Ménétrier's disease : a case of successful treatment using long-acting octreotide

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Abstract

The authors describe a 31 years old male, admitted for hematemesis, epigastric pain and lower limb edema. Laboratorial data showed haemoglobin 18.4g/dl, total proteins 2.8g/dl, albumin 1.6g/dl and hipogammaglobulinaemia. 24h urinary proteins were normal. HIV and CMV serology were negative. Upper GI endoscopy revealed markedly enlarged gastric folds covered by abundant exudative fluid. Endoscopic ultrasound showed ascites, pleural effusion and gastric wall thickening with mucosa expansion and intact submucosa. In gastric biopsies foveolar hyperplastic and regenerative mucosa were observed being suggestive of Ménétrier´s disease. Helicobacter pylori was not detected. Albumin replacement and diuretics corrected anasarca and long-acting octreotide was instituted. Nine months later, the patient was asymptomatic, serum proteins were normal (albumin 4.6g/dl and total proteins 6.5g/dl), signs of endoscopic improvement were observed with marked reduction in gastric folds and mucosal inflammation and no ultrastructural changes were detected in gastric specimens sent for electron microscopy.

Ménétrier´s Disease (MD) is a rare form of hypertrophic gastropathy characterized by massive enlargement of gastric folds causing marked protein exudation. The increase in tight junction diameter is the most consistent ultraestrutural change. Octreotide is a somatostatin analogue that acts by modulating TGFα-EGFR pathway, which has been associated with the pathogenic mechanisms. As well as other cases reported in literature, this case report highlights the potential of long-acting octreotide for MD treatment avoiding more expensive therapies like cetuximab and gastrectomy. (Acta gastroenterol. belg., **2019**, 82, **429-432**).

Key words : Ménétrier´s disease, octreotide, ultra-structure**.**

Introduction

Ménétrier´s disease (MD) is a rare hyperproliferative protein-losing gastropathy, characterized by giant hypertrophic folds, hypochlorhydria and hypo-proteinaemia (1-7). As this is an uncommon disease, epidemiologic studies are lacking and data regarding incidence and mortality remain undetermined (2). MD is typically observed in middle-aged males but both genders and all age groups may be affected (2). High risk of gastric cancer was described but this association was not clearly established (1).

The pathogenesis of MD is not completely understood. Nevertheless, recent studies suggest an increased signalling in epidermal growth factor receptor (EGFR) pathway associated with overproduction of transforming growth factor-alpha (TGF-α), which results in the proliferation of mucus producing cells and inhibition of gastric acid secretion (1). Cytomegalovirus (CMV) was confirmed as an etiological agent in paediatric patients. *Helicobacter pylori* appears to play an important role in the pathogenesis and eradication therapy is commonly associated with clinical and endoscopic remission in infected individuals (1). The increase in the tight junction width is an ultraestrutural feature that has been described and seems to justify high mucosal permeability, contributing to protein losing phenomena (3-4).

Usually, the disease has a progressive clinical course. The most common symptoms include epigastric pain, asthenia, anorexia, weight loss, vomiting and gastrointestinal bleeding. Abnormal enteric protein loss often manifests by hypoalbuminemia, peripheral edema, ascites and pleural and pericardial effusion. The diagnostic procedure of choice is upper gastrointestinal endoscopy showing markedly thickened gastric folds with relative antral sparing. Full-thickness mucosal biopsies typically exhibit foveolar hyperplasia, cystic dilatation and distortion of gastric glands (1).

Despite the lack of randomized controlled trials, several medical treatments have been attempted in last years. High-protein diets are generally recommended (1). If detected, CMV and *Helicobacter pylori* treatment is also advisable (1). Gastric antisecretory medication such as proton pump inhibitors, histamine-2 receptor antagonists and anticholinergics are usually prescribed to control symptoms and to reduce gastric protein exudation with no proven benefits (1). Octreotide is a somatostatin analogue that showed effectiveness in several cases reported in literature (5-10). Recently, a small uncontrolled trial involving nine patients treated with cetuximab, a monoclonal antibody to EGFR, showed great benefits in clinical, endoscopic and histologic remission, being proposed by the authors as a first-line therapy (11). Gastrectomy may be required to correct hypoalbuminemia and to improve quality of life in refractory patients. Surgical treatment may also eliminate the theoretical risk of subsequent gastric cancer (1).

The present report aims to improve knowledge about MD and increase scientific evidence regarding octreotide use in this form of hypertrophic gastropathy.

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Case report

A 31 years old man was admitted to the gastroenterology ward due to hematemesis, intense epigastric pain and lower limb edema, persisting for four days. His past medical history included testicular neoplasia submitted to right orchiectomy seven years before with no need of adjuvant therapy. The patient had smoking habits but no other xenobiotic exposure, chronic medication or known allergies.

At admission, he was hemodynamically stable but presented signs of dehydration, marked epigastric tenderness and moderate ascites. Testicular swelling and extensive bilateral lower limb edema were also observed. Laboratorial analysis were remarkable for haemoglobin 18.4g/dl, WBC 21.9x10^9 with 70% neutrophils, normal CRP, urea 53mg/dl (16-46), sodium 127mmol/l (135-145), total proteins 2.8g/dl (6.6-8.7), albumin 1.6g/dl (3.5-5.0) and hypogammaglobinaemia. A 24-hour urine was collected showing normal urinary protein excretion. Blood cultures were negative. Serum angiotensin converting enzyme (ACE) and beta-2-microglobulin concentration were normal. HIV serology and anti-CMV IgM and IgG antibodies were negative. Transthoracic echocardiogram did not reveal signs of heart failure but a mild pericardial effusion was detected.

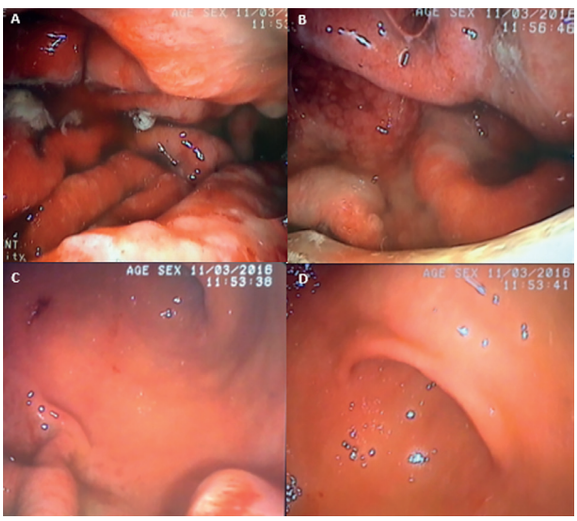

Figure 1. — Upper gastrointestinal endoscopy photographs showing marked congestive and thickened gastric folds, covered by large amount of white exudative fluid that was partially washed and aspirated during examination. These changes were found in gastric body (fig. 1A) and fundus (fig. 1B), sparing the antrum (fig. 1C and 1D).

In upper GI endoscopy, marked congestion and enlargement of gastric folds were detected, being covered by large amount of white exudative fluid. These changes affected gastric fundus and body, sparing the antrum (Fig. 1). Thoracic and abdominal CT scan was performed showing ascites, pleural effusion and gastric wall thickening with perigastric lymphadenopathy and adipose tissue swelling (Fig. 2). Endoscopic ultrasound confirmed gastric wall thickening (6mm) due to mucosa layer expansion (3.2mm) with increased body folds and preserved submucosa (Fig. 2).

Full-thickness gastric mucosal biopsies showed signs of hypertrophic gastropathy with foveolar hyperplasia and atrophy of oxyntic mucosa, being suggestive of Ménétrier´s disease (Fig. 3). *Helicobacter pylori* and cytomegalovirus were absent in immunohistochemical analysis of gastric specimens.

During the hospital stay, the patient underwent albumin replacement and diuretic therapy with complete resolution of anasarca. He was discharged under protein supplementation and medicated with esomeprazole, ranitidine, butylscopolamine and long-acting release octreotide 20mg monthly. During the following weeks, symptoms have improved and progressive normalization of the laboratorial parameters was observed.

After four months of octreotide therapy, gastric specimens were sent for Transmission Electron Microscopy (TEM). Biopsies displayed normal tight junctions of the superficial gastric cells, confirming that ultrastructural normalization was coincident with clinical improvement (Fig. 4). In the endoscopic reassessment performed nine months after starting therapy, marked reduction in gastric folds and improved signs of mucosal

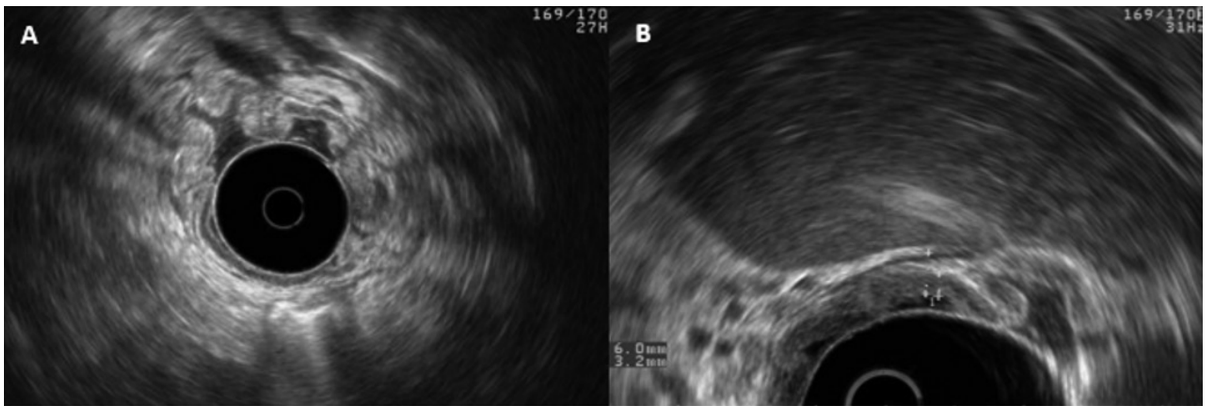

Figure 2. — Endoscopic ultrasound photographs showing gastric wall thickening (6mm) due to mucosa expansion (3.2mm) with massive enlargement of gastric body great curvature folds. Submucosa was preserved and antrum was spared.

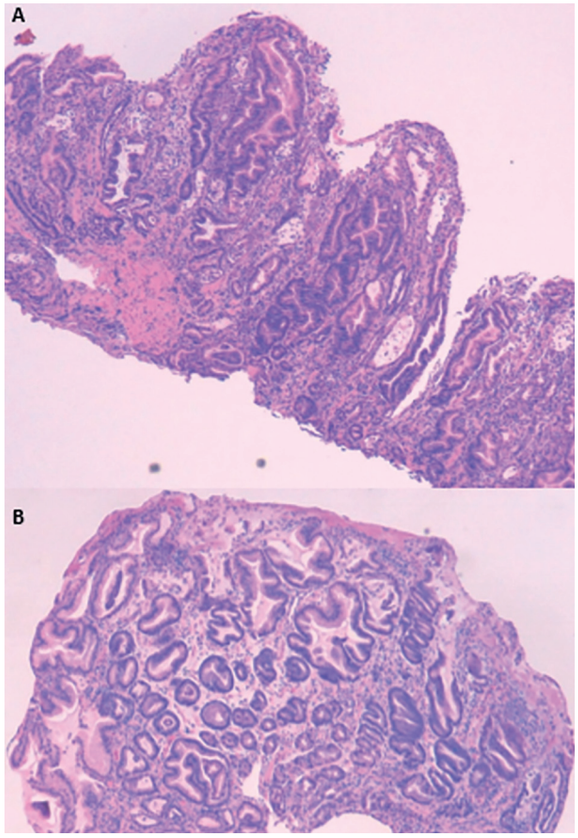

Figure 3. — Images from gastric tissue stained with H&E, where signs of hypertrophic gastropathy are evident. Tortuous and dilated glands with corium edema are observed. Oxyntic mucosa atrophy and foveolar hyperplasia are typical features of Ménétrier disease that are present in the patient gastric mucosa.

inflammation were observed (Fig. 5) despite gastric wall thickening persisting in endoscopic ultrasound. Serum analysis revealed no leucocytosis, total proteins 6.8g/dl, albumin 4.9g/dl and normal immunoglobulin concentration. The patient remained in clinical remission during this period.

Discussion

MD was first described in 1888 by Pierre Ménétrier, a French pathologist who observed enlarged gastric folds during autopsies (5). Several sporadic cases have been published addressing different clinical approaches regarding type of treatment, follow-up and patient outcome. Only two case series were published, studying retrospectively 120 and 43 patients with MD, respectively.

Advances in molecular biology improved knowledge about its pathophysiology, especially after the discovery of TGF-α/EGFR pathway oversignalling (1). Electron microscopy studies also identified alterations of gastric epithelium tight junctions and its important role in luminal protein exudation (3-4).

In this report, a young man with MD was described. Some details in clinical presentation deserve special

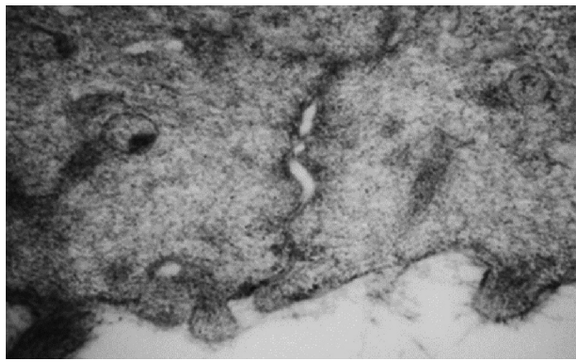

Figure 4. — Ultrastructural evaluation with TEM : Normal tight junctions after four months of long-acting octreotide.

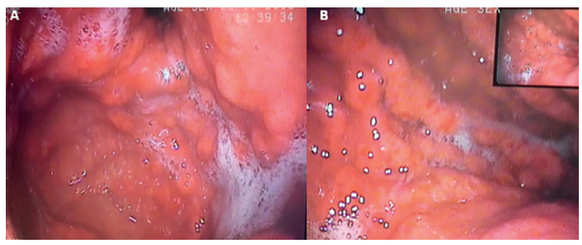

Figure 5. — Upper gastrointestinal endoscopy photographs after nine months of octreotide therapy. Marked reduction in gastric fold size and improved mucosal inflammation in fundus (Fig. 5A) and body (Fig. 5B) were evident.

attention such as the adulthood onset of the disease in a younger age and its sudden appearance contrasting with the indolent course that was previously described.[1] Another important point was the lack of any precipitant factor like CMV, *Helicobacter pylori*, toxics and allergens. Our patient symptoms were typical. The impressive endoscopic findings with extensively marked fold thickening and mucosal inflammation were striking, nevertheless correlating with the severity of laboratorial alterations. Histology allowed the definite diagnosis showing the typical pattern of foveolar hyperplasia with glandular distortion and atrophy.

The differential diagnosis of MD is broad and includes not only infectious diseases but also infiltrative disorders (eg, sarcoidosis and amyloidosis), malignancy (eg, *Zollinger-Ellison* syndrome, lymphoma, gastric carcinoma and metastasis) and varices (14). Overall, *Helicobacter pylori* is probably the most common cause of fold thickening and should be first considered in those patients. CMV infection tends to be self-limited in children, however must be distinguished from CMV gastritis that usually occurs in immunocompromised patients displaying gross ulceration, perforation and haemorrhage. These infections were excluded by non-invasive methods and pathological analysis.[14] A neoplasia should be suspected when gastric folds exhibit rigidity or when associated masses or ulcers are present (14), which was not the case. Obviously, this hypothesis threatened us since the patient had a testicular cancer few years before and considering the age group, a tumour relapse

or a gastric lymphoma were possible. Biopsies excluded these conditions and ultrasound endoscopy showed an intact submucosa that argues against lymphoma diagnosis. Unlike MD, *Zollinger-Ellison* syndrome often presents with gastric or duodenal ulcers. Gastric varices tend to have more serpentine form, be changeable in size and shape, and be confined to the cardia and fundus (10). Finally, in amyloidosis, the folds appear to exhibit more nodular thickening and amyloid deposits should be easily identified using specific dyes (14).

After MD diagnosis, our first approach aimed to stabilize the patient performing supportive care by replacing serum albumin, treating anasarca and trying to reduce epigastric pain and protein exudation using antisecretory medication. We opted to institute maintenance therapy with octreotide given its powerful antisecretory activity, reduced cost, prompt availability in a hospital setting and favourable results on preliminary reports (5-10). The treatment had a great-unexpected effectiveness as serum protein concentration gradually normalized and symptoms markedly improved with partial reversal of gastric fold thickening. Actually, recent molecular evidence suggests that octreotide may modulate EGFR signalling on several levels (5). First, somatostatin has been shown to decrease the number of EGF binding sites at cell surface suggesting an interplay between the two pathways (5). Second, at least some of the downstream effectors of somatostatin receptors are shared by EGFR pathway (5). Third, some molecular studies have shown that one of the somatostatin receptor subtypes that binds to octreotide with high affinity may hetero-dimerize with EGFR modulating downstream signalling (5). Thus, effectiveness of octreotide in MD might be attributed to interference and downregulation of overexpressed TGFα-EGFR mitogen pathway that seems to justify gastric fold growing, hypersecretion and high permeability (5). Also, gastric specimens that were collected at the control endoscopy after four months of octreotide therapy were sent for electron microscopy to search for ultraestrutural alterations in tight junctions. At this time marked clinical and endoscopic improvement were already observed and no ultraestrutural anomalies were found, confirming ultrastructural normalization after treatment as previously addressed by *SH et al* in a small report (15).

Cetuximab is emerging as a high effective treatment for MD. Its use is still off-label given the absence of trials designed for this purpose. Most patients reported to be treated with cetuximab have shown favourable outcome being possible to avoid gastrectomy and improve quality of life (7). *Food and Drug Administration (FDA)* has already allowed cetuximab use on a compassionate need basis in some patients with MD but specific guidelines regarding dosage, duration of therapy and follow-up do not exist. In spite of being advocated as a first-line therapy by some authors and although we have considered this possibility, we preferred to save this advanced therapy for the future in case of treatment failure or disease relapse.

Nevertheless, some doubts and uncertainties persist. No gold-standard method to follow this disease is defined. Our group is using symptoms, serum proteins and endoscopic features empirically to ascertain therapeutic effectiveness and disease control however this approach is not validated. Furthermore (12-13), no specific indications are available to guide medical therapy and the timing and need for endoscopic follow-up. How long will it be necessary to maintain octreotide and what should be the target of the therapy? What is the next step if disease relapse occurs after octreotide cessation? Which factors may predict therapeutic response in MD and to which patients, surgery should be considered early? All these questions concern our team and deserve reflexion by gastroenterologists.

In conclusion, this case describes a Ménétrier´s disease patient successfully treated with long-acting release octreotide. Taking into account the absence of specific orientations, the authors recommend octreotide therapy as a first-line treatment, leaving cetuximab for octreotide non-responders and gastrectomy for refractory patients. Endoscopic follow-up should be performed on a case-by-case basis according with clinical evolution, risk factors for gastric cancer, and always considering patient opinions and preferences.

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