Duodenal-Type Follicular Lymphoma
A Clinicopathologic Review

Etan Marks, DO; Yang Shi, MD, PhD

Duodenal-type follicular lymphoma (D-FL) is a newly recognized entity in the 2016 World Health Organization classification update. It has an immunophenotype similar to that of other FLs and usually carries the typical t(14;18)(q32;q21) translocation. However, unlike other FLs, D-FL is almost always diagnosed at a low stage and stays localized to the small intestine, most commonly the second portion of the duodenum, whereas the vast majority of other FLs are diagnosed at an advanced stage. Additionally, D-FL gene expression and pathogenesis appear to be more closely related to extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue than to other types of FL. Therefore, many oncologists have opted to treat this variant of FL in a “watch and wait” manner because of its excellent prognosis and the rarity of D-FL to progress even when no treatments are attempted.

Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma in the United States. It is graded by using the number of centroblasts per ×40 high-power field (hpf; hpf = 18-mm field of view) as grading criteria: grade 1 is 5 or fewer centroblasts per hpf; grade 2 is 6 to 15 centroblasts per hpf; and grade 3 is more than 15 centroblasts per hpf. Grade 3 is further subdivided into 3A (centrocytes still present) and 3B (sheets of centroblasts). Follicular lymphoma grades 1 and 2 have been combined into one entity because both are considered to have an indolent course.

As common as FL is, it only accounts for approximately 4% of gastrointestinal (GI) lymphomas. Of these, it is interesting to note that a large percentage (between 38% and 81%) arise in the duodenum. The FLs of this site are commonly localized to the intestine without nodal metastasis, similar to how primary cutaneous follicle center lymphoma stays localized to the skin. Conversely, the vast majority of patients presenting with FLs at other sites are at an advanced stage of disease. This has led the World Health Organization to recognize this entity as a distinct form of FL—duodenal-type follicular lymphoma (D-FL)—in its 2016 update.

**CLINICAL FEATURES**

Most D-FLs are detected incidentally, with endoscopy being done for reasons unlikely to be related to the D-FL, because low-stage FLs rarely cause clinical symptoms. This is most likely why FLs are detected at advanced stages in the vast majority of cases. In a study performed in Europe by Schmatz et al, the patients usually either had some type of upper GI symptoms, the D-FL was discovered while staging for other types of malignancies, or the endoscopy was part of a preventative medical examination. However, in another study performed in Japan by Takata et al, the vast majority of patients presented with no symptoms, and only a small cohort had some form of abdominal symptoms. Neither study revealed a predilection for either sex, and the median age for each study was 65 and 59 years, respectively. In the Takata et al study, 97 of 99 patients (98%) with involvement of the second portion of the duodenum had a 5-year progression-free survival. This is compared with only 19 of 27 patients (70%) without involvement of the second portion of the duodenum who had a 5-year progression-free survival.

Regarding disease staging, although Ann Arbor staging is more commonly used for FL of other sites, it appears that the International Workshop classification (Lugano classification) is more appropriate for the clinical staging of D-FL. The reason for this is that the Lugano staging criteria are commonly used for GI lymphoma staging and, because of the multifocal nature of D-FL, it is more similar to other GI lymphomas rather than the FLs of other sites. The Takata et al and Schmatz et al studies both used the Lugano staging criteria, and of the 162 patients, none were higher than a stage II.

**ENDOSCOPIC FINDINGS**

The lesions of D-FL usually appear as solitary or multiple nodules (Figure 1), or polypoid lesions, and are usually between 1 and 5 mm. These lesions can become ulcerated, and in that situation it is important to biopsy the surrounding area for a better diagnostic yield. They can be located anywhere in the duodenum, but the second portion/descending part is by far the most common area. These

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From the Department of Pathology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York.

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Reprints: Etan Marks, DO, Department of Pathology, Montefiore Medical Center/Albert Einstein College of Medicine, 111 E 210th St, Bronx, NY 10467 (email: emarks@montefiore.org or et565@aol.com).
lesions can occur in other areas of the small intestine, such as the jejunum and the ileum, along with the duodenum.\textsuperscript{8,9} In fact, multifocal disease in the small intestine is not uncommon, with 1 large series showing multiple lesions occurring in 49 of 63 cases (78%), and lesions located in the jejunum or ileum along with the duodenum in 11 of 63 cases (18%).\textsuperscript{9} In another large study, Takata et al\textsuperscript{8} found that, of the patients with D-FL in the second portion of the duodenum, only 8 of 54 patients (15%) had localized tumors, whereas the remaining 46 patients (85%) had involvement in other areas of the intestine, mainly the jejunum.

**HISTOLOGY AND ANCILLARY STUDIES**

Unlike other FLs, D-FL is usually a low-grade lesion (grades 1–2), with 1 study showing grades 1 to 2 in all 54 patients with second portion of the duodenum involvement,\textsuperscript{8} and another study showing grades 1 to 2 in all 63 patients with D-FL.\textsuperscript{9} The possibility of high-grade transformation is extremely rare but possible, because Mori et al\textsuperscript{13} reported that 1 of 27 patients (3%) developed histologic transformation to grade 3A. Usually, D-FL appears as several well-circumscribed germinal centers packed together with centrocytes and few, if any, centroblasts with no visible tingible body macrophages and without mantle zones. Sheets of small lymphoid cells with irregular nuclear contour are usually present outside the follicular structures, and the lymphoma usually involves the mucosa and submucosa. The neoplastic cells commonly involve duodenal villi (Figures 2 and 3). This is in contrast to other GI-FLs, which are commonly found between the submucosal and subserosal areas.\textsuperscript{14}

The neoplastic cells show an immunophenotype similar to that of low-grade nodal FL (NFL) by expressing CD20 (Figure 4), CD79a, CD10 (Figure 5), BCL-6, BCL-2 (Figure 6), and BACH2, and show a lack of expression for CD5, CD23, CD43, BCL-1 (cyclin D1), MUM-1, Blimp-1, and T-cell markers.\textsuperscript{9,14} They also show a low Ki-67 proliferation
rate (Figure 7). However, D-FL shows a different pattern of CD21 (Figure 8) and CD23 expression of the follicular dendritic cells (FDCs) in the germinal center compared with NFL and compared with FL found at other extranodal sites, including those of the colon and stomach. Usually, NFLs and other extranodal FLs will have an FDC network that occupies more than two-thirds of the neoplastic germinal centers. In D-FL, the FDCs are located at the periphery and occupy less than 10% of the neoplastic germinal center.8,9,14,15 It is interesting to note that Takata et al15 showed that FL cells interact with the FDCs of the germinal center, and FDCs give a growth advantage to the lymphoma cells. Therefore, the lack of FDCs and this interaction with the neoplastic FL cells may help explain the low-grade behavior of the D-FL.

PATHOGENESIS AND GENETIC FEATURES

The hallmark genetic aberration found in most FLs is the t(14;18)(q32;q21) translocation of the genes immunoglobulin heavy chain (IGH) and B-cell leukemia/lymphoma 2 (BCL2).16,17 This translocation is present in most cases of D-FL, confirming that this lymphoma is part of the FL family.9,13,15 However, unlike most FLs, D-FL appears to have a unique pathogenesis that is related to inflammation and antigen stimulation, and shares some similarities with mucosa-associated lymphoid tissue (MALT) lymphoma.

Regarding the immunoglobulin variable region heavy-chain (IgVH) gene rearrangements, D-FLs show a higher use of VH4 and VH5 than nodal cases.14,15,18 Also, in 1 study VH4-34 and VH5-51 were detected in 3 samples each.15 This selective use suggests that some antigen-dependent mechanism is involved in tumor development, similar to MALT lymphoma, which develops from chronic inflammation. In fact, there have been reports of D-FL where regression has occurred following eradication of the Helicobacter pylori organisms.19

Duodenal-type FL shows expression that differs from that of GI-FL with regard to CD27 and activation-induced cytidine deaminase (AID). CD27 shows positivity in D-FL, whereas AID is negative and the inverse is true for GI-FL.14
CD27 is a type 1 glycoprotein, a member of the tumor necrosis factor receptor family, and a marker for memory B cells.20 AID is a member of the RNA-editing cytidine deaminase family, which is specifically expressed in germinal center B cells, has been shown to be necessary for B-cell class switching, and is involved in hypermutation.21

Takata et al22 undertook the task of creating a gene expression profile for D-FL, using 10 cases, and compared it to the gene expression of 10 gastric MALT lymphomas, 18 NFLs, 5 normal duodenal mucosa, 8 nodal reactive lymphoid hyperplasias, and 4 normal gastric mucosae. After analyzing whole-genome expression data, they selected 2918 genes that were either upregulated or down-regulated to study the differentially expressed genes. They found that compared with the normal duodenal mucosa group, the top 5 upregulated genes in D-FL were the complement receptor 2, chemokine ligand 4 (CCL4), cannabinoid receptor 2, T-cell activation Rho GTPase-activating protein, and interleukin 21. The top 5 down-regulated genes were glutathione peroxidase 3, CDKN2B (p15), phospholipase A2 receptor 1, plasminogen activator, and diacylglycerol lipase.

In order to validate the expression profiles observed in the gene expression profile, immunohistochemistry was pursued for chemokine (C-C motif) ligand 20 (CCL20), CCR6, mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), and protocadherin gamma A3 (PCDHGA3), A8 (PCDHGA8), and B4 (PCDHGB4). All of these genes were upregulated in D-FL and stained positive with immunohistochemistry in the D-FL cells.22 CCL20 (also known as macrophage inflammatory protein 3a) is a chemokine expressed in follicle-associated epithelium, and CCR6, its only known receptor, is highly expressed in human dendritic cells.22,24 MAdCAM-1 is an immunoglobulin (Ig) family member with domains that display homologies to mucosa-associated Ig family members, and it appears to be important for regulating lymphocyte homing to mucosal sites.25 PCDHGA3, PCDHGA8, and PCDHGB4 represent a prominent gene family that encodes cell–cell adhesion proteins.

The above findings show that D-FLs share similar gene/protein expression profiles with both MALT lymphoma and NFL. With regard to the CCL20, CCR6, and MAdCAM-1 gene expression profiles, D-FL is similar to MALT lymphoma, and it was hypothesized that increased expression of CCL20 and MAdCAM-1, along with coexpression of CCL20 and CCR6, might play an important role in tumorigenesis. However, with regard to PCDHGA3, PCDHGA8, and PCDHGB4 gene expression profiles, D-FL is similar to NFL.

DIFFERENTIAL DIAGNOSIS

Duodenal-type FL, because of its histologic low grade and indolent behavior, can be confused with several different lymphoid entities, such as reactive follicular hyperplasia, MALT lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, and GI involvement by systemic FL.

Reactive follicular hyperplasia may have many follicles with germinal centers, but they usually vary in size and shape, have tingeble body macrophages, have polarized germinal centers, and have preserved dendritic cell meshwork, and the interfollicular lymphocytes will differ from the follicular lymphocytes. The secondary follicles will stain for BCL-6 and CD10, but not for BCL-2. MALT lymphoma is more common in the stomach than the small bowel. In low-grade lesions it is made up of small lymphocytes with irregular nuclei, and reactive germinal centers are common. It is often negative for CD5, CD10, and BCL-6, because it is derived from post–germinatal center memory B cells. Some lymphoma cells can aberrantly express CD43, and the most common genetic aberration is a t(11;18). Chronic lymphocytic leukemia/small lymphocytic lymphoma is commonly associated with lymphadenopathy or splenomegaly. When there is prominent lymphocytosis in chronic lymphocytic leukemia/small lymphocytic lymphoma, the neoplastic lymphocytes can be seen all over the body, including in the GI system. The architecture is effaced by sheets of small B cells with clumped chromatin and scant cytoplasm. CD5 is usually positive, but there is no expression for CD10 or BCL-6, and CD20 might be dimly expressed. Moreover, lymphoid enhancer-binding factor 1 (LEF1) is almost always positive in chronic lymphocytic leukemia/small lymphocytic lymphoma.

Mantle cell lymphoma can sometimes involve the GI tract and present as polyps. The infiltrate often appears nodular, can involve the lamina propria, and can have scalloped edges. The lymphoid cells are small, round, and monotonous, resemble centrocytes, and often infiltrate between glands instead of replacing them. The cells will show positivity for CD20 and CD5, but cyclin D1 positivity will be the most helpful in identifying this lesion, which correlates with the common t(11;14) present in this entity. Nodal FL will often present with generalized lymphadenopathy and bone marrow involvement. Occasionally, it can also involve the GI system. Histologically, it will appear very similar to D-FL when it is grades 1 to 2, but the staining pattern of CD21 of the germinal centers will be more diffusely positive in NFL compared with D-FL. Therefore, performing a thorough physical examination and a detailed radiologic investigation, including a positron emission tomography–computed tomography scan to rule out GI involvement by a systemic FL, is critical before a diagnosis of primary D-FL is rendered.

In general, D-FL can be differentiated from a reactive follicular hyperplasia and the other small B-cell lymphomas in several ways. First, the histology shows prominent follicles that lack tingleble body macrophages and polariza-

TREATMENT AND CLINICAL OUTCOME OF THE DISEASE

Follicular lymphoma is considered an indolent lymphoma with a fairly good prognosis, with median overall survival exceeding 12 years, but it is considered incurable with standard chemotherapy.26 Unlike FLs at other anatomic sites, D-FL is usually a low-grade lesion (grades 1–2) and mainly presents at a low stage. It is often an indolent disease, and its prognosis is similar to that of FL/neoplasia in situ.
Patients with limited-stage FLs treated with radiation therapy, usually external beam radiation therapy, have shown a long disease-free survival following therapy, with an overall survival rate of 60% to 80% at 10 years.\(^{27,28}\) Therefore, it is possible that in some instances of limited disease, radiation therapy leads to a cure. This is especially true because if a patient has not relapsed within the first 10 years, he or she is unlikely to relapse at all.\(^{30}\) This has led to radiation therapy being the treatment of choice for limited-stage disease for more than 4 decades.\(^{30}\) However, 1 study showed that among patients who received radiation therapy, 47 of 98 (48%) relapsed.\(^{28}\) Among patients who relapse, progression-free survival at 10 years is 22%.\(^{31}\) Therefore, chemotherapy has been added to some regimens and demonstrated an improved progression-free survival without an effect on overall survival.\(^{26}\)

Even with the success of radiotherapy, in the United States patients with stage I disease are treated with this modality less than 50% of the time, at least initially. Many oncologists in the United States initially take a “watch and wait” approach, which has been shown to be equally effective.\(^{32}\) The other approaches for early-stage disease consist of rituximab-chemotherapy, rituximab alone, combined modality therapy, other chemotherapies, or other therapy.\(^{26}\)

In a retrospective study of 63 patients with D-FL, the treatment modalities were watchful waiting only (24; 41%), radiotherapy (19; 33%), rituximab monotherapy (5; 9%), cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP; 2; 3%), rituximab plus CHOP (2; 3%), radiotherapy and rituximab (1; 2%), other chemotherapy protocols (3; 5%), and Whipple procedure (2; 3%); 5 patients had no control endoscopy and were not included in the therapy discussion.\(^{7}\) Patients in each treatment group showed complete regression in 7 of 24 (29%), 19 of 19 (100%), and 4 of 5 (80%) in the first 3 groups, and 5 of 8 (63%) in the following 4 groups combined (chemotherapy with or without radiation), respectively. The authors found only 2 of 63 patients (3%) had dissemination to nodal sites 5 years after initial diagnosis, and both were in the “watch and wait” group, but the remaining 61 of 63 patients (97%) did not develop lymphoma outside the small bowel.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Staget at presentation</th>
<th>D-FL</th>
<th>NFL</th>
<th>GI-FL</th>
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<tbody>
<tr>
<td>1–2(^{a})</td>
<td>I or II</td>
<td>1–2 or 3</td>
<td>III or IV(^{b})</td>
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<tr>
<td>BCL-6</td>
<td>+</td>
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<td>CD10</td>
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<td>+</td>
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<td>CD21</td>
<td>Peripheral of GC (duodenal pattern), 10% of follicle</td>
<td>Dense in GC (nodal pattern), 67% of follicle</td>
<td>Dense in GC (nodal pattern), 67% of follicle</td>
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<td>CD44</td>
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<td>IgVH use</td>
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<td>VH3, VH4, VH5</td>
<td>VH3, VH4, VH5</td>
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Abbreviations: AID, activation-induced cytidine deaminase; Blimp-1, B-lymphocyte maturation protein 1; GC, germinal center; IgVH, immunoglobulin heavy-chain variable genes; +, positive; −, negative.

\(^{a}\) The vast majority of D-FLs are of grades 1–2. However, very rare cases that transformed to high-grade B-cell lymphoma have been reported.

\(^{b}\) D-FL staging was by the Lugano classification; NFL and GI-FL staging was by the Ann Arbor classification.

\(^{c}\) Most NFLs present at stages III–IV, although a minority of cases can present at a lower stage.

CONCLUSIONS

Duodenal-type FL is a unique subtype of FL. Clinically, immunophenotypically, and genetically it is different from NFL (Table) and shares many characteristics with MALT lymphoma. However, it morphologically resembles a low-grade FL (FL1-2) and expresses BCL-2, probably because it has the unique t(14;18) that is characteristic of FLs in general. In the United States most oncologists either take a “watch and wait” approach, or they treat with radiotherapy. More recently, some oncologists have chosen rituximab or even opted for chemotherapy. However, most do not choose chemotherapy because of the good prognosis of D-FL and the toxic side effects of chemotherapy.

References


