REVIEW ARTICLE

Cirujano General

July-September 2019
Vol. 41, no. 3 / p. 202-207

Gastric linitis in lymphoma. Utility of the endoscopic ultrasound in the diagnostic

Linitis gástrica por linfoma. Utilidad del ultrasonido endoscópico en el diagnóstico. Reporte de caso y revisión

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Keywords:
Gastric linitis, lymphoma, ecoendoscopy.

Palabras clave:
Linitis gástrica, linfoma, ecoendoscopia.

ABSTRACT

Introduction: The prevalence of gastric cancer in Mexico has increased in recent years, with a predominance in men. Risk factors are alcohol, tobacco, and *Helicobacter pylori* infection, considered in our population as of a moderate risk. Although adenocarcinoma continues to predominate as the most frequent gastric malignancy, according to the WHO, a non-negligible percentage (7-8%) is occupied by extra-nodal non-Hodgkin's lymphoma and leiomyosarcomas. Appropriate diagnostic approach and differentiation between adenocarcinoma and lymphoma are crucial since prognosis and treatment depend on it. **Case report:** A 79-year-old man with asthenia, malignant hypercalcemia and an incidental gastric thickening found by tomography. Endoscopic ultrasound was performed and the diagnosis of gastric lymphoma of a diffuse variety (Ann Arbor modified II2) was established. **Literature review:** Endoscopic ultrasound is considered a tool for the diagnosis of gastric carcinoma in all variants, mainly where the disease is in deep layers. **Conclusion:** Endoscopic ultrasound is a method that leads to high diagnostic accuracy in gastric lymphoma allowing biopsies of total wall thickness for immunohistochemistry.

RESUMEN

Introducción: *La prevalencia de cáncer gástrico en México ha tenido un incremento en los últimos años con predominio en hombres. Los factores de riesgo son el consumo de alcohol, tabaco e infección por Helicobacter pylori, considerado en nuestra población como de riesgo moderado. Aunque el adenocarcinoma sigue predominando como la neoplasia maligna gástrica más frecuente, un porcentaje no despreciable del 7-8%, según la Organización Mundial de la Salud, lo ocupa el linfoma no Hodgkin (extranodal) y los leiomiosarcomas. El adecuado abordaje diagnóstico y la diferenciación son cruciales entre el adenocarcinoma y el linfoma, ya que de ello depende el pronóstico y el tratamiento.* ***Caso clínico:*** *Se comunica el caso de un hombre de 79 años con astenia, hipercalcemia maligna con hallazgo incidental de engrosamiento gástrico por tomografía. Se realizó ultrasonido endoscópico para el diagnóstico de linfoma gástrico de variedad difuso (Ann Arbor modificada II2).* ***Revisión de literatura:*** *El ultrasonido endoscópico es considerado una herramienta para el diagnóstico de neoplasias malignas gástricas en todas sus variantes, principalmente donde la enfermedad se encuentra en capas profundas.* ***Conclusión:*** *El ultrasonido endoscópico es el método que nos lleva a obtener alta precisión diagnóstica en linfoma gástrico, permitiendo la toma de biopsias del espesor total de la pared del bloque celular para realizar diagnóstico diferencial siempre con inmunohistoquímica.*

Abbreviations:
MALT = mucose associated lymphoid tissue.
DLBCL = Diffuse large B-cell lymphoma.
NHL = non-Hodgkin lymphomas.

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Received: 20/11/2017
Accepted: 13/05/2019

INTRODUCTION

The prevalence of gastric cancer in Mexico has shown an increase from 3% in 2010 to 3.26% in 2013, with a greater predominance in men (5.22%) vs women (2.21%). Mortality is 8.88%, with a rate of 5.0 per 100,000 inhabitants and greater predominance in people aged 50 years or more. According to the national histopathological record of neoplasms, Mexico City (27.7%) and Nuevo León (8.9%) have the highest frequency.

How to cite: Membrillo-Romero A, Escandón-Espinoza YM. Gastric linitis in lymphoma. Utility of the endoscopic ultrasound in the diagnostic. Cir Gen. 2019; 41(3): 202-207.

Risk-factors with a high degree of association are alcohol and tobacco consumption and *H. pylori infection*, although the Latino population also shows a moderate risk.[1] Ninety percent of gastric cancers are adenocarcinomas, and the remaining are non-Hodgkin's lymphomas (NHL) (5-8%) and leiomyosarcomas (1-3%). Differentiation between adenocarcinoma and lymphomas is crucial, as prognosis and treatment differ between them.[2] Most primary gastric lymphomas are mucosal lymphoid tissue-associated B-cell lymphoma (MALT) or diffuse large B-cell lymphoma (DLBCL).

The most widely used classification is the Ann Arbor classification (modified by Musshoff), which subdivides MALT lymphoma into the stages shown in *Table 1*.[2]

The following is a case of gastric NHL diagnosed by cytological fine needle biopsy guided by endoscopic ultrasound.

CASE PRESENTATION

A 79 year-old man with a history of three months with weight loss, asthenia, adynamia, presented with muscle spasms with lumbago irradiation, and slight limitation of mobility that worsened with activity and improved with rest. He reported hypoxia, fullness, a discrete weight loss, with no major added symptoms. Nor did examination reveal other signs. In consultation hypercalcemia greater than 14 mg/dl, hemoglobin 11.4 g/dl, hematocrit 33.3%, glucose 122 mg/dl, alkaline phosphatase 53 U/L, lactic dehydrogenase 860 U/L, sodium 138 mEq/L, potassium 3.6 mEq/L, chlorine 106 mEq/L, vitamin D 16.2 ng/dl, parathyroid hormone 12 pg/ml were found. A transabdominal ultrasound reported hepatosplenomegaly, so an extension study was initiated to rule out systemic lymphoma.

As part of the protocol, CT scan found thickening of the gastric wall of 18 mm with some regional and distant nodes *(Figure 1)*. Endoscopic ultrasound was requested for evaluation and corroboration of the increase in thickness. It showed two ulcers with greyish fibrin of necrotic aspect without visible vessels *(Figure 2)*, with retraction of gastric folds between the fundus and cardia, both of 1. 5 cm diameter and perilesional inflammatory changes. There was an increase of the gastric wall thickness of 30 mm, (normal < 4 mm) with loss of the layered ultrastructure *(Figure 3)*. With a 22 Gauge aspiration needle *(Figure 4)* a biopsy was taken from the gastric wall, samples were obtained for cytology and cell block, and they were sent for immunohistochemistry tests CD3, CK AE1-AE3, CD20. A pair of regional nodes was identified with no involvement of neighboring organs and no free fluid in the cavity. The left hepatic lobe was normal, the

Table 1: Classification of systemic lymphoma according to Ann Arbor.

Ann Arbor classification (modified by Musshoff)	Treatment
I. Affects only the stomach, respecting the lymph nodes	Erradicate *H. Pylori*
• I1 limited to mucosa and submucosa	
• I2: Invades the deepest layers of the stomach (up to serosa)	
II. Affects the lymph nodes on the same side of the diaphragm as the stomach	Erradicate *H. pylori*
• II1: local, para-gastric or para-intestinal ganglia	Radiotherapy or rituximab
• II2: distant nodes (mesenteric, para-aortic, para-cavity, pelvic or inguinal)	Rituximab ± polychemotherapy
III. Affects the lymph nodes on both sides of the diaphragm	Rituximab ± polychemotherapy
IV. Lymphoma is spread throughout the body	Rituximab ± polychemotherapy

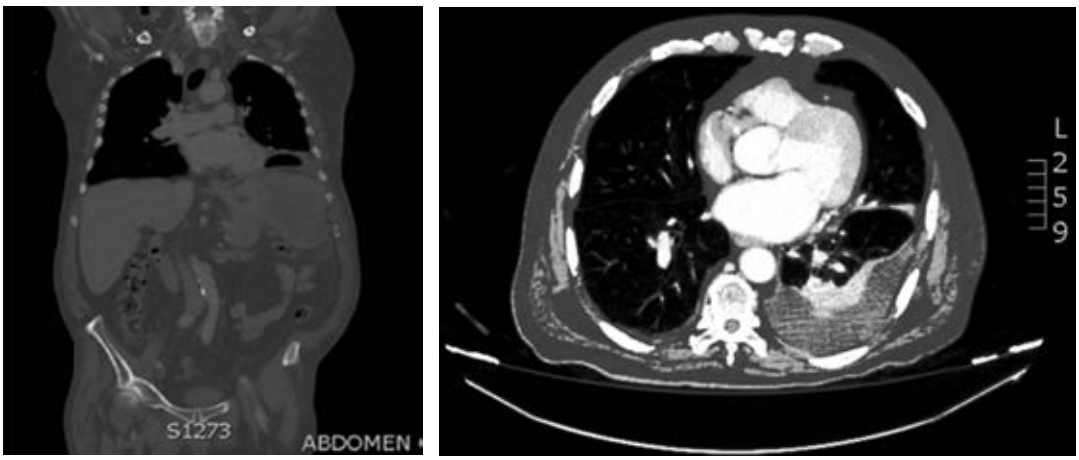

Figure 1: *Computed tomography scan showing only thickening of the gastric wall.*

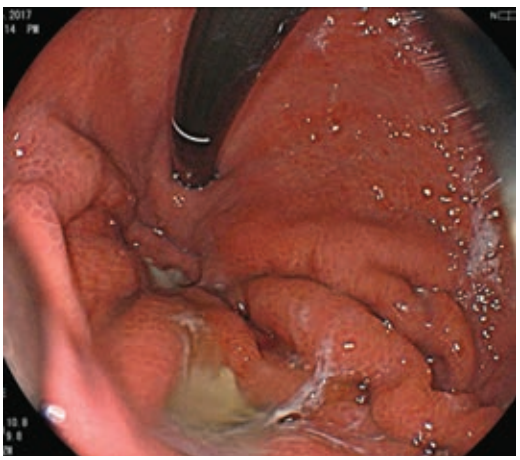

Figure 2: *Gastric fundus ulcer.*

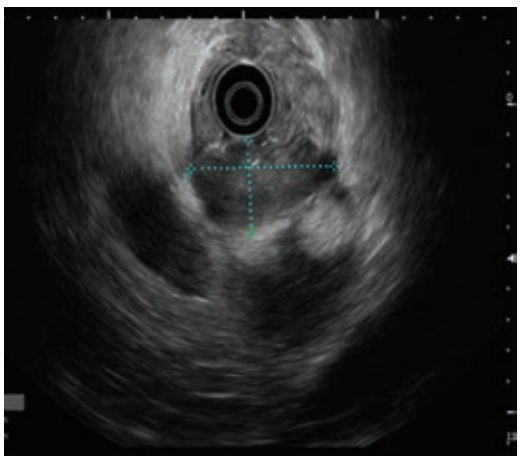

Figure 3: *Wall thickness of the stomach.*

pancreas showed no alterations. The positive pathology result for CD20 confirmed the presence of B-cell lymphoma *(Figure 5A and 5B)*, so chemotherapy was initiated.

REVIEW

Lymphomas are classified as non-Hodgkin's and Hodgkin's. Of these, Hodgkin's lymphomas rarely affect the digestive tract. Non-Hodgkin's lymphomas can be nodal and extranodal. The current classification of the World Health Organization (WHO), based on the REAL (Revised Euro-American Lymphoid) defines "clinical entities" based on a) morphological, b) immune-phenotype, c) genetic and d) clinical aspects. Thus we can group gastrointestinal lymphomas as follows:

Classification of primary non-Hodgkin's lymphomas of the gastrointestinal tract

B Cells

1. MALT lymphomas
   (a) Low grade.
   (b) High grade, with or without an associated low grade component
2. Mantle cell lymphoma (lymphomatous polyposis).

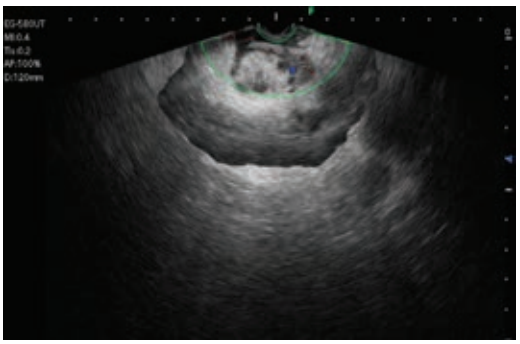

Figure 4: *Aspiration biopsy of a gastric wall lesion.*

3. Non-endemic Burkitt lymphoma.
4. Other types equivalent to the classic types originating in lymph nodes.
5. Related to immunodeficiencies.

T Cells

1. Associated with enteropathy.
2. Others not associated with enteropathy.

Non-Hodgkin's tumors may originate in non-nodal tissues such as the gastrointestinal tract and are considered primary when extra-nodal involvement is equal to or greater than 75% relative to nodal involvement.[2,3]

Most primary gastric lymphomas are mucosal lymphoid tissue-associated B-cell lymphomas (MALT) or diffuse large B-cell lymphoma (DLBCL).

The type of management of primary NHLs depends on the staging of the tumor. In this regard, endoscopic ultrasound (EUS) is considered the most accurate modality for loco-regional staging of gastric neoplasms, including gastric lymphoma.[3-5]

Primary gastric NHL or gastric infiltration secondary to systemic lymphoma occurs in 20-60% of newly diagnosed cases and is usually considered a disseminated disease requiring extensive diagnostic and treatment strategies.

The gastric submucosa does not contain lymphoid tissue under normal conditions, and the development of lymphoid tissue at this site occurs in response to *H. pylori (Hp)* infection and is therefore causally associated with chronic *Hp* infection and the development of lymphoma.[4-7] *Hp* infection results in chronic gastritis with lymphocyte infiltration although only one in 30,000 to 80,000 infected persons develops lymphoma.

The response rate to eradication treatment is related to the extent of lymphoid infiltration of the gastric wall; this can have a predictive value for the effectiveness of treatment. Considering the eradication of *Hp* as the first choice treatment in case of low-grade MALT gastric lymphomas, complete regression is achieved in 40-100% of cases.

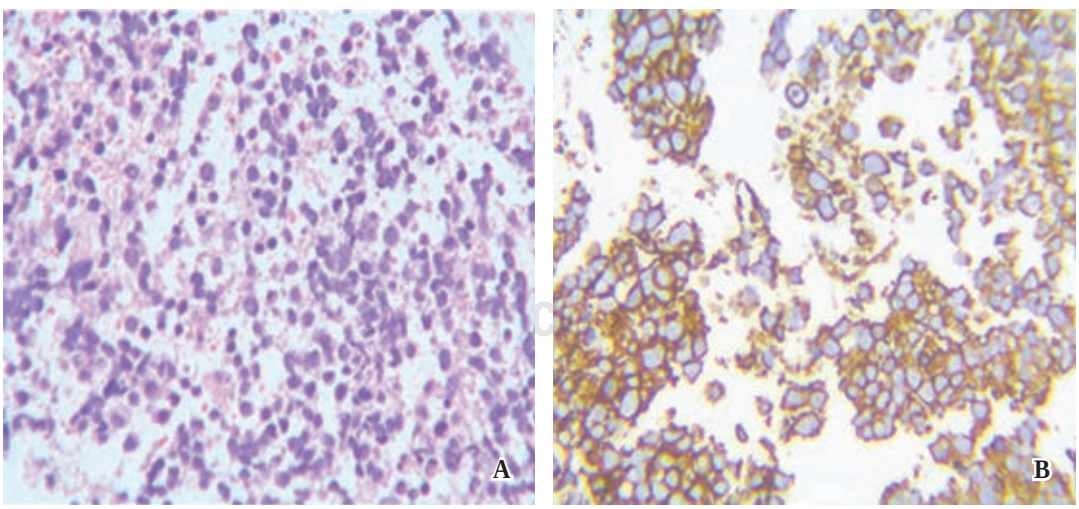

Figure 5: (A) *Cytology showing loss of cell polarity.* ***(B)*** *Immunohistochemistry positive for CD20.*

MALT gastric lymphoma appears as a painless disease, its clinical presentation has a variegated picture ranging from intermittent dyspepsia and epigastric pain to alarm symptoms such as persistent upper gastrointestinal bleeding or emesis. B-type symptoms (fever, night sweats, and weight loss) are extremely rare in this group of patients.

In gastric type MALT lymphoma, there is a proliferation of lymphoepithelial lesions. The effectiveness of CT scans in diagnosing and staging gastric cancer ranges from 53 to 70%.[8,9] Endoscopic ultrasound has been increasingly used for the diagnosis and staging of malignancies of the upper gastrointestinal tract, and its ability to delineate the gastric wall is superior to CT.[5]

The diagnosis of this type of gastric disease depends on taking endoscopically guided biopsies for many of the morphological varieties of lymphoma, namely the nodular, the ulcerous, and the infiltrating. In the diffuse one, a biopsy is often inconclusive, as the disease is below the mucosal layer, which prevents an adequate taking of biopsies with conventional forceps. In this regard, endoscopic ultrasound is the best diagnostic method in the exploration and evaluation of the gastric layers. It accurately determines the depth of the disease, makes it possible to obtain deep layer needle-biopsies and regional lymph node biopsies. It is an indispensable diagnostic method to determine the depth of infiltration into the gastric wall, the layers involved, and the presence of regional lymph nodes.[6] No ultrasound data can distinguish benign from malignant gastric lesions, although there are criteria suggestive of malignancy.[7] A diathermic trap can be used to obtain deeper specimens to increase diagnostic performance. This technique has not been widely accepted because of the risk of major complications, particularly bleeding and perforation. Besides, macrobiopsies can be negative in the presence of malignancy.[8,9]

In patients with thickened gastric folds where endoscopic biopsy is inconclusive, ultrasound-guided fine-needle aspiration (FNA) biopsy and sampling of the deeper layers of the stomach are the only ways to make an accurate diagnosis.

Echoendoscopy is superior to CT in diagnosing the locoregional spread of gastric cancer (approximately 85% in T and 80% in N staging).[2,7,8,10] It allows differentiating between a patient with early cancer and one with advanced cancer. It also allows to support with certainty an adequate treatment; that is, an endoscopic treatment by dissection when it is superficial; a surgical treatment in cases with a deep but localized lesion; and a purely pharmacological treatment in cases of advanced or systemic disease.[11,12] An echoendoscopy that shows criteria of malignancy by image plus an FNA biopsy has a diagnostic accuracy close to 90%, compared to 66% of an image by EUS. With immunohistochemical stains, the performance reaches 100% and allows a differential diagnosis. The management of MALT lymphoma is stage-dependent. EUS is currently considered the most accurate modality for local staging.[12-14]

Echoendoscopy is also useful in the follow-up of patients treated with chemotherapy since it allows the evaluation of the restoration of the gastric wall or the reduction of its thickness after successful treatment. Persistent thickening can be interpreted as a residual disease when endoscopic biopsies are negative. Immunohistochemistry tests that help to differentiate the varieties of lymphoma are the key to the diagnosis of this group of diseases.

In this case, the immunohistochemistry analysis of a cell block taken with a conventional ultrasound-guided needle was sufficient for a conclusive diagnosis.

CONCLUSION

Endoscopic imaging strongly suggests the diagnosis; however, to have a diagnostic accuracy above 90% it is necessary to resort to biopsy and immunohistochemical testing of samples, so the cell block obtained by aspiration, and not only cytology, is the method that leads to the highest diagnostic accuracy, mainly in cases where the disease is located in deep layers of the gastric wall.

Contribution. Endoscopic ultrasound is a highly accurate imaging method to evaluate diseases that affect one or more layers of the digestive wall, the image may suggest the

diagnosis of gastric lymphoma, but by using an aspiration needle to obtain histological material, diagnosis is more accurate; however, immunohistochemical tests can lead to a more accurate treatment and better monitoring of remission. Many digestive diseases, including primary gastric lymphoma or secondary infiltration, are well explored and confirmed with the use of endoscopic digestive ultrasound.

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