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Lymphoma in the duodenum: an update of diagnosis and management

Lymphoma in the duodenum

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Abstract

The presentation, subtype, and macroscopic images of lymphoma vary depending on the site of the tumor within the gastrointestinal tract. We searched PubMed for publications between 1 January 2012 and 10 October 2022, and retrieved 130 articles relating to duodenal lymphoma. A further 22 articles were added based on the manual screening of relevant articles, yielding 152 articles for full-text review. The most predominant primary duodenal lymphoma was follicular lymphoma. In this review, we provide an update of the diagnosis and management of representative lymphoma subtypes occurring in the duodenum: follicular lymphoma, diffuse large B-cell lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, mantle cell lymphoma, and T-cell lymphomas.

Key Words: Diagnosis; Diffuse large B-cell lymphoma; Duodenal neoplasms; Esophagogastroduodenoscopy; Follicular lymphoma; Gastrointestinal lymphoma

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Core Tip: Among cases of primary duodenal lymphoma, follicular lymphoma was the most predominant, followed by diffuse large B-cell lymphoma, extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma), mantle cell lymphoma, and T-cell lymphomas. A watch and wait policy is acceptable for follicular lymphoma. Observation without treatment is also an option for MALT lymphoma. However, it should be noted that duodenal MALT lymphoma has a higher rate of transformation to diffuse large B-cell lymphoma than gastric MALT lymphoma. Diffuse large B-cell lymphoma, mantle cell lymphoma, and T-cell lymphomas generally require systemic treatment.

INTRODUCTION

Gastrointestinal lymphoma is a relatively rare tumor, accounting for 1–8% of malignant neoplasms of the gastrointestinal tract [1–3]. However, detection and management of gastrointestinal lymphoma lesions is important, as 30–40% of extranodal lymphomas occur in the gastrointestinal tract [4]. The lymphoma subtype, presentation, and macroscopic images vary depending on the site of the tumor in the gastrointestinal tract. Thus, understanding of the specific features is essential for gastroenterologists to ensure prompt diagnosis and appropriate management. The stomach is the most commonly involved site of lymphomas in the gastrointestinal tract, with the duodenum being less common. Analysis of the United States population based on the Surveillance, Epidemiology, and End Results (SEER) program revealed that the prevalence of primary gastric, small intestinal, and duodenal lymphomas is approximately in the ratio of 10:3:1 [5]. Recent studies have found that some subtypes of lymphoma that develop in the duodenum are distinct from those that develop in other parts of the gastrointestinal tract. Here, we review articles describing duodenal lymphoma published within the last 10 years and provide a summary update of contemporary diagnosis and management of the disease.

SEARCH STRATEGY

We searched PubMed for all peer-reviewed articles from 1 January 2012 to 10 October 2022. No study design filters were used. Manual screening of additional relevant articles was performed using a reference list of selected articles meeting eligibility criteria. The search strategy used the keywords 'lymphoma' and 'duodenum'. The search was performed by the lead author (M.I.). Criteria for article inclusion were (1) peer-reviewed articles describing cases of duodenal lymphoma, and (2) review articles, original articles, case series, and case reports. Exclusion criteria were (1) articles written in languages other than English, (2) animal and cell studies, and (3) the primary topic of study was not duodenal lymphoma. Eligible articles were evaluated in full.

SEARCH RESULTS

Figure 1 shows a flow diagram summarizing the identification, screening, eligibility, and exclusion processes of the literature search. The initial search returned 288 articles. Among these, lymphoma was not the subject in 42 articles. Meanwhile, in 36 articles, case(s) of lymphoma was described but the duodenum was not involved. Articles on animal and cell studies (n = 31), articles in which the primary topic was not duodenal lymphoma (n = 26), and articles written in language other than English (n = 23) were also excluded. After application of the the exclusion criteria, 130 articles were retrieved from the initial PubMed search. A further 22 articles were added based on the manual screening of relevant articles. In total, 152 articles were used for full-text review.

Table 1 shows the results of the PubMed database literature search according to the lymphoma subtype. Follicular lymphoma was reported most frequently (48 articles), followed by diffuse large B-cell lymphoma (17 articles), extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma) (9 articles), enteropathy-associated T-cell lymphoma (9 articles), mantle cell lymphoma (5 articles), plasmablastic lymphoma (4 articles), monomorphic epitheliotropic intestinal T-cell lymphoma (4 articles), Burkitt lymphoma (4 articles), and anaplastic large cell lymphoma (4 articles). Other rare subtypes of lymphoma occurring in the duodenum reported within the last 10 years were also included.

PREVALENCE OF LYMPHOMA SUBTYPES IN THE DUODENUM

Analysis of the U.S. population based on the SEER program revealed a total of 1,060 cases of primary duodenal lymphoma identified between 1998 and 2015 [5]. Among the primary duodenal lymphoma, the most frequent was follicular lymphoma (41.1%), followed by diffuse large B-cell lymphoma (32.8%), MALT lymphoma (13.8%), mantle cell lymphoma (2.7%), and T-cell lymphoma (2.6%). Meanwhile, diffuse large B-cell lymphoma was the most predominant subtype in the stomach (48.9%) and small intestine (jejunum and ileum, 54.9%), while follicular lymphoma was less frequent in the stomach (2.2%) and small intestine (23.0%). A population-based study in a Japanese prefecture included 350 cases of lymphoma involving the gastrointestinal tract, whether

primarily or secondarily [6]. The affected sites were the stomach (62.6%), large intestine (15.4%), small intestine (14.3%), duodenum (6.0%), esophagus (0.3%), and appendix (0.3%). The subtypes of duodenal lymphoma (n = 21) were follicular lymphoma (61.9%), followed by diffuse large B-cell lymphoma (14.3%), MALT lymphoma (14.3%), peripheral T-cell lymphoma (4.8%), and adult T-cell leukemia/Lymphoma (4.8%).

In the following sections, we review recent advances and basic knowledge relating to the diagnosis and management of representative lymphoma subtypes occurring in the duodenum.

FOLLICULAR LYMPHOMA

As described above, follicular lymphoma is the most common subtype of lymphoma occurring in the duodenum. The majority of cases are asymptomatic and are identified serendipitously during esophagogastroduodenoscopy examinations [7,8]. Follicular lymphomas most frequently occur in the descending part of the duodenum. The typical macroscopic feature is multiple white granules [9] (Figure 2). Magnified observation is useful when it is difficult to distinguish between minute lesions of this and other diseases. Follicular lymphoma is suspected if nodular white submucosal deposits or white villus enlargement are observed by magnified observation [10] (Figure 3). Biopsy reveals small to medium-sized tumor cells that form follicular structures and diffusely invade into the villi. Immunostaining is essential for definitive diagnosis, and CD10, BCL6 and BCL2 are usually positive in follicular lymphoma [7]. In addition, the t(14;18)(q32;q21) translocation of the immunoglobulin heavy chain (IGH) gene and the BCL2 gene is characteristic of follicular lymphoma. Thus, fluorescence *in situ* hybridization analysis of chromosomal translocation provides complementary information for diagnosis.

Follicular lymphoma is an indolent lymphoma that grows slowly over years. A watch and wait policy is acceptable, provided that appropriate chemotherapy is initiated when the disease progresses and symptoms develop. Comparative study between patients with intestinal follicular lymphoma treated with rituximab-combined

chemotherapy (n = 14) and those with watch and wait policy (n = 15) showed comparable outcomes [11–13]. In addition, one prospective study of 31 patients with primary gastrointestinal follicular lymphoma revealed that spontaneous shrinkage or complete disappearance was observed in nine patients [14]. These results confirm the suitability of follicular lymphoma management using the watch and wait policy. Radiation therapy is one option for duodenal lymphomas if the lesion is localized to the field of irradiation [15]. However, duodenal lymphomas are often accompanied by jejunal and/or ileum lesions. Since the gastrointestinal lesions are sometimes negative by positron emission tomography or CT scans [16], evaluation of the whole intestines with colonoscopy and small-intestinal endoscopy is essential when radiotherapy is considered [8]. Recent research has revealed that circumferential location of follicular lesions (more than half of the circumference of the intestinal lumen) and fusion of follicular lesions (dense granular elevations with indistinct boundaries) are significant predictive factors for progression of clinical stage, extension of intestinal lesions, or transformation to diffuse large B-cell lymphoma [17]. Patients with these endoscopic features may require surveillance in the short term.

DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma can occur in any part of the gastrointestinal tract, but it is often seen in the stomach and ileocecal region, and duodenal involvement is rare [18]. Retrospective analysis of 126 patients with intestinal diffuse large B-cell lymphomas revealed that the ileocecal region was the most commonly involved (50.0%), followed by the small intestine (i.e., jejunum and/or ileum, 23.0%), duodenum (18.3%), colon (11.1%), and rectum (5.6%) [19]. Diffuse large B-cell lymphoma lesions in the duodenum and large intestine tend to be secondarily involved, while those in the ileocecal region and small intestine are *de novo* neoplasms found in limited-stage disease [19]. It has also been reported that in approximately 30% of cases, duodenal diffuse large B-cell lymphoma are accompanied by gastric lesions [19]. On esophagogastroduodenoscopy, ulcerative and protruded lesions are typical morphology of duodenal diffuse large B-

cell lymphoma [20]. Particularly, an auriculate ulcer mound is characteristic of diffuse large B-cell lymphoma [21] (Figure 4), although it is rarely seen in other lymphomas and cancers. Biopsies tend to consist of a diffuse proliferation of large B cells, with Ki-67 positivity generally greater than 40%.

Diffuse large B-cell lymphoma is an aggressive (intermediate-grade) lymphoma that progresses on a monthly basis. However, this disease often responds well to treatment and long-term remission can be expected. Neoplastic cells of diffuse large B-cell lymphoma often exist through the entire thickness of the gastrointestinal tract [18]. Thus, patients should be counseled on the risk of intestinal perforation, bleeding, and stricture after the initiation of chemotherapy [22].

MALT LYMPHOMA

MALT lymphoma is common in the stomach and occurs less frequently in the duodenum. Duodenal MALT lymphoma presents various macroscopic features (Figure 5). According to reports describing 13 cases of duodenal MALT lymphoma, nodular lesions were the predominant feature (58.3%), followed by ulcer (16.7%), flat depression (16.7%), and subepithelial tumor (8.3%) [23]. Elevated lesions have also been described in case reports [24,25]. Among these, nodular lesions showing white granular protrusions must be differentiated from follicular lymphoma [23,26]. Endoscopic biopsy specimen predominantly shows small to medium-sized lymphoma cells, mixed with varying proportions of large cells. Lymphoepithelial lesions are infrequently observed in the duodenal MALT lymphoma [27]. Immunostaining is essential for definitive diagnosis and differentiation from other B-cell lymphomas.

Although some of the duodenal MALT lymphoma lesions reportedly regress with *H. pylori* eradication therapy, the response rate is lower than that for gastric MALT lymphoma [23]. Radiation therapy is indicated for limited-stage disease in which the disease is confined to the duodenum or limited to the regional lymph nodes [28,29]. Systemic chemotherapy is administered for non-limited-stage disease. Observation without treatment is an option because MALT lymphoma generally spreads slowly, but

it should be noted that duodenal MALT lymphoma has a higher rate of transformation to diffuse large B-cell lymphoma than gastric MALT lymphoma [23].

MANTLE CELL LYMPHOMA

Mantle cell lymphoma forms multiple polypoid elevations throughout the gastrointestinal tract including the duodenum, and has been termed multiple lymphomatous polyposis [30–32] (Figure 6). Multiple lymphomatous polyposis is a typical intestinal lesion of mantle cell lymphoma. However, although infrequently, other lymphomas can also present with this feature. We reviewed 35 cases of mantle cell lymphoma with gastrointestinal involvement and the involved sites were the stomach (74.3%), colon (57.1%), ileum (47.6%), rectum (47.6%), duodenum (34.3%), cecum (14.3%), and esophagus (5.7%) [33]. Mantle cell lymphoma lesions in the intestines (from duodenum to rectum, n = 22) predominantly showed multiple lymphomatous polyposis (10 or more elevated lesions, 77.3%), followed by protruded (1–9 elevated lesions, 18.2%) and superficial lesions (4.5%). The duodenal lesions of mantle cell lymphoma often accompany erosion of the tumorous nodules [30,34]. Endoscopic biopsy specimens consist of a homogeneous growth of small to medium-sized lymphoma cells with loose nodular structures in a diffuse pattern. As for other lymphomas, immunostaining is essential for definitive diagnosis. CD5, Cyclin D1, and SOX11 are often positive in mantle cell lymphoma [35].

Despite intensive chemotherapy regimens, mantle cell lymphoma generally remains incurable and is treatment-resistant with multiple relapses. Thus, prompt consultation with hematologists is required after the diagnosis [36].

T-CELL LYMPHOMAS

In the latest version of WHO classification of hematolymphoid tumors of the digestive system, T-cell lymphomas have been classified under four major types: enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma,

intestinal T-cell lymphoma not otherwise specified (NOS), and indolent T-cell lymphoproliferative disorder of the gastrointestinal tract [36].

Enteropathy-associated T-cell lymphoma, formerly known as type I enteropathy-associated T-cell lymphoma, is the most prevalent among primary intestinal T-cell neoplasms. Lymphoma cells derive from intraepithelial lymphocytes in celiac disease patients [37,38]. In particular, 30–52% of refractory celiac disease type II transforms into an enteropathy-associated T-cell lymphoma within five years [39]. Monomorphic epitheliotropic intestinal T-cell lymphoma, formerly known as type II enteropathy-associated T-cell lymphoma, derives from intraepithelial T lymphocytes and is typically not linked to celiac disease [40–44]. Aggressive T-cell lymphoma that lacks the clinical and pathological features of enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, anaplastic large cell lymphoma, or extranodal NK/T-cell lymphoma is now categorized as intestinal T-cell lymphoma NOS [45]. Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract represents clonal proliferation of T lymphocytes within the lamina propria, most commonly in the small intestine and colon [46]. The prognosis of T-cell lymphomas is generally poor, except for indolent T-cell lymphoproliferative disorder that shows prolonged survival with persistent, chronic relapsing disease.

CONCLUSION

We reviewed relevant articles mainly published within the last 10 years associated with duodenal lymphomas and summarized updates of representative lymphoma subtypes. Though there is no doubt that endoscopic examinations play a major role in the diagnosis of duodenal lymphoma, understanding of each pathological subtype will improve the diagnosis and initial treatment response to the disease. We believe this review will be helpful for gastroenterologists and endoscopists who diagnose and treat patients with duodenal lymphoma.

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