ISSN 1669-9106

CASE REPORT

MEDICINA (Buenos Aires) 2021; 81: 470-473

MENETRIER'S DISEASE. A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

PABLO PEPA[1], TATIANA UEHARA[1], ANDRÉS WONAGA[1], AGUSTINA REDONDO[1], ALEJANDRA AVAGNINA[2], OCTAVIO MAZZOCCHI[3], PABLO ANTELO[1], CARLOS WALDBAUM[1], JUAN SORDA[1]

[1]*División Gastroenterología,* [2]*Departamento de Patología,* [3]*Departamento de Medicina Interna, Hospital de Clínicas José de San Martin, Buenos Aires, Argentina*

Abstract We present a rare case of hypertrophic gastropathy associated with protein loss. A 35-year-old man was hospitalized for bowel habit changes, abdominal pain, generalized edema and symptomatic anemia. Pertinent laboratory findings included iron deficiency anemia (Hb 6.7g/dl, ferritin 5 ng/ml) and marked hypoalbuminemia (albumin 2.5 g/dl). Endoscopic biopsy samples of giant gastric folds observed along the greater gastric curvature revealed foveolar hyperplasia and significant parietal cell loss. Endoscopic ultrasonography showed gastric parietal thickening with preserved architecture and normal gastric wall layers. Menetrier disease was diagnosed and the patient treated with cetuximab, a monoclonal antibody that inhibits ligand binding of transforming growth factor alpha (TGFa), preventing gastric mucosa cell proliferation. After twelve months of treatment, the patient referred symptoms improvement, and gastric biopsy levels of the proliferation marker protein Ki-67 had decreased.

Key words: Menetrier's disease, hypertrophic gastropathy, cetuximab

Resumen ***Enfermedad de Menetrier. Un desafío diagnóstico y terapéutico.*** Presentamos un caso infrecuente de gastropatía hipertrófica asociada a pérdida de proteínas. Un hombre de 35 años fue hospitalizado por cambios en los hábitos intestinales, dolor abdominal, edema generalizado y anemia sintomática. Los hallazgos de laboratorio pertinentes incluyeron anemia ferropénica (Hb 6.7 g/dl, ferritina 5 ng/ml) e hipoalbuminemia marcada (albúmina 2.5 g/dl). Las muestras de biopsia endoscópica de pliegues gástricos gigantes observados a lo largo de la curvatura mayor gástrica revelaron hiperplasia foveolar y pérdida significativa de células parietales. La ecografía endoscópica mostró engrosamiento parietal gástrico con arquitectura conservada y capas de pared gástrica normales. Se diagnosticó enfermedad de Menetrier y se trató al paciente con cetuximab, un anticuerpo monoclonal que inhibe la unión del ligando del factor de crecimiento transformante alfa (TGFa), evitando la proliferación de células de la mucosa gástrica. Después de doce meses de tratamiento, el paciente refirió mejoría de los síntomas y los niveles de la proteína marcadora de proliferación Ki-67 en biopsia gástrica habían disminuido.

Palabras clave: enfermedad de Menetrier, gastropatía hipertrófica, cetuximab

Menetrier's Disease (MD) is a rare hypertrophic gastropathy associated with protein loss, first described by Pierre Menetrier in 1888, whose incidence and mortality rates remain unclear.

The clinical condition is characterized histologically by enlarged gastric folds with massive foveolar hyperplasia and primarily affects adult males (mean age at diagnosis 55 years). Classic symptoms at presentation include: abdominal pain, nausea, vomiting, anemia, hypochlorhydria and peripheral edema due to protein loss across the gastric mucosa. The natural course of the disease varies significantly between adults and children. In childhood, the disorder typically presents with abrupt onset and resolves spontaneously, and has been associated with cytomegalovirus (CMV) infection[1]. In adults, onset is insidious and progression slow[2] .MD aetiology remains unknown, although previous studies have shown it to be associated with infection by pathogens such as *Helicobacter pylori* and CMV[1, 3, 4]. Some authors suggest MD pathogenesis may be linked to upregulation of transforming growth factor (TGF)[5], however targeted therapies such as *H. pylori* eradication and treatment with antibiotics, prednisone, octreotide and monoclonal antibodies have yielded inconsistent results in clinical trials[6, 7]. Notably, a number of patients with MD have presented gastric cancer, which may imply increase oncologic risk in such cases[2, 8].

Received: 8-X-2020 Accepted: 9-III-2021

Postal address: Tatiana Uehara, Hospital de Clínicas José de San Martín, Córdoba 2351, 1120 Buenos Aires, Argentina
e-mail: tatianauehara@hotmail.com

Case report

We describe the case of a 35-year-old man, with a medical history of insulin-requiring diabetes and 1-year history of bowel habit changes of constipation alternating with steatorrheic diarrhea, postprandial abdominal pain and distension associated to generalized edema. Seven days prior to consultation at our hospital, patient referred functional class III dyspnea.

Blood biochemistry results at admission showed: hematocrit 24%; Hb 6.7g; Mean corpuscular volume (MCV):69 fl; white blood cells count (WBC) 6900 cells/ml; platelet 434000 cells/ml; glycemia 303 mg/dl; blood ureic N (BUN) 36 mg/dl; creatinine 0.69mg/dl; sodium 135 mEq/l; potassium 4.5 mEq/l; aspartate transaminase 25UI/l; alanine transaminase 33 UI/l; total bilirubin: 0.1 g/dl, protein total 6 g/dl, albumin 2.5 g/dl. The 24-hour proteinuria was 0.08 g. Protein electrophoresis showed marked hypoalbuminemia and hypo-gammaglobulinemia. Serology results: HBsAg negative; Anti-HCV negative; CMV IgG reactive > 250; CMV IgM non-reactive; HIV non-reactive; TSH 2.31 µUI/ml, T4l 0.8 ng/dl, TPO < 10; and steatocrit 7% (normal values < 2%); and HbA1c 9.1%. The patient presented iron deficiency anemia with ferritin levels of 5 ng/ml; serum iron: 11**µ**/ml; transferrin 310 mg/dl; TIBC 394 **µ**g/dl. Stool analysis (bacteria, parasites and ova) was negative. Serology for celiac disease and IgA levels were normal. Fecal elastase and serum gastrin were also normal and alpha-1-antitrypsin stool clearance was high 22.7 ml/24 hours (normal values < 12.5 ml /24 hours)

Abdominal ultrasound revealed an enlarged liver with well-preserved shape and internal echo pattern, minimal peritoneal fluid and severe bowel loop distention. CT enterography showed diffuse concentric thickening of the gastric wall in the fundus and corpus, with no signs of pathological reinforcement, and presence of enlarged lymph nodes (10 mm) within the lesser omentum and three round lymph nodes along the gastrocolic ligament (Fig. 1 A).

An upper gastrointestinal endoscopy (UGE) revealed abundant thick mucus, giant gastric folds resembling cerebral gyri, friable cobblestone mucosa and a preserved antrum (Fig. 1 B). Endoscopic ultrasound (EUS) showed parietal thickening with preserved architecture of gastric wall layers (Fig. 2 A). Multiple biopsies were taken with the objective of obtaining full-thickness mucosal samples. Those from gastric corpus showed marked foveolar hyperplasia, tortuosity and dilatation of the glands, and significant parietal cell loss. Other features include deep lateral branching, *lamina propria* edema, surface erosion and smooth muscle hyperplasia. The normal gastric pit to gland ratio is 1:4, but in our case, this ratio is reversed, as depicted by Dr. Menetrier in the original description of the disease. Antral biopsies showed normal architectural features. CMV was negative morphologically and by immunohistochemistry and *Helicobacter pylori* was absent (Fig. 2 B).

MD was diagnosed and treatment instituted with high-protein diet and cetuximab. The patient received intravenous cetuximab once weekly with an initial loading dose of 400 mg/m^2 of body surface area, followed by three weekly doses of 250 mg/m^2 until completing twelve months of treatment.

Fig. 1.– A: CT enterography shows concentric thickening of the gastric wall in the fundus and corpus. B: Digestive endoscopy with thickened gastric folds with diffuse shape

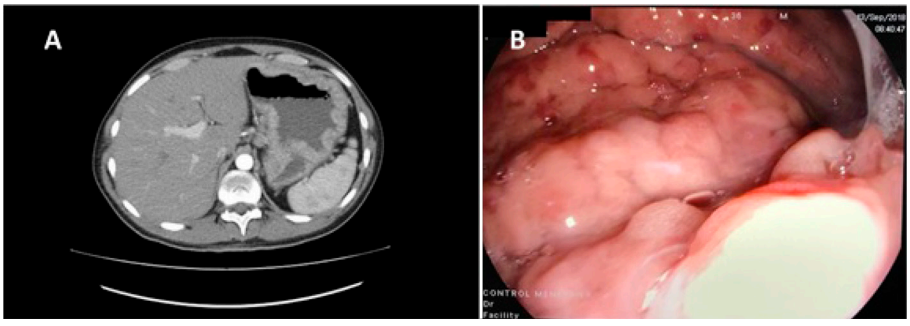
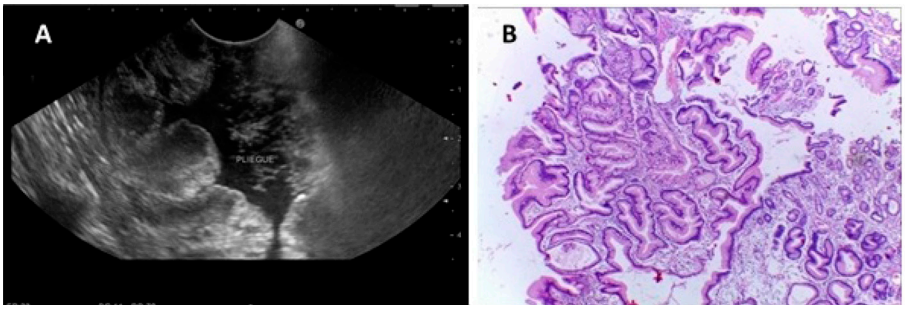


Fig. 2.– A: Endoscopic ultrasonography shows thickness of gastric wall and preservation of five-layered structure. B: Hyperplasia of the foveolar component and tortuous and dilated glands



During follow-up, significant clinical and biochemical improvement was observed. Diarrhea episodes, generalized edema and bloating resolved. Albumin levels returned to normal (3.5 g/dl). UGE performed after twelve months to monitor treatment response, showed improvement.

Biopsies assaying Ki-67, a marker of cell proliferation, were obtained to monitor treatment response. Tissue levels were 15% on pre-treatment biopsy, decreasing to 10% and later to 3%, after twelve months on cetuximab.

Discussion

Menetrier´s is a disease predominantly affecting adult patients, causing marked hypertrophy of gastric mucosal folds, typically associated with hypoalbuminemia and anemia[9]. The disease is associated with considerable morbidity and even mortality in this age group, linked to surgical resection as well as a potential risk of malignant transformation[2, 8]. Targeted therapies such as *H. pylori* eradication, antibiotics, prednisone, octreotide and monoclonal antibodies have yielded varied results in previous studies[6, 7]. This case presented all the typical clinical features of MD including epigastric pain, weight loss, hypoalbuminemia, edema and symptomatic anemia, but no nausea or vomiting[7].

The etiology of MD remains largely unknown. Some reports indicate over 90% presence of *H. pylori* in biopsies from patients with hypertrophic gastropathy[7]. In this patient however, results were negative. Some authors recommend to confirm the absence of infection through non-invasive tests such as the ^{13}C urea breath test or serology, because the modification of the intragastric environment, and the patchy distribution of the infection in the gastric mucosa may decrease the diagnostic sensitivity of invasive tests[10]. In our case the limitation was the lack of availability of other diagnostic tests to confirm the absence of *H. pylori* infection.

Infection, or other as yet unknown causes may trigger an immunologic reaction involving cytokines, such as TGF-α, and sustained antigenic stimulation may ultimately cause development of MD. Overproduction of TGF-α, one of several EGF-R ligands in the stomach, has been proposed to explain several of the clinical characteristics of MD, including decreased acid production, increased hyperplasia of surface mucous cells, oxyntic atrophy and increased mucin production[5].

There are no pathognomonic features to diagnose Menetrier's disease, and it continues to be a clinic-pathological diagnosis. It is essential to obtain a full-thickness biopsy of the involved gastric mucosa when entertaining the diagnosis of Menetrier's disease[11].

Disease diagnosis is based on clinical suspicion, presence of thickened gastric folds on endoscopy and characteristic histological alterations, including: foveolar hyperplasia, tortuous and dilated glands, reduction in parietal cell numbers and inflammatory infiltrate. In this case because the multiple biopsies taken were negative for carcinoma, USE was performed. It is the most cost-effective diagnostic method to rule out malignancy and useful for differential diagnosis since it allows adequate evaluation of thickened gastric folds (TGF) characteristics, thus supporting Menetrier disease diagnosis, particularly when thickening originates in the deep mucosa. Thickening of the deeper layers (third and fourth) is associated with malignancy, while thickening of the superficial mucosa (first and second layers) is associated with benign disease[12, 13].

Although MD has been linked to increased risk of gastric cancer (GC), the magnitude of this risk is not known, varying between 0-10% in published cases[13]. Patients should therefore be followed for a substantial period, with current recommendations suggesting endoscopic control evaluations every 1 to 2 years[14].

Differential diagnoses include infectious gastritis secondary to *H. pylori*, CMV, histoplasmosis, TB, mycoplasma, syphilis, cryptococcosis or aspergillosis; tumors such as lymphoma, adenocarcinoma, Zollinger-Ellison syndrome, infiltrative pathologies such as sarcoidosis, amyloidosis, or other causes such as eosinophilic gastroenteritis or gastric varices, making MD a diagnostic challenge.

Treatment is controversial. On this occasion, we prescribed the immunoglobulin cetuximab, a G1 (IgG1) monoclonal antibody specifically binding to the extracellular segment of the epidermal growth factor receptor (EGFR), inhibiting ligand binding of transforming growth factor alpha (TGFa), thus preventing gastric mucosa cell proliferation. Although this treatment is approved by the FDA, with 7 cases reported in the literature showing favorable response[15], indication is still limited to "compassionate" use. Current treatment of choice for MD continues to be total or partial gastrectomy depending on degree of gastric involvement and clinical symptom severity. In this case, patient's symptoms, Ki-67 serum and gastric biopsy levels improved following completion of cetuximab treatment.

Conflict of interest: None to declare

References

1. Eisenstat DD, Griffiths AM, Cutz E, Petric M, Drumm B. Acute cytomegalovirus infection in a child with Ménétrier's disease. *Gastroenterology* 1995; 109: 592-5.
2. Scharschmidt BF. The natural history of hypertrophic gastrophy (Menetrier's disease). Report of a case with 16-year follow-up and review of 120 cases from the literature. *Am J Med* 1977; 63: 644-52.
3. Badov D, Lambert JR, Finlay M, Balazs ND. Helicobacter pylori as a pathogenic factor in Ménétrier's disease. *Am J Gastroenterol* 1998; 93: 1976-9.
4. Jun DW, Kim DH, Kim SH, et al. Ménétrier's disease associated with herpes infection: response to treatment with acyclovir. *Gastrointest Endosc* 2007; 65: 1092-5.

5. Dempsey PJ, Goldenring JR, Soroka CJ, et al. Possible role of transforming growth factor alpha in the pathogenesis of Ménétrier's disease: supportive evidence form humans and transgenic mice. *Gastroenterology* 1992; 103: 1950-63.
6. Yeaton P, Frierson HF Jr. Octreotide reduces enteral protein losses in Ménétrier's disease. *Am J Gastroenterol* 1993; 88: 95-8.
7. Di Vita G, Patti R, Aragona F, Leo P, Montalto G: Resolution of Menetrier's disease after *Helicobacter pylori* eradicating therapy. *Dig Dis* 2001; 19: 17983.
8. Mosnier JF, Flejou JF, Amouyal G, et al. Hypertrophic gastropathy with gastric adenocarcinoma: Menetrier's disease and lymphocytic gastritis? *Gut* 1991; 32: 1565-7.
9. Rich A, Toro TZ, Tanksley J, et al. Distinguishing Ménétrier's disease from its mimics. *Gut* 2010; 59: 1617-24.
10. Santolaria Piedrafita S, Conde García R, Abascal Agorreta M, et al. Resolución de la enfermedad de Ménétrier tras la erradicación de la infección por *Helicobacter pylori*. *Gastroenterol Hepatol* 2004; 27: 357-61.
11. Rich A, Toro TZ, Tanksley J, et al. Distinguishing Ménétrier's disease from its mimics. *Gut* 2010; 59: 1617-24.
12. Lim H, Lee GH, Na HK, et al. Use of endoscopic ultrasound to evaluate large gastric folds: Features Predictive of Malignancy. *Ultrasound Med Biol* 2015; 41: 2614-20.
13. Ramia JM, Sancho E, Lozano O, Santos JM, Domínguez F. Enfermedad de Ménétrier y cáncer gástrico [Ménétrier's disease and gastric cancer]. *Cir Esp* 2007; 81: 153-4.
14. Patel M, Mottershead M. Disease recurrence following cetuximab completion and declining a gastrectomy: what next to manage Ménétriers disease? *BMJ Case Rep* 2014; 2014: bcr2014204954. doi: 10.1136/bcr-2014-204954.
15. Fiske WH, Tanksley J, Nam KT, et al. Efficacy of cetuximab in the treatment of Menetrier's disease. *Sci Transl Med* 2009; 1: 8ra18.