Med Clin (Barc). 2015;144(10):470–474

MEDICINA CLINICA

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Diagnosis and treatment

Large gastric folds: Differential diagnosis☆

Pliegues gástricos engrosados: diagnóstico diferencial

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ARTICLE INFO

Article history:
Received 4 November 2014
Accepted 20 November 2014
Available online 14 January 2016

Large gastric folds: differential diagnosis

The gastric mucosa presents mucosal folds in the fundus that extend longitudinally along the gastric body to the antrum, where they become flat. In the presence of thickened gastric folds, two factors need to be assessed: subjectivity and degree of air insufflation. Various conditions are associated with gastric fold thickening. To facilitate their study, these are divided into: (1) hyperplastic gastropathies, in which there is an increase in the number of oxyntic gland cells; and (2) non-hyperplastic gastropathies (Table 1).

Hyperplastic gastropathies

Ménétrier's disease

This rare disease, also known as hyperplastic hypersecretory gastropathy or protein-losing enteropathy, is of unknown prevalence and more commonly affects middle-aged male patients.

Its aetiology is unknown. The cytomegalovirus (CMV) seems to be responsible for the disease in children,[1,2] while in adults it is associated with other microorganisms, apart from CMV, such as *Helicobacter pylori (H. pylori)*, herpes simplex virus and *Mycoplasma pneumoniae*; it has even been related with ulcerative colitis.[3–6] In all cases, *H. pylori* should be ruled out and, at least in children, CMV should also be discounted. The pathogenic mechanism is an increase in the transforming growth factor α (TGF-α) and activation of the epidermal growth factor receptor (EGFR), which results in a proliferation of mucosal cells from the gastric body and fundus.[7,8]

From a clinical point of view, it may cause abdominal pain, hyporexia, vomiting, digestive haemorrhage or diarrhoea.[8] Hypoproteinaemia or hypoalbuminaemia without urine protein should be considered possible indicators of the disease. This alteration is due to the loss of proteins through the gastric mucosa, which may lead to oedema, ascites, pleural or pericardial effusion. In children, the disease appears around the age of 3, is of sudden onset and causes intense vomiting and generalised oedema; but the prognosis is good, with spontaneous resolution in weeks.[1,2] However, in adults it is chronic. It is characterised by an alkaline pH during gastric aspiration due to the action of the TGF-α, which reduces gastric acid secretion. The malignancy risk of Ménétrier's disease (ME) is a controversial subject.[9]

The endoscopy shows enlarged, tortuous, cerebriform-like folds in the fundus and in the major curve of the gastric body, the antrum generally being preserved (Fig. 1). The ecoendoscopy shows thickening only of the first 2 layers of the gastric wall (superficial mucosa and deep mucosa with *muscularis mucosae*).[9–11] Macrobiopsies with macro forceps or polypectomy snares are recommended so as to include *muscularis mucosae*.[11]

The histological study is not pathognomonic. ME is characterised by diffuse foveolar hyperplasia, tortuous-like gland proliferation with cystic dilations and loss of parietal and main cells, which are replaced by mucosal cells. The lamina propria may contain a mild inflammatory infiltration.[8,9]

Treatment should consider nutritional supplements, a hyperproteic diet, intravenous albumin or diuretics. In children, due to its self-limited progression, conservative treatment is usually enough, and ganciclovir is considered in severe cases of more than two weeks duration, immunosuppressed patients or newborns.[12] In adults, *H. pylori*[13] eradicating treatment is indicated. If the disease continues, the typical treatment is surgery (total gastrectomy or sub-total gastrectomy with preservation of the antrum), since it also eliminates the risk of potential malignisation. However, the discovery of various medical treatments has made it possible to reserve surgery for refractory cases. The disease has

☆ Please cite this article as: García García de Paredes A, Martínez González J, Crespo Pérez L. Pliegues gástricos engrosados: diagnóstico diferencial. Med Clin (Barc). 2015;144:470–474.

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Table 1
Differential diagnosis of thickened gastric folds.

Hyperplastic gastropathies
Ménétrier's disease
Zollinger–Ellison syndrome or gastrinoma
Hyperplasia of parietal and enterochromaffin cells secondary to the use of PPI
Non-hyperplastic gastropathies
Infections
Gastritis by *Helicobacter pylori*
Other infections
Syphilis
Tuberculosis
Cryptococcosis
Histoplasmosis
Aspergilosis
Neoplasia
Gastric adenocarcinoma
Gastric lymphoma
Gastrointestinal stromal tumours
Miscellaneous
Amyloidosis
Sarcoidosis
Crohn's disease
Eosinophilic gastroenteritis
Lymphocytic gastritis
Polyposis syndromes

been treated with H2 receptor antagonists, proton pump inhibitors (PPI), anticholinergics, somatostatin analogues (octreotide)[14,15] and anti-EGFR monoclonal antibodies (cetuximab). Though there are doubts about the actual efficiency of each of these treatments, it seems reasonable to consider them before surgery. Of these treatments, those with most recent evidence are octreotide and cetixumab—the latter giving promising results.[15–17] If a medical treatment is chosen, given the controversy regarding the risk of gastric cancer, an endoscopic follow-up is recommended.

Zollinger–Ellison syndrome

This is characterised by very high gastrin levels[18] resulting from functioning neuroendocrine tumours (gastrinomas) which are usually located in the gastrinoma triangle that comprises the duodenum, pancreas and adjacent lymph nodes.[19] The sporadic form is found in 80% of patients and is usually diagnosed in the fifth decade of life. In the remaining 20% of patients it is part of the multiple endocrine neoplasia type 1 (MEN-1) syndrome, which also presents parathyroid and pituitary tumours; diagnosis usually occurs in younger patients.[19]

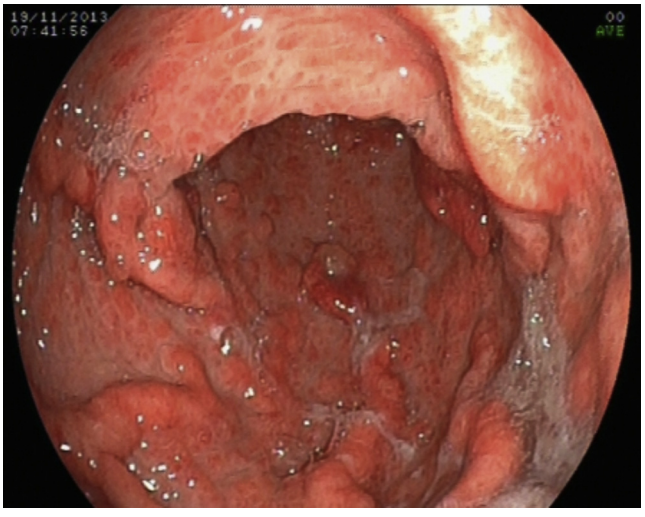

Fig. 1. Thickened, tortuous gastric folds with oedematous and polypoid mucosa in a patient with Ménétrier's disease.

The clinical manifestations include those resulting from gastric acid hypersecretion: multiple and recurrent ulcers located in the duodenal bulb in 75% of patients, though they may be located in other uncommon areas[19]; peptic oesophagitis, which can be very severe and is one of the causes of "black oesophagus"; and diarrhoea due to the inactivation of pancreatic enzymes and damage to intestinal villi.

If diagnostic suspicion exists, serum gastrin must be determined in a fasting state, and PPI should be withdrawn 3–7 days earlier. Slightly elevated serum gastrin levels (>110 pg/ml) are not sensitive and specific enough. However, gastrin figures above 1000 pg/ml, in the presence of acid gastric pH, practically determine the diagnosis.[20] If, on gastrin determination, doubts about diagnosis remain, the secretin stimulation test helps distinguish this syndrome from other causes of hypergastrinaemia, so gastrin figures above 200 pg/ml post-stimulation have 83% sensitivity and 100% specificity for the diagnosis of gastrinoma.[20] Radiological (computed tomography, magnetic resonance imaging and octreoscan) and endoscopic techniques (ecoendoscopy) permit local and distance assessment. MEN-1 syndrome should be ruled out in young patients with a family history or other manifestations, such as hyperparathyroidism.

The treatment of Zollinger–Ellison syndrome includes: (a) treatment of functional syndrome, for which the development of acid antisecretory agents has significantly reduced the morbidity and mortality of the ulcerative disease. High PPI doses are recommended, and these are adjusted on the basis of the clinical activity and cicatrisation of ulcers[19]; and (b) treatment of the tumour: if the tumour is localised and has no distant dissemination, then surgical resection is curative in 50% of cases, with an 80% chance of survival at 10 years. However, only 30% of gastrinomas meet removal criteria on diagnosis.[21] MEN-1 syndrome gastrinomas have no clear surgical indication given that they are multifocal and present high recurrence rates. If metastasis exists, there are several options: octreotide, hepatic lesion resection, artery embolisation with or without chemotherapy infusion, radiofrequency or systemic chemotherapy, which lead to 30% survival at 10 years.[19,21]

Hyperplasia of parietal and enterochromaffin cells secondary to proton pump inhibitors

PPIs block the H^+-K^+ATPase pump of parietal cells, thus reducing gastric acid production. This hypochlorhydria stimulates the secretion of gastrin, which has a considerable trophic effect on parietal cells, resulting in gastric fold thickening. The trophic effect also affects enterochromaffin cells of the gastric fundus and body, which may result in a gastric carcinoid tumour.[22] This can be distinguished via the history of continued PPI consumption and a compatible histology (increased number of parietal cells, sometimes with protrusion into the gland lumen and dilation of oxyntic glands without foveolar hyperplasia[9]). The suspension of PPIs normalises the gastric mucosa hystology.

Non-hyperplastic gastropathies

Infections

Gastritis by Helicobacter pylori

Infection caused by *H. pylori* has high prevalence and affects more than 50% of the population although this varies from one country to another.[23] It is the most common cause of gastric mucosa thickening.[24] The histological study shows bacilli on the mucous surface and an intense infiltration of polymorphonuclear cells, and