Incidental Findings of Duodenal-Type Follicular Lymphoma by Endoscopic Screening: A Case Report

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ABSTRACT
Introduction: Follicular Lymphoma (FL) is a B-cell neoplasm arising from the germinal center. Gastrointestinal FL is a rare case, accounting for less than 4% of all primary lymphoma of the gastrointestinal tract. Duodenal-type Follicular Lymphoma (DTFL) was included in an entity of primary intestinal FL. However, in the 2017 World Health Organization (WHO) Classification, this entity was included in a specific variant called DTFL. In this article, we report a case of DTFL in a 56-year-old man which was incidentally found during upper gastrointestinal endoscopy.

Case Presentation: We report a case of incidentally found DTFL in a 56-year-old man during an endoscopy. The endoscopic finding showed a small, hypertrophic, or nodular lesion on part two duodenum. Microscopic evaluation of duodenal mucosa consists of proliferative atypical lymphoid cells arranged in follicular architecture. The lesion was confined to the lamina propria. The atypical lymphoid cells were dominated by monotonous centrocyte-like cells, small-sized, with scant cytoplasm, and cleaved nuclei. There were some scattered larger centroblast-like cells with multiple nucleoli. No mantle zone and tingible body macrophage were found. The immunohistochemical evaluation showed positivity for CD 20, CD 10, Bcl-6, and Bcl-2 in the follicular structure. CD 21 was dominantly stained at the periphery of the follicular structure, and Ki-67 was low.

Conclusions: According to clinical data, endoscopic findings, and histopathological and immunohistochemical findings, the patient was diagnosed with DTFL.

INTRODUCTION

Follicular lymphoma (FL) is a B-cell neoplasm arising from the germinal center, usually involving lymph nodes. FL is one of the most common Non-Hodgkin Lymphoma, with the highest incidence reported in Western Europe and the United States, while the incidence in Eastern Europe, Asia, and other developing countries is lower [1,2]. The most common location of extranodal lymphoma is in the gastrointestinal tract [3].

FL accounts for about 20% of all lymphoma cases. It occurs predominantly in an adult with a mean age of 60 years, and is slightly more common in women, with men to women ratio of 1.7. The predilection for this neoplasm is in nodal, but it can also occur in other locations such as the spleen, bone marrow, and Waldenström’s ring [1]. However, primary gastrointestinal FL is rare [4].

Duodenal-type follicular lymphoma (DTFL) accounting less than 4% of all lymphomas in the gastrointestinal tract [5]. This entity is very rare with only a few cases ever reported [2]. Previously DTFL was included in primary intestinal FL. However, it turns out that primary FL that arises from the small intestine, especially the duodenum, has different clinical and biological features. Hence, in the 2017 WHO classification, it was included in its specific variant [1,4]. In thirty-eight to eighty-one percent of cases, the lesion originates from the duodenum. The most common location is in part two of the duodenum. DTFL is an indolent lymphoma with a long clinical course and has a relatively good prognosis, even without any treatment [5,6]. It is imperative to not over-diagnose this lesion so that the patient could avoid any unnecessary aggressive treatment. More literature about DTFL is needed to ensure the behavior, prognosis, and best therapeutic strategy considering that this entity is still new with a limited number of cases.

Patients usually did not have any symptoms or come to the physician with a non-specific upper gastrointestinal symptom [7]. Some patients present with jaundice that is usually caused by obstruction by a tumor located in the ampulla of the vater [5,8]. Due to the lack of symptoms in most patients, this lesion is often found...
incidentally on endoscopic examination for other purposes, such as in chronic gastritis or gastrointestinal reflux disease [5,9]. In this article, we report a case of DTFL in a 56-year-old man which was incidentally found during endoscopic.

CASE PRESENTATION

A 56-year-old male visited one of the hospitals in Denpasar for a routine health check-up in February 2021. The patient was asymptomatic. A small hypertrophic or nodular lesion on part two duodenum was found incidentally during upper gastrointestinal endoscopy as seen on Figure 1. Duodenal bulb, fundic, corpus, antrum, and pyloric were not remarkable. A biopsy was done on the nodular lesion and the sample was sent to the anatomic pathology laboratory for further evaluation.

On microscopic examination, the tissue fragments were lined by a simple columnar epithelium with a scattered goblet cell in between. The duodenal mucosa contains the proliferation of neoplastic lymphoid cells forming a nodular or follicular architecture confined to the lamina propria (Figure 2). Figure 3 showed the atypical lymphoid cells were dominated by monotonous centrocyte-like cells, small-sized, with scant cytoplasm, and cleaved nuclei. There were some scattered larger cells with more dispersed chromatin and multiple nucleoli (centroblast-like). There was no tingible body macrophage in the follicular structure and no mantle zone on the periphery of the follicle.

From the routine histopathological examination and based on morphology, the patient was diagnosed with a lymphoproliferative lesion, with a differential diagnosis of duodenal-type follicular lymphoma dan mantle cell lymphoma. This specimen was further evaluated by immunohistochemistry.

Figure 1. The endoscopic finding showed a small, multiple hypertrophic or nodular lesion arranged in clusters on part two duodenum. Mucosa outside the lesion was smooth.

Figure 2. (A) Microscopic evaluation duodenal mucosa containing the proliferation of atypical lymphoid cells arranged in follicular or nodular architecture (arrow); (B) Lesion was confined in the lamina propria of duodenum (HE, 40x).

Figure 3. (A) The atypical lymphoid cells were dominated by a monotonous centrocyte-like cell, small sized, with scant cytoplasm, and cleaved nuclei (arrow); (B) There were some scattered larger centroblast-like cells with more dispersed chromatin and multiple nucleoli (arrowhead). No mantle zone and tingible body macrophage were found. (HE 400x).
Figure 4. Immunohistochemical staining pattern (A) CD20 was stained in the neoplastic cells within the follicular structure and interfollicular area; (B) CD10 stained the B cell within germinal centre; (C) BCL6 stained the B cell in the germinal centre; (D) BCL2 stained the B cell in the germinal centre; (E) CD21 stained dominantly in the periphery of the follicular structure; (F) CD23 stained dominantly in the periphery of the follicular structure; (G) Ki-67 was stained less than 10 percent; (H) Cyclin D1 negative in the follicular structure; (I) CD3 negative in the follicular structure; (J) CD5 negative in the follicular structure; (K) MUM1 negative in the follicular structure; (L) AE1/3 negative.

BCL2: B-Cell Lymphoma 2; BCL6: B-Cell Lymphoma 6; MUM1: Multiple Myeloma 1.
On immunohistochemical staining seen in Figure 4, CD20, CD10, Bcl-6, and Bcl-2 were positively stained in the follicular structure. CD21 was dominantly stained at the periphery of the follicular structure, and Ki-67 was low (less than 10%). CD3, CD5, Cyclin D1, MUM-1, and AE1/AE3 were negative in the follicular structure. According to the morphology and immunohistochemical pattern, this patient was eventually diagnosed with a duodenal-type follicular lymphoma. After the diagnosis, the clinician suggested watchful waiting. However, the patient was lost to follow-up.

DISCUSSION

In general, FL and DTFL have similar morphological features. However, clinically, DTFL resembles Mucosal Associated Lymphoid Tissue (MALT) lymphoma more than nodal FL, because it is usually confined to the duodenum as a localized disease. Moreover, gene expression analysis showed that the gene expression profile in DTFL is also more closely related to MALT lymphoma [10]. Morphologically, DTFL is a polypoid lesion consisting of proliferative neoplastic lymphoid cells with follicular or nodular architecture. The lesion is usually limited to one area, from the mucosa to the submucosa. In contrast, follicular lymphoma in other locations is often found in the submucosal and subserosa layer, with transmural infiltration [1,6,11]. This lesion consists of centrocyte-like cells with relatively monotonous size and scattered centroblast-like cells which meet the criteria for grade 1 or 2 in the nodal follicular lymphoma grading system [1]. No mantle zone and tingible body macrophages were found [2,4,6]. Neoplastic cells often involve the duodenal villi [5]. These neoplastic lymphoid cells can also infiltrate the lamina propria around the lymphoid follicles. This finding will be easily observed on immunohistochemical examination [1,4,9]. In this case, histopathological examination showed fragments of duodenal mucosal tissue containing proliferative neoplastic lymphoid cells forming nodular architecture confined to the lamina propria. These neoplastic lymphoid cells are small and monotonous, with scant cytoplasm and cleaved nuclei (centrocyte-like). Some scattered larger cells with oval nuclei, more dispersed chromatin, and multiple nucleoli located peripherally near the nuclear membrane (centroblast-like). No tingible body macrophages were seen in the follicular structure, and no mantle zone surrounding the follicle structure was seen. This finding is in line with the literature.

DTFL showed a chromosomal translocation (14;18) (q32; q21) between the Immunoglobulin heavy chain (IgH) and B Cell Lymphoma 2 (BCL2) genes. Similar translocation was also seen in FL, as well as ongoing mutations similar to FL at other sites. However, DTFL shows fewer genetic abrasions than FL in other locations. Some evidence suggests the expression of gene profiles are overlap with extranodal MALT lymphoma. Based on microarray data obtained by quantitative polymerase chain reaction for CCL20 and MADCAM1, DTFL and MALT lymphoma both had increased expression. However, nodal FL showed contrasting findings [2,9]. DTFL also frequently exhibits positivity for memory B-cell marker, CD27, but does not express Activation Induced Deaminase (AID), and instead expresses the BTB domain and the CNC homolog 2. AID is associated with ongoing mutations and class-switching that are usually expressed in the germinal center and FL nodal. Broad Complex-tramtrack-bric a brac and Cap’n’collar homology 2 (BACH2) is a transcription factor that heterodimerizes with the Maf oncoprotein, which is required for class-switching recombination and somatic hypermutation of immunoglobulin genes on activated B cells. The presence of BACH2 expression without AID expression is a typical finding in duodenal-type FL [12].

The grading system for FL is assessed based on the number of centroblasts in a high-power field (with a magnification of x 40 and an area of 0.159 mm2). If five or fewer centroblasts are found in a high-power field, it is assigned as grade 1. If 6 to 15 centroblasts are found in a high-power field, it is assigned as grade 2, and if more than 15 centroblasts are found in a high-power field, it is assigned as grade 3. Grade 3 follicular lymphoma is further grouped into Grade 3A (if centrocytes are still found) and Grade 3B (if centroblasts are found in sheet form). Grade 1 and 2 follicular lymphomas are considered low grade because they are both indolent, and there is a considerable variation when observed by different pathologists, especially in small biopsy samples [1]. DTFL usually has a low histological grade, with a long clinical course (indolent) with behavior resembling in situ follicular lymphoma or extranodal marginal zone lymphoma [4,6]. Six to eight centroblasts per one high power field were found in this case, so this case was assigned a low grade.

The recommended staging system is the Lugano classification because this staging system is more commonly used to stage lymphoma in the gastrointestinal tract. DTFL is often multiple, it is considered more like gastrointestinal lymphoma than nodal lymphoma [5].

The immunophenotype of DTFL is similar to FL found in lymph nodes. They express CD20, CD79A, Bcl-2, CD10, and Bcl-6 [6,12]. DTFL shows a characteristic Follicular dendritic cells (FDC) distribution pattern, which is distributed in the periphery of the neoplastic follicles or nodules [5,6,12]. FDC expression patterns are shown by CD21 and CD23 staining. Generally, FL in other locations had FDCs in more than 2/3 of neoplastic cells in the follicular area. However, in DTFL, FDCs are located at the periphery and account for less than 10% of
neoplastic cells [5,7]. Studies by Takata et al [13] suggest that FL cells interact with FDCs in the germinal center, thereby increasing lymphoma cell proliferation. The lack of interaction between FL cells and FDCs in DTFL contributes to better behavior. In addition, Ki-67 in DTFL is lower compared with nodal FL [6,12]. CD5, CD23, CD43, Bcl-1 (Cyclin D1), MUM-1, Blimp-1, and T cell markers are not expressed [2,5]. Consistent with the literature, this case showed positivity of CD20, CD79A, Bcl-6, and CD10 on the follicular structure cells, confirming the germinal center origin. Bcl-2 stains positively on follicular structures, which is supposed to be negative in typical germinal center B cells [2]. Ki-67 in this case was also low (stained in less than 10% of most follicular structures). In addition, CD21 was stained on follicular dendritic cells in the periphery of the lymphoid follicle [1,5].

Due to its low histological grade and indolent behavior, this lesion can be confused with other lymphoid neoplasms such as reactive lymphoid hyperplasia, MALT lymphoma, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Mantle Cell Lymphoma (MCL), and systemic FL with gastrointestinal involvement [5]. Normal and reactive follicles usually have heterogeneous populations with many tingible body macrophages, good polarization, and negative Bcl-2 expression in the germinal centre [2]. MALT lymphomas rarely form nodules and lymphoepithelial lesions are commonly found [14]. MALT lymphoma usually occurs in the stomach and predominantly consists of small round and monocytoid cells. This type of lymphoma usually expresses B cell marker and Bcl2 but is negative for CD10 and Bcl6. CLL/SLL usually form interstitial infiltrations to distinct tumor formation and may form a proliferation center. CLL/SLL express B cell markers, CD5, CD23, LEF1, and CD200. MCL also commonly involves the gastrointestinal tract. The lesion usually manifests as multiple lymphomatous polyposis. Morphologically, MCL consists of small neoplastic lymphocytes with a uniform population without centroblasts. Immunophenotypically, MCL expresses B cell markers, Bcl2, CD5, CyclinD1, SOX10, and negative for germinal centre markers Bcl6 and CD10 [15].

DTFL should also be distinguished from nodal FL with duodenal involvement. Systemic lesions and/or intestinal involvement by lymphoma of the mesentery or peritoneal origin need to be ruled out by imaging studies and bone marrow biopsy [9]. In this case, there was no lymph node enlargement in any other locations. Unfortunately, the limitation of this case is that the patient did not undergo any other imaging studies or bone marrow biopsy.

DTFL is a localized disease (Stage IE or IIE) with an excellent survival rate, even if untreated [1]. During follow-up, involvement of more distal small bowel areas such as the jejunum or ileum is found in about 80–85% [1,4]. DTFL has a long-term survival rate, with median overall survival exceeding 12 years [5]. Overall survival (OS) in 5 years is 100% and Progression Free Survival (PFS) in 5 years is 93% [11]. However, the literature also reports that some cases of DTFL underwent a histological transformation into diffuse large B cell lymphoma [11,16] and progressed to nodal disease although it is very rare (< 10%) [5,9]. Therefore, further studies with more subjects are needed to determine the long-term prognosis in patients with DTFL since this entity is very rare [2,5].

Some clinicians prefer to watch and wait. However, some oncologists gave therapies such as radiation, chemotherapy, and administration of rituximab [1,6]. Several therapeutic options include resection, chemotherapy, and radiation. There is currently no therapeutic consensus as well as the interval of observation for DTFL [2]. A study done by Tari et al. [17] compared the efficacy of asymptomatic intestinal follicular lymphoma patients receiving chemotherapy with patients undergoing a watch-and-wait strategy. The study showed that there was no difference in progression-free survival in the two patient groups. A report in an experienced center with 21 cases of DTFL showed that radiation therapy may be an effective option for initial therapy. However, available data regarding therapeutic outcomes in patients receiving radiotherapy are still very minimal because of the low incidence [10]. Clinicians, in this case, suggested a watchful waiting, however, after diagnosis, the patient was lost to follow-up. Thus, data regarding further treatment and the patient’s medical state were not available.

CONCLUSIONS

Duodenal-type Follicular Lymphoma (DTFL) is a specific subtype of follicular lymphoma in the gastrointestinal tract, which is biologically different from nodal follicular lymphoma. However, they have the same morphology, with a lower histological grade. There is currently no therapeutic consensus for this lesion. Some literature showed that the watch-and-wait strategy is better. However, some oncologists chose to give therapy, such as chemotherapy, radiation, and rituximab. DTFL is an indolent lesion with an excellent prognosis and a long survival rate, even without treatment. Thus, it is imperative to not over-diagnose so that the patient could avoid any unnecessary aggressive treatment. Nonetheless, it is undeniable that further research with larger samples and longer follow-ups are needed to ensure the prognosis and best therapeutic strategy considering that this entity is still new with a limited number of cases.
DECLARATIONS

Competing interest
The author(s) declare no competing interest in this paper.

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