Prognostic Assessment and Treatment of Primary Gastric Lymphomas: How Endoscopic Ultrasonography Can Help in Tailoring Patient Management

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Abstract

Endoscopic ultrasonography (EUS) has recently gained a pivotal role in the management of gastric lymphomas, especially in the diagnostic workup. Its accuracy and reliability have overcome those of other imaging techniques, such that it represents an invaluable tool for the management of gastric lymphomas. Although this technique is operator dependent, its application in large series has proved its reliability. Thus, it has generally been considered a useful tool for providing information crucial in deciding the treatment program, especially for mucosa-associated lymphoid tissue (MALT) lymphomas, for which EUS can provide an accurate evaluation of disease extension and treatment response probability. Limited-stage disease, confined to the submucosa, has a greater probability to respond to sole *Helicobacter pylori* eradication. In contrast, the value of EUS in response assessment and follow-up monitoring is still debated, with discordant opinions about its reliability and clinical advantages, because normalization of the EUS findings occurs with a considerable delay compared to the histologic evaluation. In the follow-up setting, preliminary data have indicated that persistently positive EUS findings in low-grade gastric lymphoma could represent a warning for a possible relapse. However, in high-grade gastric lymphoma, such findings do not have any clinical implications.

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Introduction

Primary gastric lymphoma (PGL) accounts for 30% to 45% of extranodal non-Hodgkin lymphomas in eastern[1] and western countries,[2] with an upward trend in both incidence and survival owing to progress in diagnosis and treatment choices.[1-3]

Histologically, it is possible to distinguish 2 main categories, an indolent disease, ie mucosa-associated lymphoid tissue (MALT) lymphoma, and a more aggressive disease, mainly represented by diffuse large B-cell lymphoma (DLBCL), although some specimens will show features of both histologic types (MALT lymphoma with foci of DLBCL and DLBCL lymphoma with residue of MALT).[4-8]

The prognostic assessment and treatment decision depend on several factors. Apart from the exceptional need for a surgical approach, *Helicobacter pylori* (HP) infection status, disease extension and response to first-line treatment are central in determining the clinical course.[9-11] This approach has improved the prognosis, especially for patients suffering from MALT lymphoma, for whom the disease-specific survival rate has been > 90% at 5 years and about 80% to 90% after 10 years. This scenario is different for high-grade gastric lymphomas, for which the 5-year disease-specific survival rate has been about 65%.[12]

The increased awareness of the biology of PGLs and the new treatment modalities have also induced a change in the diagnostic and staging modalities of the disease. Several studies have reported that endoscopic ultrasonography (EUS) is a helpful and accurate

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imaging technique in the study and description of PGLs. Its application has also been evaluated in the several steps of PGL management with different, and seldom contrasting, findings, according to the step analyzed. The present review has focused on its role in the diagnostic workup, response assessment, and follow-up evaluation of patients affected by PGL.

EUS Is the Most Reliable Technique in the Diagnostic Workup of Gastric Lymphoma

The aspecific clinical features of the disease, ranging from dyspepsia to hematemesis and/or melena,[10] usually lead to the performance of endoscopy. However, because the lymphoma has usually developed in the submucosa layer, the endoscopic evaluation will sometimes miss the presence of the neoplastic mass.[13-15] The findings of PGLs at endoscopy can vary from a normal gastric pattern to aspecific gastric lesions, with an ulcerative, a polypoid or a diffuse infiltrative pattern[16] that can also occur in more frequent conditions, such as nonsteroidal anti-inflammatory drug–related gastritis. However, over time, the ability to diagnose PGL has been increasing, being biopsy during endoscopy the first act in diagnosing the disease.[13-15]

Once the diagnosis has been made, the next step is to verify the relationship between the lymphoma and HP infection. From a biologic viewpoint, the status of persistent inflammation due to HP infection is able to create, in the context of the gastric wall, a chronic inflammatory state, with the development of an "acquired" mucosa-associated lymphoid tissue (MALT) of the stomach. Basically, the development of gastric lymphoma can be divided into 2 steps[17,18]:

1. HP-dependent: a strong relationship is present between tumor growth and the inflammatory background created by the HP infection; usually at this step, the tumor is confined to the mucosa and submucosa layers
2. HP-independent: cumulative DNA damage has led to the formation of immortalized lymphocytes, and, as a consequence, the tumor is no longer dependent on the presence of HP; usually at this step, the tumor has invaded the muscularis mucosae

These biologic considerations are fundamental in understanding why limited disease will respond greatly to HP eradication treatment, while HP eradication treatment alone will not be sufficient in advanced-stage disease.[17,18] In addition to the biologic considerations, investigators have tried to develop useful tools to help to distinguish gastric lymphomas according to their HP-dependent or HP-independent status.

Abdominal computed tomography (CT) is a common procedure in the evaluation of patients with gastric lymphoma. However, gastric MALT lymphomas will sometimes have a normal appearance on the CT scan,[19] with a wall thickness < 5 mm.[20] Additionally, low sensitivity has been observed in detecting perigastric lymph node involvement using CT.[21] Three-dimensional CT has increased the sensitivity (80%) and specificity (90%) of the technique in describing gastric wall lesions.[22] The sensitivity in detecting gastric lesions has also been ameliorated by the use of oral contrast agents, by which luminal constriction, dilatation (small bowel mainly), or cavitation can be observed.[20] However, CT will fail to distinguish involvement of the different gastric layers, with only vague information possible.

In contrast, EUS can provide a precise description of the abnormalities present in a specific gastric wall layer. Thus, its use has been central in establishing locoregional staging, giving information for the prediction of response to HP eradication, which, in some series of early-stage MALT lymphoma, has reached 100%.[9,23-26] The first pioneer investigations have established that EUS can be used to measure the entirety of gastric wall involvement and to detect perigastric lymph node involvement, with an accuracy of about 95%, greater than the sensitivity of CT at 85%. Thus, EUS has been the procedure of choice in assessing the size and depth of gastric wall lesions and perigastric nodes,[27,28] while the involvement of distant sites can still be better defined using CT.[29]

EUS has also shown the best accuracy in differentiating gastric wall lesions.[30] The pattern of horizontal spread has been related to PGL more than the vertical spread, which is more likely to be found in gastric carcinoma.[31] Also, the imaging pattern of the gastric wall is more homogeneous and pronounced in gastric lymphomas than in other subepithelial lesions, with an enlargement of gastric folds and preserved appearance of mucosa on endoscopy.[32] The American Gastroenterological Society has reported that EUS is a reliable tool for differentiating intramural or external gastric masses with high accuracy.[33]

The pioneer study by Suekane et al[34] related the morphologic and histopathologic pattern of subepithelial lesions. They showed that localized lesions with a horizontal expansion have a greater probability of being related to low-grade lymphoma than mass-forming or diffuse infiltrative lesions, which were more likely to be high-grade lymphomas. Nevertheless, it is difficult to translate these peculiar minutiae into clinical practice. Therefore, the trustworthiness of EUS in distinguishing benign from malignant lesions is low, and a biopsy is always required.[35]

Endoscopy with mapping biopsy specimens ($\geq$ 8 biopsies) represents the best diagnostic method, and this is critical, because different lesions can be found with EUS, and the histological evaluation is mandatory to determine the proper treatment.[36]

In contrast to CT, EUS, with a standard probe at 5 MHz, will be able to detect the 5 gastric layers. Using probes with a greater frequency, $\geq$ 7 layers can be seen. Previous studies debated whether a direct correspondence was present between the echoendoscopic and histologic layers.[37,38] Currently, the consensus is that the layers identified using EUS do not fully correspond to the histologic layers[33,39] (Table 1). Furthermore, EUS can differentiate the involvement of the first or second layer with an accuracy of about 83%.[19] PGLs usually arise in layer 2, 3, or 4,[40] such that it will

Table 1 Correspondence Between Anatomic and Echographic Layers of Stomach According to American Gastroenterological Association[33]

Echographic Layer	Anatomic Correspondence
Layer I	Superficial mucosa
Layer II	Deep mucosa
Layer III	Submucosa plus acoustic interface between submucosa and muscularis propria
Layer IV	Muscularis propria minus acoustical interface between submucosa and muscularis propria
Layer V	Subserosa fat and serosa