Article

The many rare faces of follicular lymphoma - Part 2

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Abstract: Follicular lymphoma (FL), a well defined mature B-cell lymphoma, rarely presents with great morphological variations that could mimic either other malignancies or disguise themselves with only subtle neoplastic feature. In the second part of this series, we present more FL morphologic variants, including FL with signet ring cells, FL with HRS-like cells, FL with anaplastic/pleomorphic cells, FL with sclerosis, FL microlymphoma, FL with prominent sinus histiocytosis, and FL neurolymphomatosis. Although uncommon, some of these FL variants pose diagnostic pitfalls for the practicing pathologists.

Keywords: Follicular lymphoma; morphologic variants; neurolymphomatosis; diagnostic pitfalls

Introduction

Follicular lymphoma (FL) is a mature B-cell lymphoma of germinal center origin, characterized by overexpression of CD10, BCL2 and BCL6 in the lymphoma cells. In the last paper, the author had described 6 rare morphologic variants of FL [1]. In this paper, we will continue to illustrate several morphologic variations of FL that can be easily missed or wrongly diagnosed. Surgical pathologists with special interest in lymph node patholoy and hematopathologists should be aware of these quite rare faces of FL to avoid diagnostic pitfalls.

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Materials and Methods

With approval of the Institutional Review Boards of St. Eugenio Hospital, Rome, Italy and of University of California San Diego (UCSD)/VA San Diego Healthcare System (VASDHS), San Diego, California, USA, FL cases were retrieved from the archives of the Department of Pathology, St. Eugenio Hospital and the Pathology and Laboratory Medicine Service, UCSD/VASDHS. Fresh lymph node specimens were fixed in 10% formalin fixatives and paraffin embedded before being sectioned at 3 μm in thickness. Hematoxylin-eosin (H&E) stains were routinely performed on either a ST5010 Autostainer XL (Leica, Milano, Italy) or a Ventana Symphony H&E Slide Stainer (Ventana, Tuscon, AZ). Immunohistochemical stains were performed on either Dako Omnis stainer (Dako, Denmark) or Ventana BenchMark automated stainer (Ventana, Tuscon, AZ) using antibodies against AE1/3, BCL2, BCL6, BOB1, CD3, CD10, CD15, CD20, CD23, CD30, CD45, CD79a, cyclin D1, Ki-67, MUM1, OCT2, PAX5, and S100 (Dako, Denmark & Ventana, Tuscon, AZ). Six-color flow cy-

tometry was also performed on a BD FACSCanto™ II (BD Biosciences, San Jose, CA) at the VASDHS with all the fluorochrome conjugated BD antibodies. All the stains were performed with appropriate positive and negative controls.

Results and Discussion

FL with signet ring cells

A lymph node was biopsied from a 68-year-old male with retroperitoneal lymphadenopathy. The histological sections showed portions of lymph node with nodular and diffuse proliferation of small centrocytes admixed with numerous large centroblasts with peripherally located nuclei, irregular nuclear contour, and vesicular chromatin [Figure 1A, B]. The nuclei were indented by centrally located large cytoplasmic vacuoles, consistent with the so called signet-ring cells. By immunohistochemistry, all these cells were positive for CD20 and the markers of germinal center origin, CD10 and BCL6 [Figure 1C]. BCL2, as well as IRF4/MUM1 and CD30, was expressed by only a subset of neoplastic cells. Aberrant expression of CD23 was detected in the lymphoma cells [Figure 1D] with cytoplasmic immunoglobulin lambda light chain restriction [Figure 1E, F]. Proliferation index as assessed by Ki67/MIB1 staining was approximately 80-90% in the diffuse centroblast rich areas. The neoplastic cells were negative for AE1/AE3 and S100. A diagnosis of diffuse large B-cell lymphoma (30%)/grade 3A FL (50%) with unusually large number of signet ring cells arising from a low-grade FL (20%) was made.

Signet ring cell lymphoma is a rare morphologic variant of non-Hodgkin lymphoma composed of cells with a "signet ring" appearance. It has been described in B-cell lymphomas, most often as a variant of FL, as well as in T-cell lymphomas.

The term "signet-ring cell lymphoma" was introduced by Kim, *et al*. in 1978, to characterize a FL with clear cytoplasmic vacuoles that resembles mucin-producing signet-ring carcinomas [2]. Since then, the majority of the reported cases were low-grade B-cell lymphomas, such as FL, marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL) and small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), with signet-ring cells [3–6]. Rare diffuse large B-cell lymphoma (DLBCL) also showed signet-ring cells [7]. So did anaplastic large-cell lymphoma (ALCL) [8].

Unfortunately, signet-ring cell differentiation is more frequently observed in many non-lymphoid malignancies. In fact, time and time again identification of signet-ring cells on histologic section immediately prompted a diagnosis of poorly differentiated adenocarcinoma. Nevertheless, other malignant tumors such as liposarcoma, malignant melanoma, mesothelioma, may show signet-ring cell differentiation as well [9]. Even benign lesions, such as florid nodal histiocytic reaction and extreme foreign-body inflammatory response against silicon (silicon lymphadenopathy) and polivinilpirrolydone, may assume signet-ring cell morphology [10]. Therefore, signet-ring cell differentiation in lymphomas represents a diagnostic pitfall and challenge that may lead to extensive immunohistochemical workups.

Using immunohistochemistry some investigators demonstrated the presence of immunoglobulins within the vacuolar contents of the signet ring cells in the reported FL cases [11, 12]. The immunoglobulins were usually confined to a narrow peripheral rim of the vacuoles. As a peculiar feature in lymphomas, signet ring cell morphology in rare FL represents an extreme example of FL with striking plasmacytic differentiation.

FL with HRS-like cells

From a 45-year-old male with para-esophageal mass were harvested four fragments of lymph nodes, measuring 1.0 to 2.6 cm in diameter. The H&E sections showed a vaguely nodular and focally diffuse (absence of follicular-dendritic meshwork as demonstrated by CD21/CD23 staining) lymphoid proliferation [Figure 2A]. Medium and high magnification re-

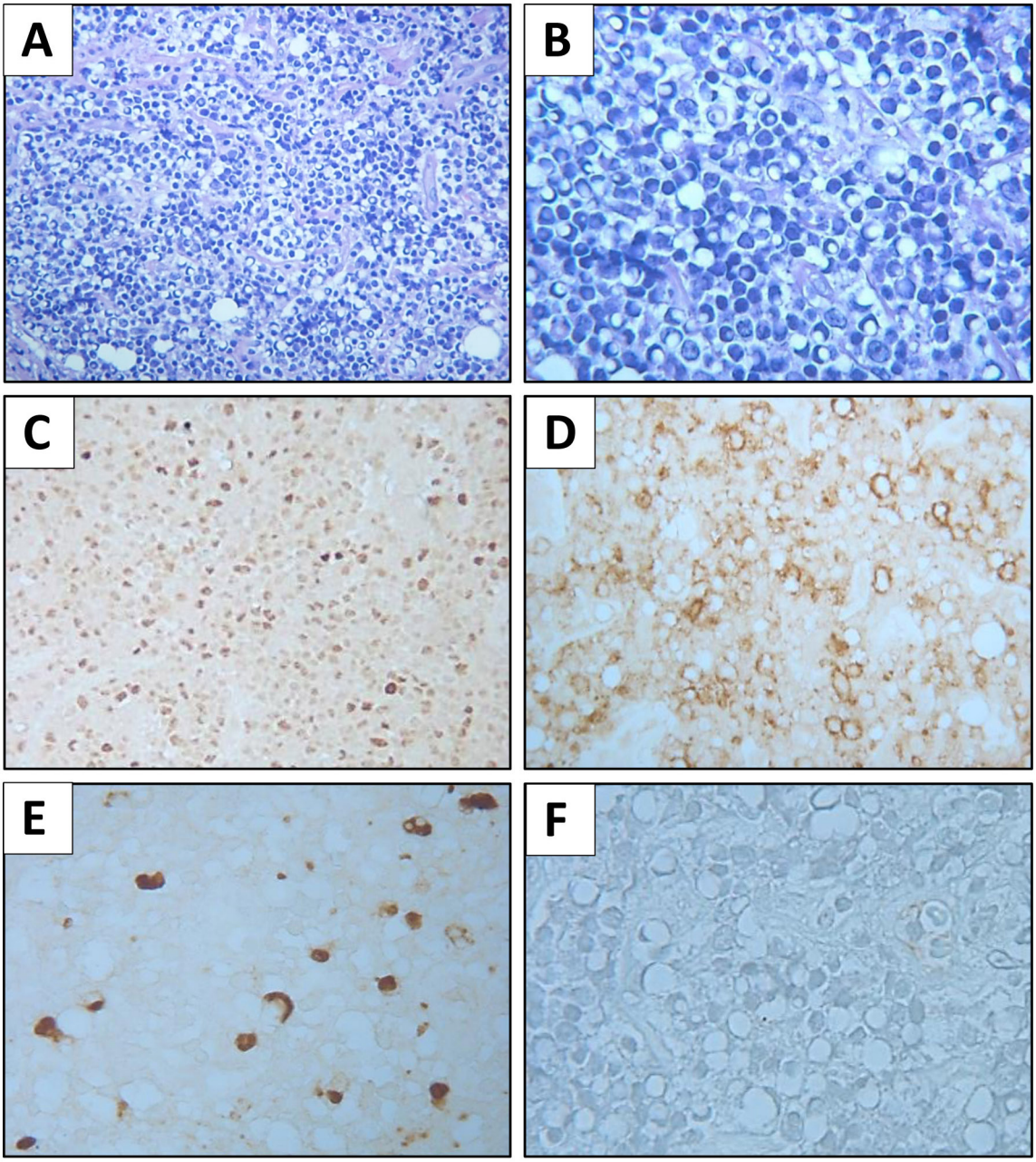

Figure 1: Follicular lymphoma with signet-ring cells. (A) A totally effaced lymph node shows neoplastic nodules composed of small cells with clear cytoplasmic vacuoles (H&E, original magnification x200); (B) High magnification shows prominent signet-ring cell morphology (H&E, original magnification x400); The large "signet-ring" cells are (C) BCL6+, (D) CD23+, (E) positive for immunoglobulin light chain kappa, but (F) negative for immunoglobulin light chain lambda (IHC, original magnification x400).

vealed a population of small centrocytes intermixed with scattered large cells that were morphologically similar to Hodgkin-Reed-Sternberg (HRS) cells [Figure 2B]. These large atypical cells demonstrated ho-

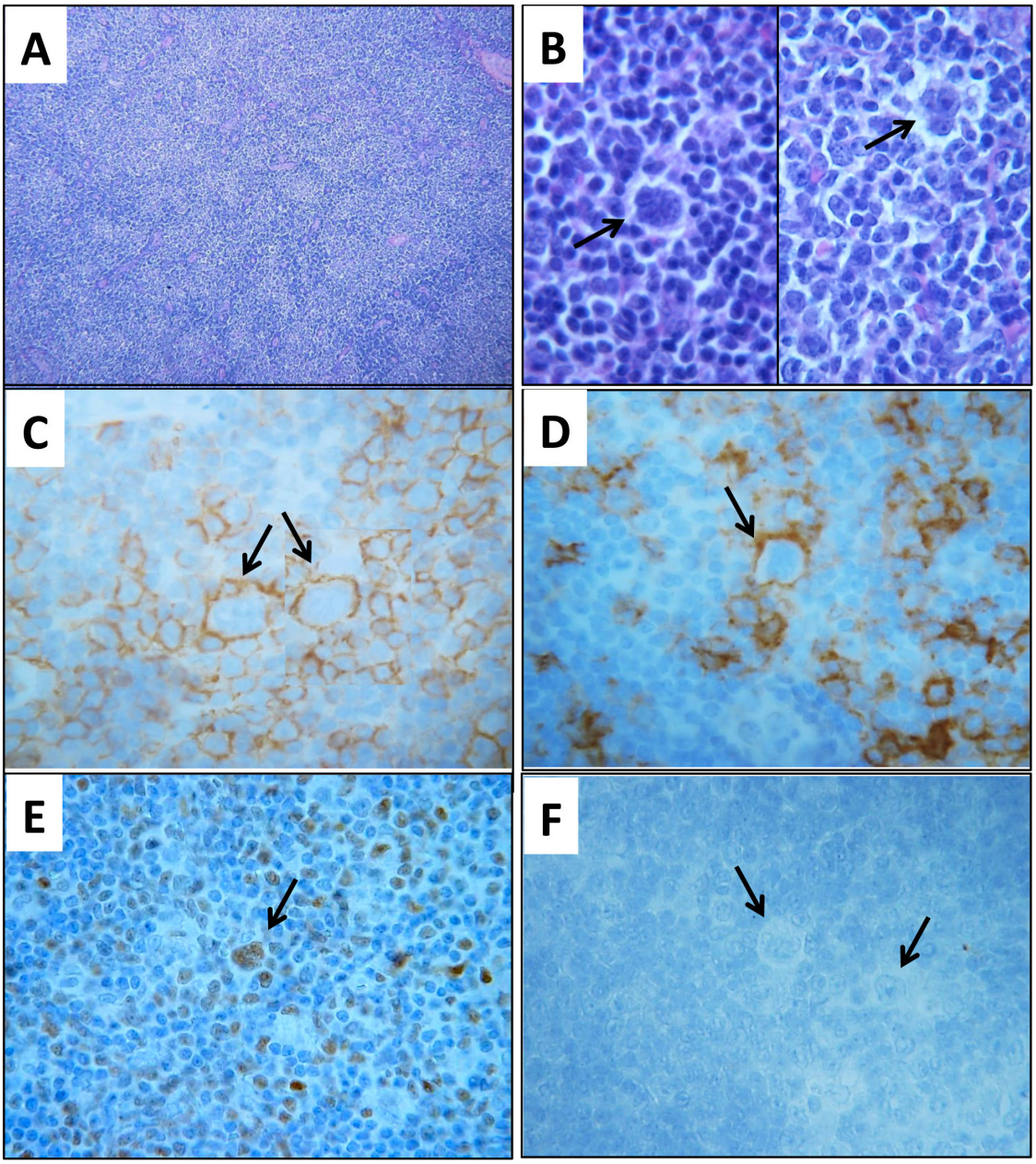

Figure 2: Follicular lymphoma with HRS-like cells. (A) Nodal architecture was totally effaced by vague lymphoid nodules (H&E, original magnification x20); (B) High power shows rare large neoplastic cells with multilobated nuclei and prominent nucleoli (HRS-like cells) (H&E, original magnification x400). The HRS-like cells are CD20+ (C), CD10+ (D), and BCL6+ (E), but negative for CD30 (F) (IHC, original magnification x400).

mogenous expression of CD20, CD10, BCL2, and BCL6, but were negative for CD30 [Figure 2C-F]. This immunophenotype supported a diagnosis of FL, grade 2, predominantly diffuse pattern, with "HRS-like" cells.

Rare cases of low-grade B-cell lymphomas and T-

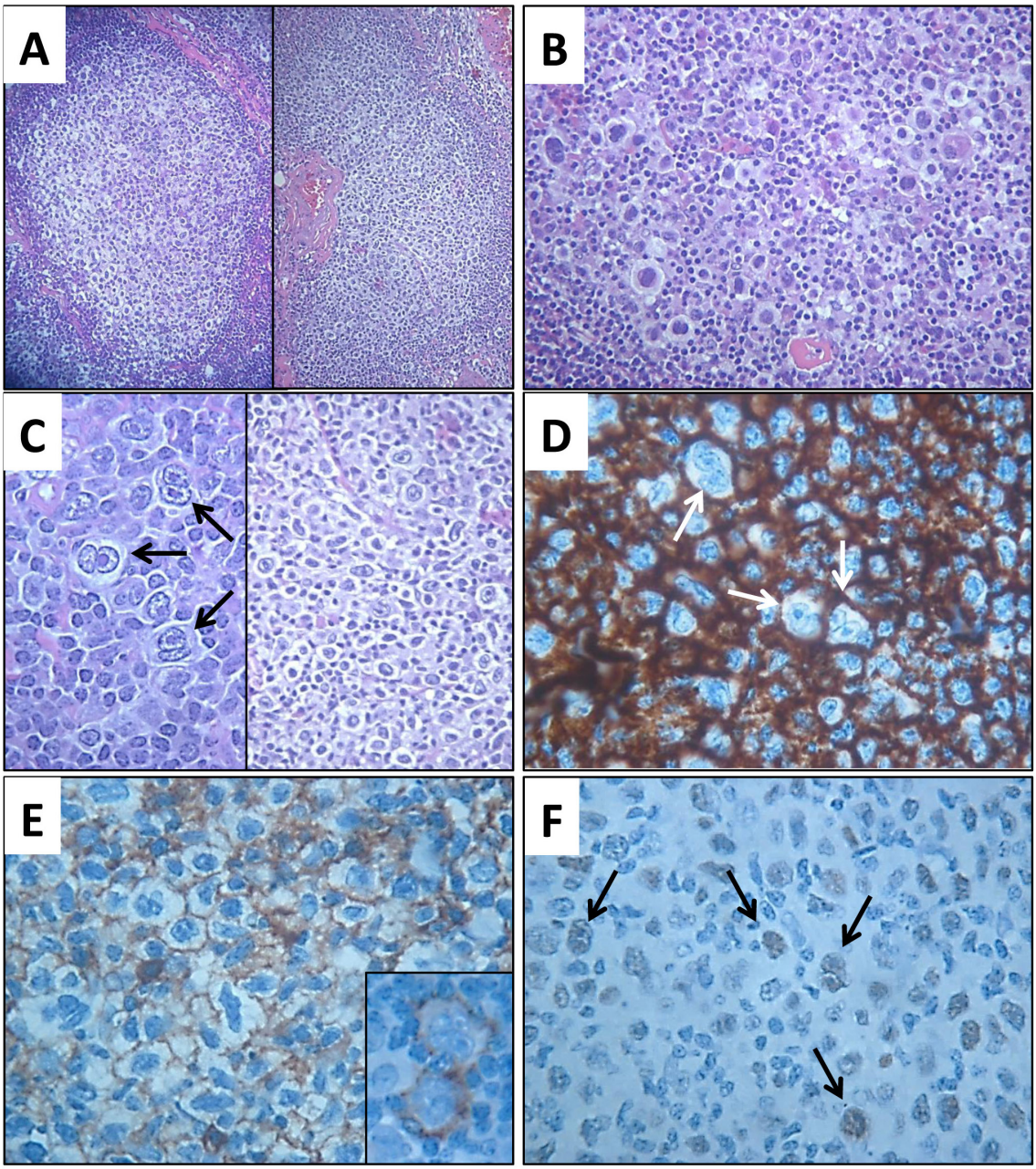

Figure 3: Follicular lymphoma with clear anaplastic/pleomorphic cells. (A) Two neoplastic follicles composed of numerous large cells with abundant clear cytoplasm (H&E, original magnification x100); (B) Higher power shows the large anaplastic/pleomorphic clear cells (H&E, original magnification x200); (C) Scattered large anaplastic cells (indicated by arrows) (left, H&E, original magnification x400) and immunoblast-like clear cells (right, H&E, original magnification x400). The large anaplastic cells were CD20+ (D), CD10+ (E), and BCL6+ (F) (IHC, original magnification x400).

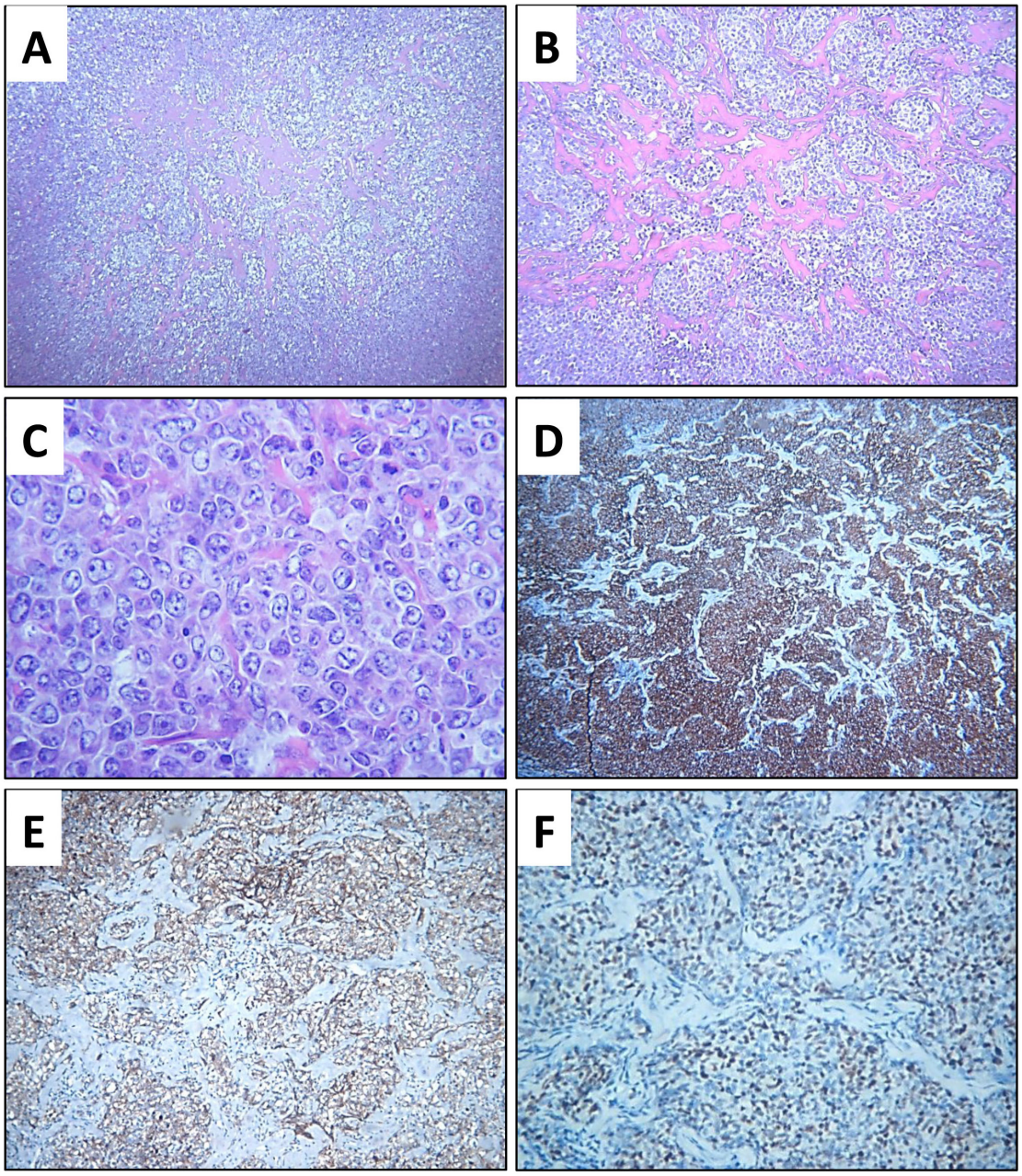

Figure 4: Follicular lymphoma with prominent sclerosis. (A) Nodal architecture was totally effaced by proliferation of predominantly small lymphoid cells in a background of prominent interstitial sclerosis (H&E, original magnification x20); (B) Histology shows the eosinophilic collagenous fibrosis under the medium power (H&E, original magnification x40); (C) Diffuse areas were composed of atypical large centroblasts (H&E, original magnification x400). The neoplastic cells are CD20+ (D), CD10+ (E), and BCL6+ (F) (IHC, original magnification x100).

cell lymphomas may occasionally show the presence of scattered large atypical cells that may resemble the HRS cells. Low-grade B-cell lymphomas with "HRS-like" cells may include CLL, MZL and FL [13]. In

the setting of FL, the so called "HRS-like" cells may be detected within the neoplastic follicles and/or between them. Furthermore, these cells can be few or numerous. Unlike CLL, these "HRS-like" cells in FL are negative for Epstein-Barr virus (EBV) by *in situ* hybridization (EBER). In FL, the "HRS-like" cells are usually positive for CD45, CD20, CD79a, PAX5 (strong nuclear stain), BCL2, CD10 and BCL6, although in some cases CD10 can be negative. Furthermore, CD30 may be variably expressed by the "HRS-like" cells, while CD15 is often negative. Despite this, CD15 may rarely be expressed by the "HRS-like" cells; then a differential diagnosis of composite lymphoma or classical Hodgkin lymphoma (cHL) transformed from FL [14] should be carefully considered, especially when "HRS-like" cells are numerous. A large panel of immunostains is warranted that include CD45, B-cell markers (PAX5, CD79a, and CD20), germinal-center markers (CD10 and BCL6), BOB1, OCT2, CD30, IRF4/MUM1, and Fascin. It is important to be aware that concomitant expression of BCL6 and CD10 has never been found in true HRS cells and that these two markers may be used as convincing evidence to support the germinal center origin of the "HRS-like" cells [13].

When grading FL, the "HRS-like" cells have to be counted as centroblasts. From a molecular point of view, it has been shown that "HRS-like" cells have identical immunoglobulin heavy chain gene rearrangement to those of the neoplastic centrocytes and centroblasts, suggesting a common cell origin in spite of their distinct morphology [15].

FL with anaplastic/pleomorphic clear cells

Two lymph nodes, measuring 2.7 and 1.5 cm in diameter, were resected from the right neck of a 72-year-old female. Histology revealed portions of lymph node completely effaced by numerous back-to-back follicles composed of predominantly large atypical cells [Figure 3A], which had abundant clear cytoplasm, lobated nuclei, vescicular chromatin and prominent nucleoli (immunoblast-like) admixed with many large cells with anaplastic/pleomorphic nuclei [Figure 3B, C]. The immunoblast-like cells were CD10+, CD20+, BCL2+, and BCL6+ [Figure 3D-F], whereas the large anaplastic/pleomorphic cells were BCL6+ while CD10 was downregulated or absent. Furthermore, the large anaplastic/pleomorphic cells were negative for IRF4/MUM1 and showed a variable expression of BCL2. A subset of these large anaplastic/pleomorphic cells was positive for CD30, but negative for CD15. Many immunoblast-like lymphoma cells were also present in the interfollicular area, which might represent early DLBCL arising from FL grade 3B.

This case represents a very rare FL composed of entirely large cells with clear cytoplasm and with either immunoblast-like or anaplastic/pleomorphic nuclei. Such an anaplastic/pleomorphic "clear cell variant" of FL has not yet been reported in the literature.

Sclerosing variant of FL

A 2.2 cm left cervical lymph node was resected from a 62-year-old female patient. Histology revealed portions of lymph node completely effaced by a vaguely nodular and diffuse lymphoid infiltration in a background of prominent sclerosis, compartmentalizing and anastomosing hyalinized collagenous bands (fibrosis) separating the tumor cells into clusters [Figure 4A]. Bands of sclerosis extended from within the node to the nodal capsule [Figure 4B]. The clusters of neoplastic cells were composed of large atypical centroblasts [Figure 4C] that were CD20+, CD10+, BCL6+, IRF4/MUM1+, but were negative for BCL2, CD5, and cyclin D1 [Figure 4D-F]. Proliferation index by Ki67/MIB1 staining was approximately 90%. This lesion was finally diagnosed as DLBCL (20%) and FL, grade 3B (80%), with interanastomosing and compartmentalizing sclerosis.

This case represents an example of the so called sclerosing variant of FL. Likewise some degree of interstitial eosinophilic scleroialinosis is quite common, in particular for those FL arising in retroperitoneum

[16]. In 1975, Bennet concluded that nodular sclerotic lymphosarcoma was a clinicopathologic variant of the lymphomas of follicular center cell origin [17]. As a matter of fact, it now seems probable that extensive sclerosis is essentially confined to FL rather than other low-grade B-cell lymphomas. Although the majority of sclerosing variant of FL occur in retroperitoneal (periaortic), mediastinal, or inguinal lymph nodes, it can present in any lymph nodes and rarely even extranodal sites [18]. However, prominent fibrosis and scleroialinosis are rare in peripheral lymph nodes. Nodal fibrosis usually presents with two patterns. The first pattern shows marked sclerosis composed of broad interanastomosing and compartmentalizing collagenous bands which partially separate lobules of the lymphomatous infiltrate. Under low power, the morphology resembles that of cHL nodular sclerosis subtype. The second pattern displays delicate hyalinized, compartmentalizing collagenous bands concurrent with depletion of lymphoid cells which appear dispersed like the so-called "indian files" (in breast pathology) among the interstitial fibrosis.

Differential diagnosis of sclerosing FL may be challenging, since it histologically also mimics the idiopathic retroperitoneal fibrosis [19, 20]. The cellular infiltrates in idiopathic retroperitoneal fibrosis are, however, polymorphic with collections of eosinophils, plasma cells and mature lymphocytes dispersed in bland collagenous tissue with small foci of fibroblastic proliferation. Attention to cytologic details of small cleaved centrocytes and large centroblasts, careful immunohistochemistry workup for CD20, CD10, BCL2, and BCL6, and evaluation of proliferation index by Ki67/MIB1 staining should easily differentiate this process from sclerosing FL. Furthermore, presence of broad collagenous band formation may resemble the nodular sclerosis cHL. The large HRS cells and polymorphic inflammatory infiltrates in cHL, together with the immunohistochemical stains for CD45, CD30, CD15, IRF4/MUM1, PAX5, Fascin and EBER should provide adequate grounds for differential diagnosis.

We should be aware that peripheral T-cell lymphomas (PTCL) may also exhibit a collagenous compartmentalization of the lymphomatous infiltrates, similar to that of sclerosing FL [21]. However, the collagenous bands are usually more delicate in T-cell lymphomas and are associated with proliferation of post-capillary venules which are absent in the sclerosing FL. Careful immunostains for T-cell markers should be able to differentiate these two diseases. Sometimes fibrosis in FL may be associated with prominent spindle cells proliferation with myofibroblastic differentiation, mimicking inflammatory pseudotumor of the lymph node [22]. Furthermore, the authors' experience suggests that whenever examining a nodal inflammatory peudotumor-like lesion, we should always consider excluding a syphilis infection by immunohistochemistry or Warthin-Starry stain.

FL associated with prominent sinus histiocytosis

Left cervical lymph node biopsy from an 81-year-old male harvested two lymph nodes measuring 1.5 and 1.3 cm, respectively, in its largest dimension. The patient had mediastinal and extensive peripheral lymphadenopathy and hypercalcemia. H&E sections of the lymph nodes showed numerous lymphoid follicles of varying sizes and prominent sinus histiocytosis in the medulla [Figure 5A]. Flow cytometry was noncontributory due to nonspecific staining of kappa and lambda light chains. Although the lymphoid follicles did not completely lose the mantle zone, polarization and reactive tingible body macrophages were absent [Figure 5B]. Instead, scattered large centroblasts averaged >16/hpf; some were focally infiltrating the interfollicular area and became confluent. They were positive for CD20, PAX5, and weakly positive for CD10 and BCL2 [Figure 5C-F]. A high-grade (grade 3) FL was diagnosed.

The numerous variably sized lymphoid follicles and prominent reactive sinus histiocytosis gave a first impression of reactive follicular hyperplasia, particularly with a noncontributory flow cytometry

result. Reactive sinus histiocytosis associated with FL is extremely rare. Only two cases of sinus histiocytosis with massive lymphadenopathy associated with FL have been reported thus far [23–25], but no emperipolesis was seen in this case. Although it can be difficult to distinguish follicular hyperplasia and high grade FL when numerous tingible body macrophages are present, flow cytometry result is inconclusive and/or the neoplastic lymphoid follicles are negative for BCL2, careful examination of the follicular polarization, the centroblasts and their distribution, and the B cell population that cannot be accounted for by polytypic kappa and lambda expressions all lead to a conclusion of a high grade FL.

Micro lymphoma in a lipoma

A 68-year-old male with chronic cholecystitis admitted for surgery was incidentally found to have mesenteric lymphadenopathy by CT. FNA of his lymph node showed a clonal CD10+ small B-cell population by flow cytometry. During his laparoscopic cholecystectomy, a "lymph node" was biopsied which measured 3.5 x 2.5 x 0.4 cm and showed a tan-yellow cut surface. Histology revealed a lipoma with focal lymphoid tissues measuring 0.3 cm in the largest dimension [Figure 6A-C]. There were several lymphoid follicles which are CD20+, CD10+, and BCL2+ by immunohistochemistry. Flow cytometry of the lymphoid tissue revealed a small population of CD10+ and surface immunoglobulin light chain kappa-restricted B cells. A diagnosis of FL was made.

Thanks to the advancement of imaging studies incidental FL is no longer scarce, but micro involvement of a lipoma by lymphoma is extremely rare. Focal small lymphoid follicles buried in a lipoma are often seen in the lymph nodes harvested with colectomy and other surgical procedures. They often show either follicular hyperplasia and/or reactive sinus histiocytosis [26–28]. When a small focus of lymphoid follicles is present in a large fragment of fibroadipose tissue, it is often regarded as follicular hyperplasia without further investigation. Portion of this specimen was submitted to flow cytometry because of suspicion for malignant lymphoma, which detected a monotypic B-cell population. The diagnosis of FL was further confirmed by a later bone marrow biopsy that showed a small population of CD10+ monotypic B cells with the same immunoglobulin light chain restriction.

This case represents an indolent low-grade FL, stage IV, incidentally detected by CT scan and histologically confirmed in a lipoma. This example reminds us of the subtle feature and sneaky nature of some FLs. With a prepared mind, they will not be able to escape your sharp eyes.

Neurolymphomatosis

A 67-year-old male patient with a history of Hepatitis C, basal cell carcinoma, squamous cell carcinoma and low-grade B-cell lymphoma in the skin presented with reported pain and enlargement of his right breast area, skin changes and hard lump on his back. Two fragments of yellow fibroadipose tissue were resected from his right axilla. They measured 2.5 x 1.0 x 1.0 cm and 4.2 x 2.5 x 2.0 cm. Histological sections show portions of lymph node completely effaced by back-to-back lymphoid nodules, with focal infiltration to the perinodal adipose tissue and peripheral nerves [Figure 6D-F]. Some nodules were composed of small to medium-sized lymphoid cells with cleaved nuclei, loose chromatin and inconspicuous nucleoli, whereas in other areas large centroblasts predominate. Mitoses are abundant in these areas. Flow cytometry and immunohistochemistry findings were consistent with FL with 30% proliferation index. He was treated with 6 cycles of RCHOP and followed up at home.

Peripheral neurolymphomatosis refers to infiltration of the peripheral nerves by either lymphoma or non-neoplastic lymphocytes [29]. Later, neurolymphomatosis was defined to also include lymphoma involvement of central nervous system [30–34]. Be-

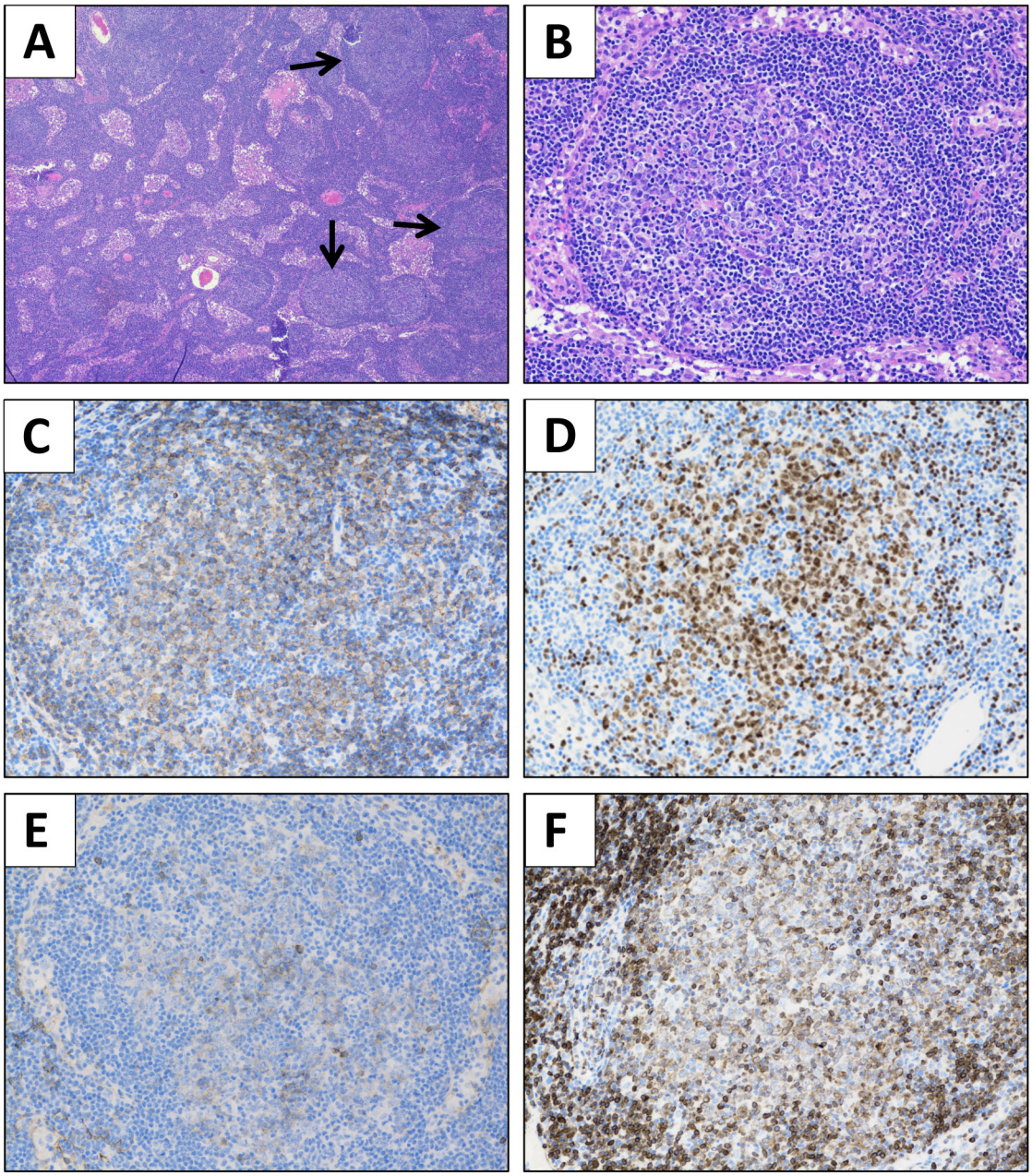

Figure 5: Follicular lymphoma with prominent reactive sinus histiocytosis. (A) Lymphoid follicles associated with sinus histiocytosis (H&E, original magnification x40); (B) A closer look at a lymphoid follicle (H&E, original magnification x200); (C) CD20+ and (D) PAX5+ follicular center B cells (IHC, original magnification x200); Weakly CD10+ (E) and BCL2+ (F) centroblasts (IHC, original magnification x200).

cause of the tumor infiltration of nervous systems, neurolymphomatosis often presents with one or more of the following presentations: 1) painful involvement of nerves or roots; 2) cranial neuropathy with or without pain; 3) painless involvement of peripheral nerves; 4) painful or painless involvement

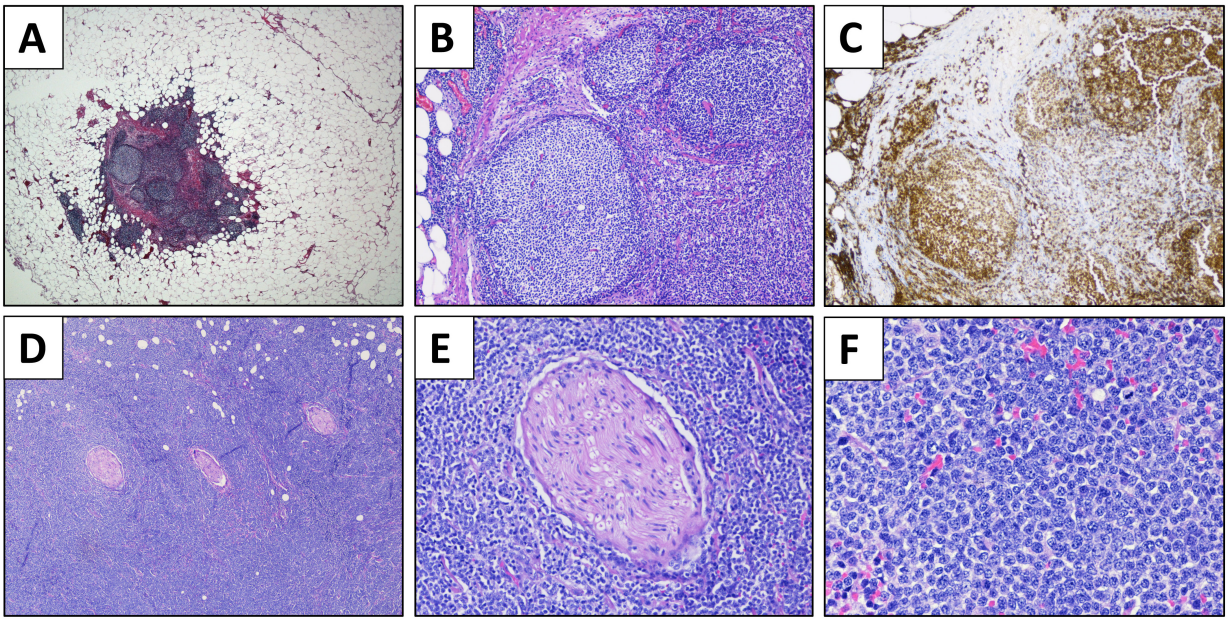

Figure 6: Micro follicular lymphoma in a lipoma. (A) A small lymphoid nodule is surrounded by adipose tissue (H&E, original magnification x20); (B) The lymphoid nodule is composed of several lymphoid follicles (H&E, original magnification x200); (C) The lymphoid nodules are BCL2 positive (IHC, original magnification x200). Neorolymphomatosis. (D) Lymphoid cells infiltrate the nerves (H&E, original magnification x40); (E) Small lymphoid cells infiltrate a nerve (H&E, original magnification x200); (F) High magnification shows the large centroblasts (H&E, original magnification x400).

of a single peripheral nerve. Although most of the reported causes of neurolymphomatosis were diffuse large B-cell lymphoma [34], FL is one of the malignant lymphomas that involve the peripheral nerves [29]. Our patient had a low grade FL with focal high grade transformation infiltrating the right brachial axis nerves with reported pain of his right breast area, which meet one of the criteria of neurolymphomatosis.

Conclusion

FL is the most common well characterized mature B-cell lymphoma, with well defined morphologic criteria and specific immunophenotypic markers. However, FL also varies in morphology, immunophenotypes, and clinical presentations. We have presented only several rare variants of FL encountered in our practice, with an intention to serve as appetizers to stimulate the interests in the FL variants and to raise awareness of the practicing surgical pathologists and hematopathologists.

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