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Case report

Primary duodenal follicular lymphoma: Case report and literature review

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Abstract

Primary gastric lymphomas are rare diseases; however, they are the most common extranodal presentation of non-Hodgkin lymphomas. 30% of non-Hodgkin lymphomas correspond to follicular lymphomas and at the same time, nearly 10% of follicular lymphomas are produced in the gastrointestinal tract. Risk factors for gastric lymphomas such as *Helicobacter pylori* infection, immunosuppression after solid organ transplantation, inflammatory bowel disease, and human immunodeficiency virus (HIV) infection were described. Follicular duodenal lymphoma was recognized as a variant of follicular lymphoma in 2016 according to the World Health Organization (WHO) classification, considering that it is a condition with special biological and clinical characteristics. Its diagnosis is usually incidental or mild and nonspecific symptoms may occur. The histological grade is usually low, and the clinical course is benign; Therefore, in most cases, expectant treatment has been adopted as an option. Other therapies with similar effectiveness are radiotherapy, the use of rituximab, and immunochemotherapy. There is not enough evidence to date to generate a single management protocol for this pathology.

Keywords

Folicular lymphoma, Duodenal lymphoma, Extraganglionar non-Hodgkin's lymphoma.

INTRODUCTION

The gastrointestinal tract is an important component of the immune system and contains lymphoid tissue in varying amounts and types. The esophagus and stomach have little mucous lymphoid tissue, unlike the intestine, in which it is abundant, predominantly in the mucosa and submucosa. This tissue is known as *mucosal-associated lymphoid tissue* (MALT). The monoclonal proliferation of MALT in response to chronic antigenic stimulation or inflammation may lead to the development of various forms of gastrointestinal lymphoma[1]. Primary lymphomas of the gastrointestinal tract are rare; however, they correspond to the most common extranodal location in which non-Hodgkin lymphomas (NHL) develop, as they correspond to 30% of cases[2,3].

Duodenal-type Follicular Lymphoma (DFL) is a rare variant of follicular lymphoma (FL), recently recognized as a subtype of the latter in the World Health Organization (WHO) classification due to its distinctive nature[4].

CASE PRESENTATION

A 42-year-old female patient with no medical history consulted in December 2013 for long-standing dyspeptic

symptoms and an endoscopic study that reported chronic atrophic gastropathy, adenomatous-looking major papilla, and elevated lesion in the third portion of the duodenum. Endoscopic ultrasound(EUS) was performed, which revealed mucosal thickening in the third portion of the duodenum without compromising other layers; a biopsy was taken and the report suggested a lymphomatous process. The immunohistochemistry study confirmed FL grade 1, and the thoracoabdominal tomography performed at that time showed no nodal involvement.

The patient abandoned the controls and reconsulted in February 2020. A new esophagogastroduodenoscopy was performed, in which a normal duodenal bulb and the second portion of the duodenum with nodular, whitish, and friable mucosa were identified. Biopsies showed low-grade LF, and immunohistochemistry with negative MUM markers, kappa, lambda and CD3 positive in companion lymphocytes compatible with low-grade DFL (**Figure 1**). A control tomography scan was performed in which no nodal or other organ involvement was found. Currently, the patient is under management and follow-up by medical oncology.

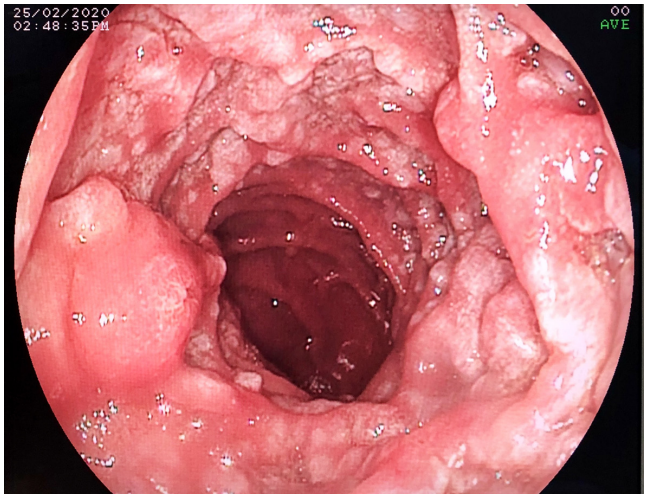

Figure 1. Endoscopic findings: Granular-looking nodular lesions in the second portion of the duodenum.

DISCUSSION

FL is one of the most common low-grade B-cell lymphomas, accounting for 30% of all NHL in Western countries[4]. The gastrointestinal tract is the most frequent location of extranodal presentations, and about 10% of all LFs are of gastrointestinal origin[5]. Several risk factors for the development of gastrointestinal lymphomas have been identified, such as *Helicobacter pylori* infection, post-solid organ transplant immunosuppression, inflammatory bowel disease (IBD), and human immunodeficiency virus (HIV) infection[3]. The distinctive genetic alteration of LFs is the t (14; 18) (q32; q21) translocation of immunoglobulin (Ig) heavy chain genes. In addition, certain similarities have been described in the genetic profile with MALT lymphoma. These similarities are associated with antigenic stimulation in chronic inflammation. It is suspected that DFL may follow a course similar to MALT lymphoma, which originates from preexisting inflammation[6].

The first case of DFL was reported in 1997, and gastrointestinal FL was historically established as a disease in the decade of 2000. As it was recognized as an entity, case series were reported and, as a result, it was established that primary follicular intestinal lymphoma corresponds to a variant of the classification of follicular lymphomas according to the WHO classification. Within this, duodenal lymphoma is also recognized as a specific entity, which has the characteristics of a low-grade localized FL, but is distinct from another gastrointestinal FL[7]. Duodenum (65%), ileum, and jejunum (20%) are the sites of the gastrointestinal tract most frequently affected by FL, although cases have also been reported in the colon, rectum, and stomach[5].

DFL occurs predominantly in middle-aged adults with similar distribution between men and women[8]. Most patients are asymptomatic, therefore, the diagnosis is usually incidental, usually during an endoscopic study indicated for unrelated reasons. When present, clinical manifestations are generally upper gastrointestinal symptoms such as pain, abdominal discomfort, vomiting, and, less frequently, gastrointestinal bleeding[7,9]. Endoscopic findings are in most cases described as single or multiple nodular whitish lesions of granular appearance and not submucosal appearance; in other cases, they are referred to as small polypoid nodules between 1 and 5 mm. Less frequently, they present as erosions or ulcers; in this case, it is important to take samples from the surrounding area for greater diagnostic performance. Some authors have reported the identification of opaque whitish spots, enlarged villi, and a pattern of vascular dilation in the villi as characteristic findings of this pathology when using electronic staining. The whitish coloring of intestinal lesions is attributed to the infiltration of lymphomatous cells into villi[8-10]. Most cases are presented as localized pathology, but when the small intestine study is completed, up to 85% of patients with DFL have jejunal or ileal involvement[9].

Histologically, the neoplastic follicles are similar to those identified in nodal disease, composed of a uniform population of centrocytes, usually with nuclear clefts and some centroblasts. The histological grade is defined according to the number of centroblasts per 40 high power fields (CAP): grade 1: 5 or less centroblasts per CAP, grade 2: 6-15 centroblasts per CAP, and grade 3: More than 15 centroblasts per CAP. Grade 3 is subdivided into 3a: Centrocytes still present and 3b: Centroblast sheets[11,12]. More than 95% of

cases of DFL are grade 1 to 2 (low grade)[4,7]. A typical histological finding is the "duodenal pattern" in which follicular dendritic cells are located on the periphery of neoplastic follicles, unlike nodal disease, in which they form a dense mesh within follicles[5].

Lymphomatous cells show an immunophenotype similar to that of low-grade nodal disease, with CD20 and CD10 antigens expression, and B-cell lymphoma type 2 (BCL-2) and type 6 (BCL-6); the Ki-67 proliferation rate is low. Unlike a systemic disease, DFL does not express activation-induced cytidine deaminase (AID) and expresses positivity for immunoglobulin A (IgA), BACH2 and CD27 antigen[2,5,8].

Once histologic confirmation is present, the staging process includes a complete physical examination, neck and thoracoabdominal tomographic study, as well as blood chemistry studies (blood count, lactate dehydrogenase [LDH], kidney function, liver enzymes), and bone marrow aspiration. Positron emission tomography (PET scan) may be considered, especially if radiation therapy is considered appropriate and the double-balloon enteroscopy study is completed to evaluate the entire small intestine. Some criteria have been proposed to determine whether this is a primary gastrointestinal lymphoma: Absence of palpable adenomegaly, absence of mediastinal adenomegaly, normal differential leukocyte count, disease limited to the intestine and adjacent nodes, without liver or spleen involvement[13,14].

Depending on the single or multiple involvements in the gastrointestinal tract, degree of intestinal wall infiltration, secondary lymph node involvement of adjacent or distant organs, the disease can be staged from I to IV (Lugano Classification) (**Table 1**)[15].

DFL is considered a painless condition with an excellent prognosis and average survival rates of more than 12 years. Taking into account the usually asymptomatic course of this condition and the low frequency of histological progression or transformation, on the one hand, expectant management has been proposed as a valid option for these patients, as it has been shown to be an equally effective strategy even with spontaneous remissions in some cases. Furthermore, patients treated with radiation therapy as initial therapy have been reported to have 10-year survival rates of up to 80%; therefore, this therapy may be curative in some cases, considering that relapse after this time is unlikely. When relapse occurs, survival decreases to 22% at 10 years. Adjuvant chemotherapy has not shown any additional benefit after radiation therapy[8,16]. Rituximab monotherapy (humanized monoclonal antibody anti-CD20) has been a treatment option in FL, and its effectiveness has been demonstrated with prolonged remissions, even relapses, or as a second line of treatment. Expectant management has also been compared with immunochemotherapy at follow-ups of up to 149 months, and similar results were found[9]. All of these could then be valid treatment strategies, although there is no consensus so far on the best management option for DFL.

Table 1. Lugano classification for extranodal lymphomas[15]

Classification	Features
Stage I	Involvement of a single lymph organ
Stage IE	Unique extra lymphatic involvement with the absence of nodal involvement
Stage II	Involvement of two or more nodal zones on the same side of the diaphragm
Stage III	Nodal involvement on both sides of the diaphragm
Stage IV	Disseminated commitment

CONCLUSIONS

DFL is a rare condition with particular clinical presentation and biological behavior. It has been recently recognized as a variant of FL according to the WHO classification. It is usually asymptomatic and rarely presents a histological transformation or progression to nodal disease. There is not enough evidence in the literature to establish a management protocol; However, taking into account its particular benign behavior, expectant management can be considered in most cases. Other therapeutic options that have proven highly effective include the use of radiation therapy, rituximab, and immunochemotherapy.

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