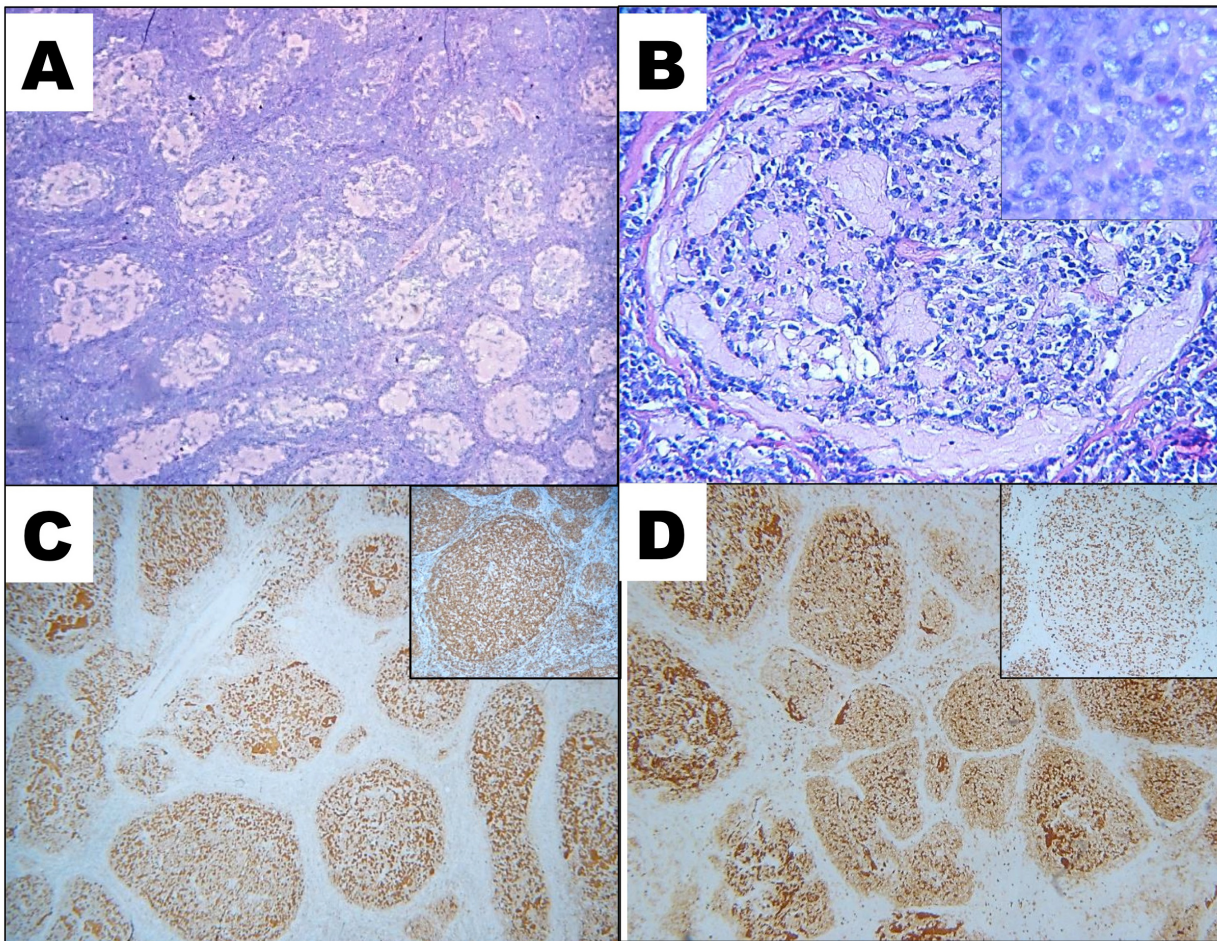


Figure 3: Follicular lymphoma with abundant amorphous eosinophilic precipitate.

(A) Nodal architecture totally effaced by many back-to-back lymphoid nodules with abundant extracellular amorphous eosinophilic precipitate (H&E, low magnification); (B) Medium magnification reveals a neoplastic follicle loaded with extracellular eosinophilic precipitates (H&E); inset, large centroblasts (H&E, high magnification); (C) Strong CD20 expression in the neoplastic lymphoid follicles (IHC, low magnification); inset, strong BCL2 expression (IHC, low magnification); (D) Strong CD10 expression in neoplastic follicles; inset, Ki67/MIB1 stain shows a high proliferation index (IHC, low magnification).

cells is reduced by the extracellular accumulation of abundant PAS-positive materials [15], FLs can potentially be interpreted incorrectly as benign lesions.

All the reported FLs with abundant eosinophilic precipitate show a total effacement of the nodal architecture by numerous neoplastic nodules/follicles. In these previously reported cases, there were 6-15 centroblasts/hpf, which corresponds to Grade 2 by "Berard criteria" [19]. On H&E stained sections,

many follicles contained amorphous eosinophilic extracellular material. This material was PAS-positive and diastase-resistant, and was negative for Congo red. Interestingly, the amorphous extracellular material was also positive for CD20 suggesting that the material may be remnants of B-cell membranes. As early as in 1973, Dorfman had already noted that nodular lymphomas contained PAS-positive amorphous eosinophilic material that appeared blue with

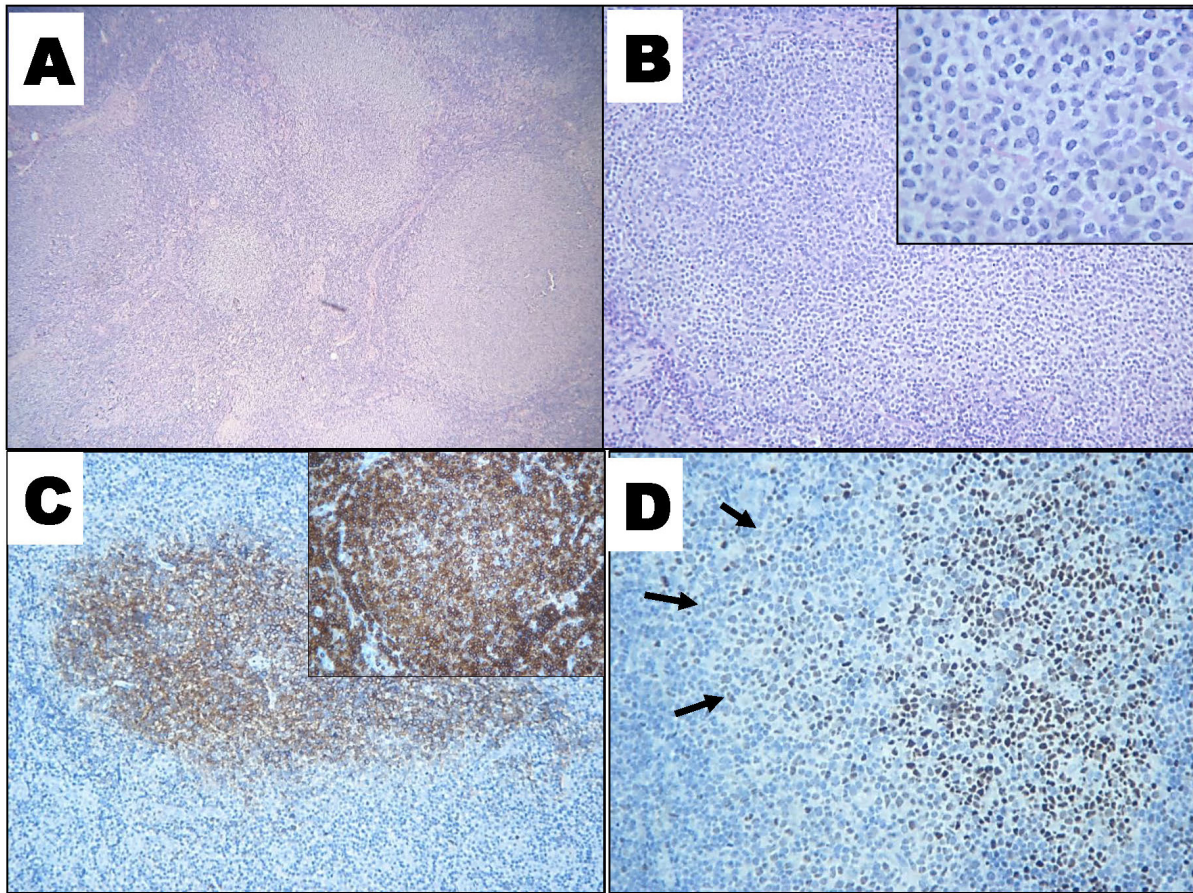


Figure 4: Follicular lymphoma with marginal zone differentiation.

(A) Nodal architecture totally effaced by a multinodular pattern of proliferation (H&E, low magnification); (B) Neoplastic follicles surrounded by broad bands of pale neoplastic component (H&E, medium magnification); inset, monocytoid cells with abundant clear cytoplasm, small cleaved nuclei, clumped chromatin, and inconspicuous nucleoli (H&E, high magnification); (C) Strong CD10 expression in follicular cells, but negative in perifollicular monocytoid B cells (IHC, medium magnification); inset, BCL2+ neoplastic GC B-cells (IHC, medium magnification); (D) Weak nuclear stain for BCL6 in perifollicular monocytoid B-cells (indicated by arrows) revealing their GC origin (IHC, medium magnification).

Masson trichrome stain [20]. Based on ultrastructural studies this material however did not appear to be collagen, but rather be accumulated membranous structures. Our case showed similar histological and immunophenotypic findings to those of the previously reported FLs with abundant eosinophilic precipitate, with the only difference being higher grade cytology.

Follicular lymphoma with marginal zone differentiation

A right neck lymph node was resected from a 74-year-old male patient. Under low magnification, the nodal architecture was completely effaced by a multinodular pattern of lymphoid proliferation [Figure 4A]. Under medium power, the neoplastic follicles were surrounded by broad bands of pale neoplastic components. High magnification showed

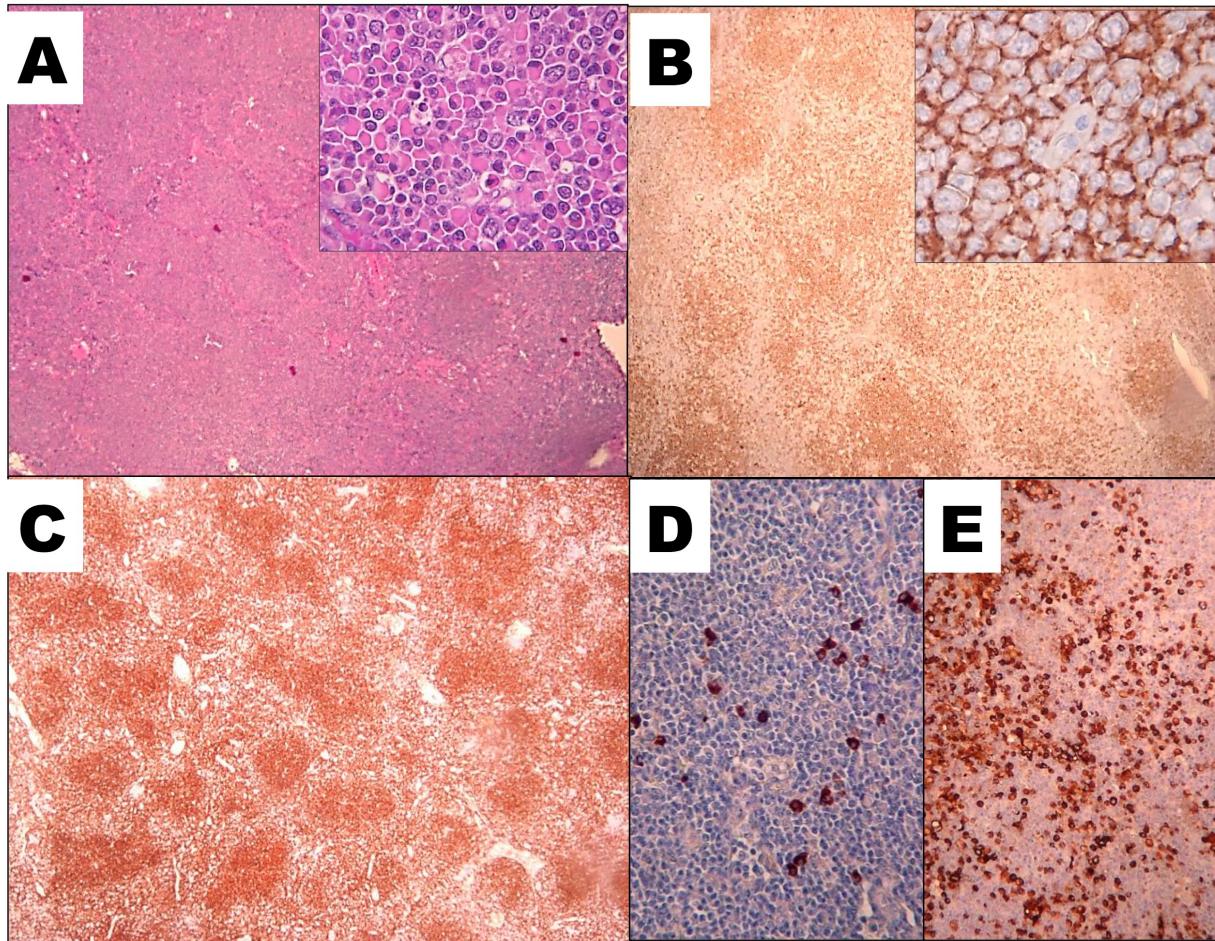


Figure 5: Follicular lymphoma with plasmacytic differentiation.

(A) Nodal architecture totally effaced by a multinodular (follicular) pattern of growth (H&E, low magnification); inlet, centroblasts and striking plasma cell differentiation (H&E, high magnification); (B) CD20-positive lymphoma cells (IHC, low magnification); inlet, high magnification (IHC); (C) CD10-positive lymphoma cells (IHC, low magnification); (D) Kappa-negative lymphoma cells (IHC, medium magnification); (E) Lambda-positive lymphoma cells (IHC, medium magnification).

that the pale neoplastic cells had abundant clear cytoplasm, round and cleaved nuclei with clumped chromatin, and inconspicuous nucleoli, consistent with monocytoid B-cells [Figure 4B]. The lymphoid follicles were positive for CD20, CD10 and BCL2, but the perifollicular monocytoid B-cells were CD10 negative [Figure 4C]; BCL6 was variably expressed by perifollicular monocytoid B-cells; some follicles showed high grade cytology (Grade 3A). Ki-67/MIB-1 immunostain revealed a high proliferation index

[Figure 4D]. The strong expression of BCL2 and CD10 revealed the neoplastic nature of the lymphoid follicles, thus it represented a low grade follicular lymphoma with marginal zone differentiation and focal (5-10%) Grade 3A lesion.

Differentiating nodal marginal zone lymphoma (NMZL) from FL is not always straightforward [21]. In particular, differential diagnosis between FL with marginal zone differentiation (occurring about in 8% of FL cases) and NMZL with prominent follicu-

lar colonization can be difficult, especially in cases whose morphologies and immunophenotypes are ambiguous [22]. Fortunately, GC B-cell markers such as CD10 and BCL6 are usually expressed by the neoplastic marginal zone monocytoid B-cells, although sometimes they can lack CD10 (as in this case). In fact, the three markers routinely used in the diagnosis of FL, CD10, BCL2 and BCL6, could show variable expression and are often diminished or absent in the interfollicular and diffuse components of FL.

It is well documented that the monocytoid B-cells in FL with marginal zone differentiation are clonally related to the GC B-cells [23]. Some studies showed a common clonal origin for both neoplastic GC B-cells and the surrounding monocytoid B-cells [24]. It is also of interest that FL with marginal zone differentiation has been associated with specific chromosomal abnormalities including trisomy 3, an abnormality also associated with marginal zone lymphomas [25] and t(14;18) negative FL [26]. Since FISH is readily available nowadays, demonstration of the t(14;18) can be used to confirm the GC origin of a lymphoma since 85% of FLs carry this translocation.

Distinction between NMZL and FL without t(14;18) and/or lack GC markers such as CD10 and BCL6 remains controversial. Even recent gene expression profiling and comparative genomic hybridization studies [27, 28] suggest that FL without t(14;18) genetically resembles NMZL more than classical FL. Morphologic overlap exists between FL with marginal zone differentiation and marginal zone lymphomas that secondarily colonize normal follicles. Indeed, differentiating marginal zone lymphoma with colonized follicles associated with residual CD10+ GC cells from FL with marginal zone differentiation lacking CD10 and/or BCL6 can be very difficult, if it is not impossible. Furthermore, the lack of CD10 does not exclude FL, nor does its expression eliminate a marginal zone lymphoma, as CD10+ marginal zone lymphomas rarely also occur [29].

Two new markers, HGAL and LMO2, have re-

cently been used to diagnose FL, and the HGAL is particularly useful in detecting the interfollicular and diffuse components of FL [30]. HGAL was found to be specifically expressed in the cytoplasm of germinal center B-cells, but absent in mantle and marginal zone B-cells [31]. Its high specificity for GC B-cells makes it an ideal marker for the detection of GC-derived B-cell lymphomas. HGAL was expressed in the majority of FLs regardless of grade (88-97%). In addition, all cases that lacked CD10 and BCL2, expressed HGAL. These properties make HGAL a highly beneficial addition to a panel of immunological markers in the workup of small B-cell lymphomas, because of not only its high specificity and sensitivity for FL, but also its efficacy in detecting the interfollicular and diffuse components of FL. These findings attested HGAL as a superior marker in the diagnosis of problematic FL cases and for differentiating FL from other mimics with a follicular architecture. The second marker LMO2 was expressed in 70% of the FL cases. Although the overall sensitivity is less than that of HGAL, LMO2 as a marker is comparable to CD10 and BCL2 and superior to BCL6. Since LMO2 does not appear to be down regulated in higher grade FL or in the interfollicular and diffuse components of FL, its utility in diagnosing FL without t(14;18) and/or lack GC markers such as CD10 and BCL2 is almost comparable to that of HGAL.

The differential diagnosis between FL with marginal zone differentiation and NMZL with prominent follicular colonization remains a challenge. Detection of some residual BCL2+/BCL6+/CD10+ follicles is the proof that the tumor probably represents a FL with prominent marginal zone differentiation. On the other hand, in the absence of remnant neoplastic follicles and for those CD10-/BCL6- and t(14;18) negative cases, use of the new GC markers such as HGAL and LMO2 plus careful cytogenetic/molecular studies by FISH and or PCR analysis are needed for the correct classification of the tumor.

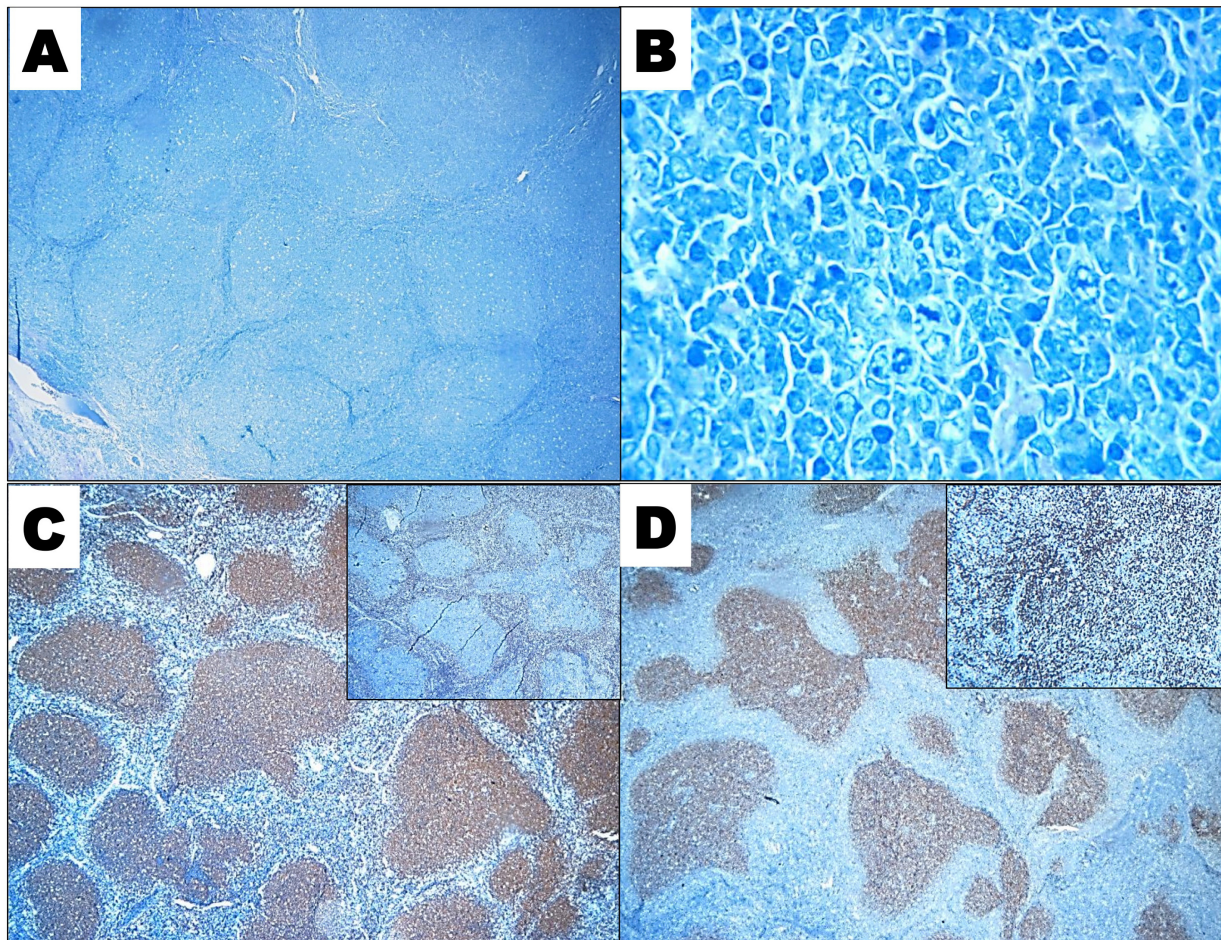


Figure 6: Follicular lymphoma, pediatric type.

(A) Nodal architecture effaced by large expansile serpinginous follicles with no polarization and attenuated mantle zone (H&E, low magnification); (B) Monotonous proliferation of medium-sized blastoid cells (H&E, high magnification); (C) Strong and diffuse expression of CD20 by the lymphoid follicles and the scattered interfollicular neoplastic B cells (IHC, low magnification); inset: lack of BCL2 expression by neoplastic follicles (IHC, low magnification); (D) Strong CD10 expression in the serpinginous follicles and reduced expression by the interfollicular neoplastic B cells (IHC, low magnification); inset: high proliferation index (90%) by Ki67/MIB1 stain (IHC, low magnification).

Follicular lymphoma with plasmacytic differentiation

A 71-year-old male with axillary lymphadenopathy was biopsied with two lymph nodes (2.5 cm and 5.5 cm in diameter) submitted to pathology. Low magnification showed a lymphoproliferation with nodular/follicular pattern [Figure 5A] and prominent invasion of perinodal fibroadipose tissue. CD23 immunostain revealed partial preservation of follicular dendritic cell meshwork. Nodular/follicular

areas were composed of predominantly small centrocytes, with focal areas having a prominent interstitial scleroialinosis. Some areas showed a very low proliferative index (by Ki67/MIB1 staining), whereas high-grade (Grade 3A/3B) and diffuse areas had a very high proliferative index (by Ki67/MIB1 staining). GC markers such as CD10 [Figure 5C] and BCL6 were expressed as well as BCL2. Inside some follicles and in most interfollicular areas, neoplastic

B-cells showed striking plasmacytic differentiation [Figure 5A & 5B, inlets] as demonstrated by strong lambda light chain restriction [Figure 5D & 5E].

Plasmacytic differentiation is the second most common type of maturation seen in a variety of B-cell lymphomas. It is well recognized that the neoplastic GC B-cells, like their normal counterparts, may show post GC maturation into memory B-cells and plasma cells [32–35]. Nevertheless, plasma cell differentiation is only rarely seen in FL presumably due to blocked differentiation. Plasmacytic differentiation or significant immunoglobulin production occurring in FL would correspond to what happens in reactive GCs after antigen stimulation. To date, FLs with plasmacytic differentiation have been reported in about 3% of the FL cases [33]. Plasma cells were most frequently found in the interfollicular areas while intrafollicular plasma cells were noted in only 12% of the FLs with plasmacytic differentiation. Nonetheless, plasma cells may have both interfollicular and identifiable intrafollicular distribution. The neoplastic components with striking plasmacytic differentiation generally show features of mature plasma cells and express markers such as CD38, CD138, and IRF4/MUM1. The surgical pathologists/hematopathologists should be aware of this fact and not misinterpret the findings as a plasma cell neoplasm, lymphoplasmacytic lymphoma or marginal zone lymphoma with plasmacytic differentiation. Indeed, marginal zone lymphoma with plasmacytic differentiation and prominent follicular colonization can easily be confused with FL with striking plasmacytic differentiation. Moreover, high-grade FL with plasmacytic differentiation could also be confused with diffuse large B-cell lymphoma with plasmacytic differentiation.

The centrocytic/centroblastic and plasmacytic components of FL with plasmacytic differentiation are clonally related and frequently carry the BCL2 gene rearrangement [34]. Furthermore, none of the abnormalities associated with marginal zone lymphomas (such as trisomy 3, MALT1 translocation or trisomy 18) have been identified in the FL with plas-

matic differentiation, supporting the notion that these FLs with plasmacytic differentiation are truly different from those marginal zone lymphomas with plasmacytic differentiation and prominent follicular colonization. The presence of significant plasmacytic differentiation in a FL may have clinical implications such as increased incidence of para-proteins, association with peripheral blood absolute lymphocytosis [35] and a higher clinical stage.

Follicular lymphoma, pediatric type

A 2.5 cm lymph node was resected from a 19-year-old pregnant woman with left cervical lymphadenopathy. Whole body computerized tomography (CT) scan and bone marrow biopsy were negative. Serial sections of the node revealed a multinodular cut surface. The H&E sections showed that the nodal architecture was effaced by large expansile serpiginous follicles [Figure 6A]; confluent follicles with starry-sky pattern, attenuated mantle zone, and no polarization. High magnification showed proliferation of monotonous medium-sized blastoid cells [Figure 6B]. The neoplastic lymphoid follicles were CD20+, CD10+, and BCL6+, but were negative for BCL2 by immunohistochemistry [Figure 6C]. Some interfollicular B-cells also weakly expressed CD10 and BCL6 [Figure 6D]. Proliferation index of the neoplastic cells was approximately 90% by Ki67/MIB-1 staining. FISH studies were negative for t(14;18) (*IGH-BCL2*) and *BCL6* gene rearrangement. Molecular studies revealed either the *IGH* gene rearrangement or the immunoglobulin kappa light chain restriction. All the clinical, morphological, immunophenotypic and molecular/cytogenetic findings were consistent with a follicular lymphoma, pediatric type (WHO Classification). The patient was managed conservatively without any treatment.

The 2008 WHO Classification recognizes a distinctive variant of FL mainly seen in children and young adults [36, 37]. Pediatric FL is biologically and clinically distinct from conventional FL. It differs from the adult counterpart morphologically, immunophe-

Table 2: Diagnostic criteria for pediatric follicular lymphoma*

1. Expansile, serpiginous and/or confluent follicles with a starry-sky pattern, absence of polarization and attenuated mantle zone; sometimes nodal tissue gives the appearance of "a node within a node";
2. High-grade (grade 3) cytology with "blastoid" cells;
3. High proliferation index by Ki67/MIB1 immunostain;
4. Lack of BCL2 expression and t(14;18)(q32;q21).

*: Reference [37].

notypically and genetically, and is usually an indolent disease, presenting most often as an isolated cervical lymphadenopathy in the head and neck region [38]. Axillary and/or inguinal adenopathy may also be found. Nodal architecture is often totally effaced by expansile, serpiginous and confluent follicles with a starry-sky pattern due to the many scattered tingible-body macrophages inside the follicles, mimicking florid follicular hyperplasia without polarization. The mantle zone is usually thin and attenuated. Follicles are composed of a population of atypical medium-sized to large centroblasts with "blastoid", high grade cytology and high proliferation index (by Ki67/MIB1 staining). Typical centrocytes and centroblasts may be present or quite rare. Grading is usually not required in contrast to its adult counterpart. Neoplastic cells express GC markers such as CD10 and BCL6, while BCL2 expression is typically negative and the neoplasm does not have the t(14;18)(*IGH-BCL2*). Overlap with florid follicular hyperplasia remains a practical problem, as pediatric FL lacks specific immunophenotype and genetic aberrations. PCR for *IGH/IGK/IGL* gene rearrangements is strongly recommended in the work up for diagnosing pediatric FL, although clonality alone should not be used to distinguish "atypical" florid follicular hyperplasia from lymphoma. In fact, whether some cases of pediatric FL may represent limited clonal expansion in florid follicular hyperplasia is still under much debate [39]. In another word, whether these "pediatric FL" are truly malignant or actually represent a "benign" clonal proliferation with low malignant potential remains a question. Because of these, strict criteria must be followed in the diagnosis of pediatric FL (Table 2). Cases with

similar characteristics may occasionally be seen in the young adult patients [40]. On the other hand, not all cases of FL in children are pediatric FL.

Conclusion

I have presented several rare faces of FL. Due to the morphological variations and overlapping features with other lymphoproliferative diseases, they pose a challenge to practicing surgical pathologists and hematopathologists in their diagnosis of lymph nodes. Although some of the differential diagnostic criteria remain controversial, familiarity with these patterns of variation will lead to better diagnosis of FLs and more favorable clinical outcome for patients.

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