

Ménétrier's disease associated with gastric adenocarcinoma in a child – imaging aspect

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Article received: 6/29/2016

Accepted for publication: 7/26/2016

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<http://dx.doi.org/10.1590/1806-9282.62.06.485>

CASE REPORT

Female patient aged 18 years and 8 months, with diagnosis of hypertrophic gastritis since the age of 10, when she started having sporadic vomiting, weight loss, and anemia (Hb = 5.0 at diagnosis in August 2007).

On her first upper gastrointestinal endoscopy (UGE) performed at the Instituto da Criança (ICr) at HC-FMUSP, in August 2007, it was seen globally hypertrophied and swollen gastric mucosa, with an infiltrative lesion with ill-defined margins. A biopsy confirmed hyperplastic gastritis with a pattern of Ménétrier's disease.

Outpatient follow-up was initiated at Pediatric Gastroenterology Service of ICr in January 2008, with periodic clinical evaluation and UGE. The patient progressed in the following months with poor appetite and episodes of upper gastrointestinal bleeding and melena, requiring hospitalization in the city of origin and transfusions of blood concentrates. In the following years, she showed less recurrent episodes of bleeding than as seen in the first years after diagnosis, but continued undergoing serial UGEs for disease control and malignant surveillance, maintaining the same macroscopic and microscopic pattern. The patient has been submitted to extensive research for *Helicobacter pylori* in gastric biopsies, all with negative results, the same occurring with immunophenotyping for cytomegalovirus (CMV). Clinically, she continued to show poor weight gain, but with proper growth and no generalized edema at any time.

In 2009, a computed tomography (CT) with intravenous contrast of the abdomen was performed, which showed marked diffuse and symmetric thickening of the gastric folds, with no evidence of nodular lesions (Figure 1).

In 2015, a control UGE with biopsies showed she maintained the macroscopic appearance of intense hypertrophy of gastric folds in the body and fundus with a reddish pseudotumoral appearance, uneven and multilobulated surface. In the pathological examination, signs of malignancy were found, a characteristic of moderately differentiated invasive adenocarcinoma, of no special type, negative for *H. pylori* (Figure 2). Two heterogeneous vegetative lesions were found (Figure 3) on a new CT scan.

The patient underwent total gastrectomy in 2015, with no need for adjuvant therapy.

DISCUSSION

Ménétrier's disease is considered rare by the Office of Rare Diseases of the National Institutes of Health, which means a prevalence of less than one in 200,000 individuals.² The disease was first described in 1888 by French pathologist Pierre Ménétrier (1859–1935).¹ It is a chronic and rare acquired gastric disease of unknown cause, but has been associated with some gastric diseases, including bacterial and viral infections: cultures and biopsies have shown an association with CMV, *H. pylori*, herpes simplex, and *Mycoplasma pneumoniae*.³

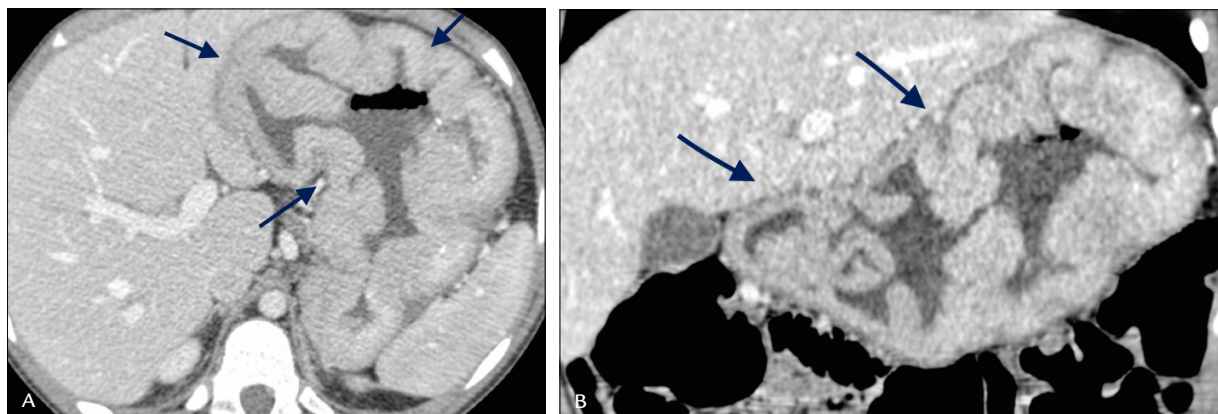


FIGURE 1 Axial (A) and coronal (B) CT scans performed with contrast show diffuse and redundant thickening gastric wall with no suspicious lesions (arrows).

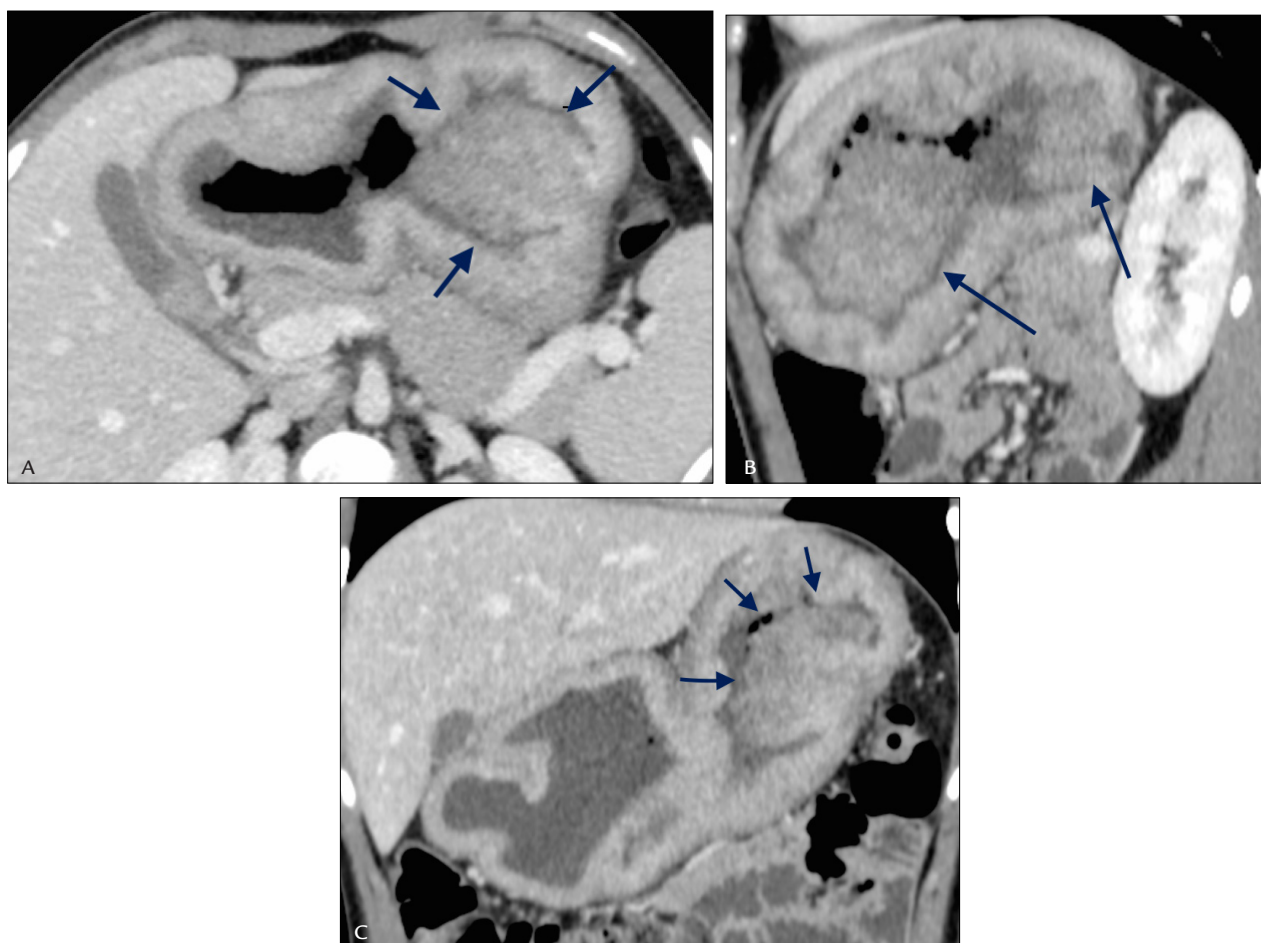


FIGURE 2 Axial (A), sagittal (B), and coronal (C) CT scans performed with contrast show two vegetating lesions (arrows) in the large gastric curvature, in addition to diffuse parietal thickening.

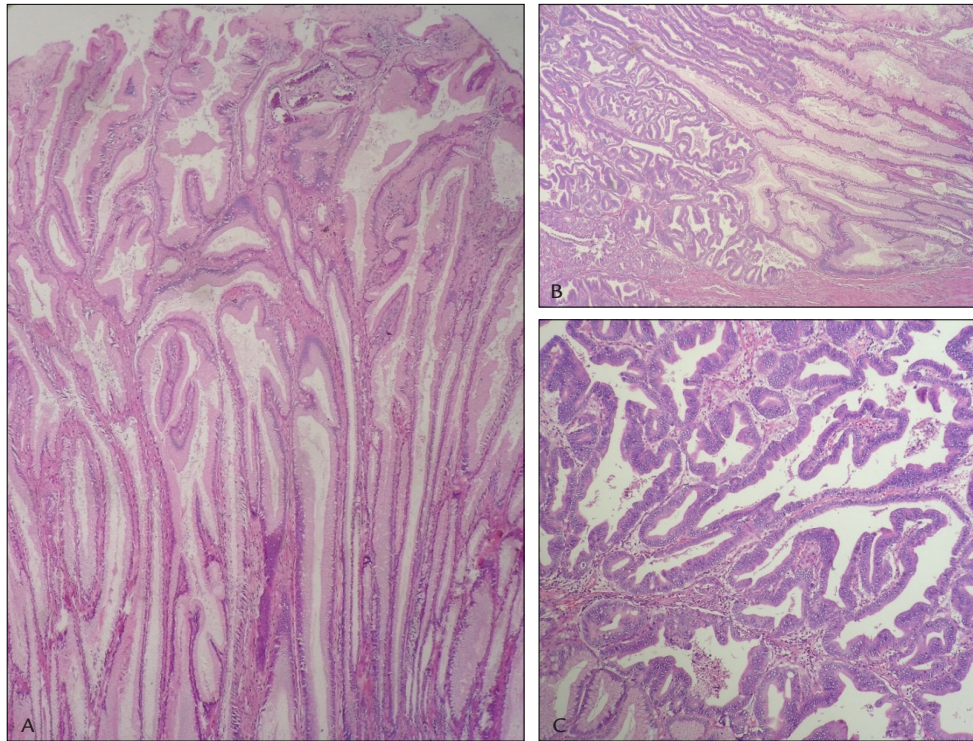


FIGURE 3 A. Non-neoplastic gastric mucosa. The glands show marked foveolar hyperplasia, with elongated and tortuous appearance, and cystic dilatation in some locations (not shown here). The lining cells are fully differentiated, with abundant intracytoplasmic mucin without cytologic atypia or intestinal metaplasia. The findings are characteristic of Ménétrier's disease (hematoxylin-eosin, 100X). B. Adenocarcinoma, which refers to the left half of the image, in contrast with the surrounding gastric mucosa. The high nuclear-cytoplasmic ratio and the loss of nuclear polarity of the tumor cells confer a "bluish" aspect to the tumor. In the adjacent mucosa, cell nuclei retain their position in the basal pole of the cell and intracellular mucin is preserved (hematoxylin-eosin, 40X). C. Gastric tubular adenocarcinoma. Markedly tortuous and dilated glands are seen, covered by hyper-proliferating atypical cells, with increased nuclear size (karyomegaly), high nuclear-cytoplasmic ratio and loss of normal nuclear polarity (hematoxylin-eosin, 200X).

Ménétrier's disease is characterized by a marked thickening of the gastric folds with proliferation, stretching and cystic dilation of the gastric glands, protein-losing gastroenteropathy, and hypoalbuminemia.⁴⁻⁶ There are assumptions that the mucosal changes in Ménétrier's disease are secondary to increased production of growth factor.^{1,2,6,7}

The disease has been reported in children but it is more common in adults, especially in the age range of 30 to 60 years.⁷ While it is a progressive disease in adults, it rarely needs aggressive treatment in children due to its benign nature, and it usually subsides spontaneously within 1 to 5 months with supportive care alone.³

Patients present various characteristic signs and symptoms, including epigastric pain, nausea and vomiting, asthenia, anemia, anorexia, weight loss, hypochlorhydria, and abnormal enteric protein loss associated with subcutaneous edema.^{7,8} The classic triad is gastrointestinal symptoms, peripheral edema, and giant gastric folds.⁷

The diagnosis of Ménétrier's disease is done using a combination of complementary tests such as radiography, ultrasonography (USG), tomography, pH-metry, UGE, and histology.^{2,7,10}

Gastric involvement is more prominent in the great curvature and it is usually found in the fundus and gastric body, but it can be diffuse, affecting all parts of the stomach, especially in children. Hypoproteinemia can cause irregular thickening of the folds of the small intestine.¹¹

On contrast-enhanced radiographies, Ménétrier's disease is characterized by the presence of giant, abnormally thickened, twisted and tortuous gastric folds, yet flexible, with contrast trapped between folds, forming linear spicules perpendicular to the gastric contour. The folds are usually less than 1.0 cm thick in the fundus, and 0.5 cm in the antrum, and parallel to the major axis of the stomach. Sometimes, large and irregular folds can mimic polyps, and hypersecretion of mucus can di-

lute the barium-based contrast, therefore limiting the analysis of the mucosal lining.^{2,3,7,11}

USG is an affordable and non-invasive examination, which can be used both in the initial investigation and to assess disease progression. USG shows five layers of the gastric wall: hyperechogenic layer (mucosa), hypoechogenic layer (muscularis mucosa), hyperechogenic layer (submucosal), hypoechogenic layer (the muscularis propria), and another hyperechogenic layer (subserosal, serous, and interface).¹⁰

On CT scans, the enlarged folds protrude into the gastric lumen and distort the mucosal surface. In general, the serosal surface remains smooth and the gastric wall between folds remains normal or only slightly thickened. After intravenous administration of contrast medium, hyperenhancement of the folds is noted. CT findings generally correspond to those of the UGE. Thus, TC, less invasive and generally less costly and more affordable than UGE, can be useful not only for diagnosis but also for follow-up of patients with Ménétrier's disease.^{2,3,11}

On UGE, the gastric mucosa shows marked irregular thickening, edema, and spongiform and tortuous appearance, with the folds resembling the brain. Gastric pH is generally alkaline. Endoscopic ultrasound has been used to evaluate gastric thickening. Five layers can be identified in a normal endoscopic ultrasound, corresponding to the mucosa, muscularis mucosa, submucosa, muscularis propria, and serosa. Studies show that in Ménétrier's disease only the second layer (muscularis mucosa) is thickened. The mucosa also shows increased echogenicity, while the submucosa and the muscularis propria remain normal. Endoscopic ultrasound is useful in Ménétrier's disease to evaluate differential diagnoses to causes of diffuse hypertrophy of the gastric folds, and especially due to the possibility to perform a secure biopsy.^{2,3,12}

Scintigraphy can help, indicating protein loss from the stomach.¹⁰ However, a certain and definitive diagnosis cannot be made, requiring confirmation by histological analysis.⁷

Histologically, hypertrophy of the gastric folds, more evident in the body and fundus of the stomach in patients with Ménétrier's disease, presents massive expansion of the layer of mucous cells (foveolar hyperplasia), with a reduction in parietal cells, causing reduction of acid secretion. Although in some cases the parietal cells are preserved, in the vast majority there is a reduction in the number of these cells specialized in acid secretion in the stomach. It is important to note that, apparently, there are no inflammatory cells, intestinal metaplasia or dysplasia.^{2,7,8}

The totality of clinical, imaging, laboratory, and histological findings help differentiate Ménétrier's disease from other entities.²

Therapeutic techniques include anticholinergic drugs, prostaglandins, proton pump inhibitors, prednisone, and histamine blockers, associated with a high-protein diet. All treatments produced variable results.²

It is known that Ménétrier's disease increases the risk for gastric cancer around 2 to 15% over a lifetime, but the magnitude of this risk is uncertain because of the rarity of cases. The exact risk of developing gastric cancer is unknown and there is no consensus regarding screening with UGE.^{2,8,9} Nevertheless, CT findings are equivalent to those of UGE for Ménétrier's disease in children. Therefore, CT, a less invasive examination with less costs and more affordable than UGE, can be as useful as the UGE for the follow-up of these patients.⁴

Malignant diseases of the gastrointestinal tract are very rare in children, accounting for approximately 1.2% of all malignancies. Gastric adenocarcinoma (GAC) is extremely rare in children, accounting for about 0.5% of all malignancies of the gastrointestinal tract.^{13,14} It usually affects patients between 50 and 70 years, and is uncommon before the age of 40. The etiology of GAC is multifactorial, and risk factors include alcohol consumption, smoking, high-sodium diet, few vegetables, foods with nitrous components, and infections such as Epstein-Barr and *H. pylori*. But all of these factors are unknown in children, and only recently it was related to mutations in the E-cadherin gene (CDH-1). GAC appears in children sporadically as a consequence of inherited syndromes or after treatment of gastric lymphomas.^{13,14}

Differential diagnoses for pediatric gastric tumors include stromal tumors, hemangioma, lymphoma, squamous cell carcinoma, carcinoid tumors, fibroids, polyps from hereditary syndromes, leiomyosarcoma, and lipoma.^{13,14}

Symptoms vary according to the site of involvement and the extent of the tumor. Tumors located in the cardia lead to dysphagic symptoms, while tumors located distal to the cardia gastric produce nonspecific symptoms such as abdominal pain, loss of appetite, weight loss, vomiting, anorexia, fatigue, bloating, hematemesis, and melena.¹³⁻¹⁵

Barium-contrast radiography can be used for initial investigation as an alternative in locations without access to more complex tests. The main findings are polyps, ulcers, discontinuation and thickening of the folds, areas of barium filling defect, loss of gastric distension, and stenoses.^{16,17}

USG examination is easily accessible, inexpensive, and does not use ionizing radiation, but it is operator-

-dependent. The findings are wall thickening, usually diffuse, or a hypoechoic mass with echogenic center or “pseudo-kidney” sign.¹⁶

CT is the method of choice because, in addition to identifying the primary tumor, it assesses the signs of local invasion, regional and distant lymph node involvement, as well as metastases. Imaging findings vary depending on the type and grade of the tumor, including diffuse or segmental thickening with intravenous contrast enhancement, masses, ulceration, and loss of distensibility.^{16,19}

UGE is the method of choice for definitive diagnosis, because it is more sensitive and allows biopsies to be performed for histopathologic analysis.¹⁶

Endoscopic ultrasonography is currently the best method for assessing the primary tumor as well as evaluating the local extent of the tumor and the presence of compromised regional lymph nodes.¹⁹

Recent studies have demonstrated the role of MRI in the diagnosis of early gastric carcinomas that are not seen on other imaging tests.²⁰

The rarity of gastric cancer in children makes this diagnosis a very remote possibility among pediatricians. Also, the initial nonspecific gastrointestinal symptoms eventually lead to a significant delay in diagnosis, resulting in late start of appropriate treatment. As a result, gastric adenocarcinomas in pediatric patients have more advanced stage at diagnosis, presenting worse prognosis compared to adults.^{13,14}

Treatment of GAC in children is usually based on methods used in adults, due to the rarity of this disease in pediatric populations, and therefore there is no standard treatment model.^{13,15}

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