Published in final edited form as:

Gut. 2010 December ; 59(12): 1617–1624. doi:10.1136/gut.2010.220061.

Distinguishing Ménétrier's Disease from its Mimics

Amy Rich¹, Tania Zuluaga Toro², Jarred Tanksley³, William H. Fiske¹, Christopher D. Lind¹, Gregory D. Ayers⁴, Hubert Piessevaux⁵, Mary K. Washington⁶, and Robert J. Coffey¹

¹ Department of Medicine, Vanderbilt University Medical Center

² Department of Pathology, Vanderbilt University Medical Center

³ Department of Cell and Developmental Biology, Vanderbilt University Medical Center

⁴ Department of Biostatistics, Vanderbilt University Medical Center

⁵ Gastroenterology Department, Cliniques Universitaires St-Luc Université Catholique de Louvain

⁶ Department of Pathology, Vanderbilt University Medical Center

Abstract

OBJECTIVE—Ménétrier's disease (MD) is a rare hypertrophic gastropathy characterised by giant rugal folds, hypochlorhydria, protein loss and a classic constellation of symptoms - nausea, vomiting, abdominal pain and peripheral oedema. It is considered a clinical diagnosis that, at times, may be difficult to establish. We propose firm diagnostic criteria for MD by delineating the clinicopathological features that best differentiate MD from its mimics.

DESIGN—Forty-eight patients referred to Vanderbilt University Medical Center for consideration of enrolment in a clinical trial to treat MD patients with cetuximab were evaluated for a definitive diagnosis by assessment of clinical presentation, pertinent laboratory values and histopathological features.

RESULTS—MD was confirmed in 25/48 (52%) of the patients. We designated the remaining 23 patients as mimics of MD; the most common diagnoses among the MD mimics were gastric polyps or polyposis syndromes (13/23, 57%). Gastric slides were available from 40 of 48 cases for detailed histological analysis (22/25 MD cases and 18/23 non-MD cases). Foveolar hyperplasia, glandular tortuosity and dilatation, and a marked reduction in parietal cell number were present in all 22 MD cases; lamina propria smooth muscle hyperplasia and oedema characterised most cases (18/22 and 19/22, respectively); more than half had prominent eosinophils (11/22) and/or plasma cells (12/22) in the lamina propria. The clinical presentation of MD patients was characterised by significantly younger age at onset, male predominance and increased vomiting compared to non-MD, and lower prevalence of anaemia compared to non-MD with polyps; there was trend towards increased frequency of peripheral oedema in MD versus non-MD.

CONCLUSIONS—MD is most accurately diagnosed by clinicohistopathological analysis including esophagogastroduodenoscopy with gastric pH, appropriate laboratory tests (complete blood count, serum albumin, serum gastrin, *H. pylori* and cytomegalovirus serology) and full thickness mucosal biopsy of the involved gastric mucosa.

Corresponding Author: Robert Coffey, robert.coffey@vanderbilt.edu, Tel: 615-343-6228, Fax: 615-343-1591, Department of Medicine, Vanderbilt University Medical Center and Nashville Veterans Affairs Medical Center, Nashville, Tennessee, USA.

Competing Interest
None to declare.

Keywords

Ménétrier; Juvenile Polyposis syndrome; hyperplastic polyps; gastric cancer

Ménétrier's disease (MD), first described in 1888, is a rare form of acquired gastropathy characterised by giant rugal folds in the gastric body, foveolar hyperplasia and markedly decreased or absent oxyntic glands with antral sparing. In normal gastric mucosa, the pit to gland ratio is about 1:4, but in MD this ratio can be reversed as the surface mucous cell compartment expands to occupy nearly the entire mucosal thickness.[1] MD can present with variable signs and symptoms, but the classic constellation includes abdominal pain, nausea, vomiting and peripheral oedema secondary to protein loss across the gastric mucosa with resultant low serum albumin. MD patients often exhibit hypochlorhydria with relatively normal serum gastrin levels. MD usually presents in adults (mean age at diagnosis is 55) with an insidious onset and a progressive clinical course.[2,3] However, in children, the disorder is characterised by abrupt onset and spontaneous resolution, which has been linked to cytomegalovirus (CMV) infection.[4–8] Various treatments have been reported to provide therapeutic benefit to adult patients, such as *H. pylori* eradication, prednisone, antibiotics, non-steroidal anti-inflammatory drugs, anti-cholinergic agents and octreotide therapy; however, each has yielded inconsistent benefits, and none have been evaluated in a clinical trial.[9–26] The only definitive treatment is total gastrectomy. A recently published clinical trial from our group reported that MD patients treated with cetuximab, a monoclonal antibody to the epidermal growth factor receptor (EGFR), showed significant clinical and biochemical improvement in all 7 patients that completed the one-month trial with subsequent histological reversion to normal or near normal in 4 of these patients.[27–29]

The pathogenesis of MD is related to increased EGFR signalling in the stomach. *In vitro*, administration of transforming growth factor- α (TGF- α), one of seven mammalian EGFR ligands, stimulates gastric epithelial growth, inhibits acid production and increases mucin levels, which are features of MD. TGF- α immunoreactivity is increased in the gastric mucosa of affected individuals, and TGF- α -overexpressing transgenic mice simulate biochemical and histopathological features of MD in humans.[28,30–34] Based upon these observations, our group successfully used cetuximab as treatment for a patient with MD who was inoperable due to coexisting primary pulmonary hypertension.[35] We then went on to recruit additional patients for an open-label clinical trial of cetuximab for treatment of advanced MD.[27,29]

As part of the clinical trial, a single team of investigators evaluated 48 individuals over a 10-year period for possible enrolment. MD was confirmed in 25 of 48 individuals who were either self-referred or referred by outside physicians. Given the rarity of this disorder and lack of firm diagnostic criteria, we sought to share our experience via this retrospective study. Herein we describe the clinical and histological features of MD, characterise the conditions that mimic MD, and propose a diagnostic algorithm for clinicians and pathologists when MD is suspected.

MATERIALS AND METHODS

Clinical records and pathological material from 48 patients referred to Vanderbilt University Medical Center (VUMC) for consideration of enrolment in a clinical trial for treatment of MD were reviewed. Gastric biopsy slides obtained from outside institutions were reviewed for 23 patients, and additional endoscopies with biopsies were performed at VUMC for 25 patients. Patients' chief complaint(s) and/or presenting symptom(s),

esophagogastroduodenoscopy (EGD) results, CT scan results and laboratory data were collected from the medical records.

The original presumptive diagnosis of MD was largely based on enlarged gastric folds on EGD and foveolar hyperplasia affecting the gastric body on histological evaluation. Symptoms in all patients were refractory to other medical therapy, such as proton pump inhibitors (PPIs), anti-cholinergic medications or anti-emetics for at least 6 months. Gastric pH was ascertained by colorimetric paper analysis of freshly isolated gastric juice obtained at the time of EGD.

Pathological material was further analysed from 40 subjects referred for entry into the clinical trial for treatment of MD to determine histological features most characteristic of MD and its mimics. Gastric biopsies were evaluated for overall architecture, foveolar hyperplasia, glandular tortuosity and dilatation, mucosal oedema and presence of parietal cells. Gastric biopsies were also assessed for the presence of intraepithelial lymphocytes, eosinophils (>10 per high powered field), plasma cells (>10 per high powered field) and smooth muscle cell hyperplasia in the lamina propria.

Statistical Methods

Age at diagnosis and lab values were summarized using the median (range) of these data by disease group. Patient complaints at diagnosis were tabulated as frequencies and percentages by disease groups. Statistical comparisons were made between: 1) MD patients (n=25) and total non-MD patients (n=23), and 2) MD patients and non-MD patients with polyps (n=13) using the Wilcoxon rank sum test for continuous variables and the 'N-1' chi-square test for categorical variables.[36]

RESULTS

The total group of 48 patients referred to VUMC for possible MD was evaluated using clinical, endoscopic and histological criteria. Twenty-five of 48 (52%) of this population met study criteria for MD. The cases that did not meet criteria for MD (23/48, 48%), referred to as total non-MD patients, represent a number of other conditions (Table 1). The most common entities mistaken on endoscopic or histological grounds for MD were gastric hyperplastic polyps or polyposis syndromes with gastric involvement. For purpose of analysis, we designated this subgroup as non-MD patients with polyps, which comprised 13/48 (27%) of the total referred population, or 13/23 (57%) of total non-MD patients. Three patients within this subgroup had Juvenile Polyposis syndrome (JPS). Two of these patients had predominantly gastric polyps and were found to harbour a germline *SMAD4* mutation (see Discussion).

Table 2 compares the clinical features of MD patients, total non-MD patients and non-MD patients with polyps. MD patients were 17 years younger ($p=0.002$) than total non-MD patients, and were more commonly male ($p=0.023$). MD patients were 12 years younger ($p=0.017$) and more likely to be male ($p=0.048$) than non-MD patients with polyps. Vomiting was a chief complaint of MD patients (12/25, 48%); there was significantly less vomiting among total non-MD patients (3/25, 13%; $p=0.01$) and nearly so among non-MD patients with polyps (2/13, 15%; $p=0.051$). MD patients tended to be more likely to present with peripheral oedema than non-MD patients ($p=0.11$). Nine of 13 (69%) non-MD patients with polyps experienced anaemia compared to 7 of 25 (28%) MD patients ($p=0.016$); however, differences in anaemia between the MD group versus the total non-MD group were not significant ($p=0.419$).

When classic signs and symptoms of MD are considered as a group (abdominal pain, nausea, vomiting and oedema), we observed that 3 of 25 (12%) MD patients had all 4 classic signs/symptoms; one (4%) had 3, 11 (44%) had 2, 8 (32%) had only one and 2 (8%) had none of the classic findings. Overall, only 16% of MD patients had 3 or 4 of the classic findings, highlighting the difficulty of diagnosing MD on clinical grounds alone.

One of the MD patients had sudden onset and spontaneous resolution of symptoms. This individual had positive acute and convalescent titres for CMV, and enlarged cells with viral inclusions characteristic of CMV infection were identified in the gastric epithelial cells and surrounding stroma (Supplemental Figure 1). Three additional MD patients had either a waxing-and-waning or a spontaneously remitting version of the disease without confirmed viral serology. One patient (1/25, 4%) was found to have gastric cancer in the setting of MD.

As expected, most MD patients had a high gastric pH (median value 6); however, some had a gastric pH as low as 1 (Figure 2). Compared to the total non-MD group, the MD group had a higher gastric pH ($p=0.020$). Gastrin levels in MD ranged from 20 to 740 pg/mL (normal 0–100 pg/mL) with a median value of 121 pg/mL. While the median serum albumin value in MD was low (2.8 g/dL), a range of 1 to 4 g/dL was seen (normal 3.5–5.0 g/dL). Compared to either the total non-MD or non-MD with polyps groups, the MD group had a lower median serum albumin ($p=0.0005$; $p=0.007$, respectively).

Available gastric slides from 40 MD and non-MD patients were further evaluated to determine histological features that discriminated between MD and its mimics. Twenty-two of these 40 subjects (55%) had MD. Foveolar hyperplasia, tortuosity or “corkscrewing” of the glands, dilatation of the glands and a marked reduction in parietal cell number were present in all patients with MD (Figure 3A), including the individual with co-existing gastric cancer (Figure 4). A thick layer of adherent mucin that usually survives processing can also be seen. MD cases retain mucosal architecture, with gastric glands mostly found in parallel, and with some areas of deep lateral branching and cystic dilatation. Lamina propria smooth muscle hyperplasia and lamina propria oedema were present in most cases (18/22 and 19/22, respectively). Roughly half had prominent eosinophils (11/22; Figure 3B) and/or plasma cells (12/22) in the lamina propria. Prominent intraepithelial lymphocytes, characteristic of the hypertrophic lymphocytic gastritis (HLG) variant of MD (see Discussion), were not a feature of any of our cases.

Antral sparing is a feature of MD as it was originally described. However, there were several cases in which the antrum was grossly involved on EGD, and these cases were sampled and reviewed. Of note, we did not routinely sample and analyze normal appearing antrum for microscopic changes. Antral biopsies were available for 4 MD patients, and all revealed similar changes similar to the gastric body biopsies, i.e. no antral sparing as determined by histological analysis.

Hyperplastic polyps and juvenile polyps, like MD, were characterised by foveolar hyperplasia. However, polyps show a loss of parallelism of the glandular units with distortion of mucosal architecture. Additionally, lamina propria eosinophils were less conspicuous, and lamina propria smooth muscle fibres much less prominent than in MD. The gland to stroma ratio was lower in polyps. JPS was indistinguishable histologically from other hyperplastic or hamartomatous polyps (Figure 3E), demonstrating loss of tissue architecture and a more oedematous lamina propria with fewer glandular units than MD (Figure 3C, D).

Other histological findings in patients referred for evaluation of possible MD on clinical grounds are not likely to be confused morphologically with MD because of the lack of

foveolar hyperplasia; these conditions included fundic gland polyps, parietal cell hyperplasia without foveolar hyperplasia and PPI effect.

DISCUSSION

This retrospective study of MD sought to describe the clinical, biochemical, endoscopic and histological features that distinguish MD from its mimics, and thereby guide the clinician in how to best approach patients with a possible diagnosis of MD. Accurate diagnosis requires close communication between the referring physician, endoscopist and pathologist since MD is a clinicopathological diagnosis that requires careful correlation of clinical, laboratory, imaging and pathological findings.

The most common mimics of MD in our referral group are various forms of polyps and polyposis syndromes, JPS being the most common. MD is more likely to cause vomiting, whereas polyps are more likely to be associated with anaemia. MD is also more likely to present with peripheral oedema than non-MD entities, although this did not reach statistical significance. This study supports the previous finding that MD patients are more likely to be men. However, in the present study, MD patients were 40 years old on average, and were 17 years younger than total non-MD patients, which stands in contrast to previously reported average age of diagnosis of 55 years for MD and an increased risk for MD with advanced age.[23,37] It is possible that the earlier age of diagnosis of MD in our experience compared to earlier reports reflects easier access to EGD and/or a greater awareness of this disease. We also report here a case of gastric cancer occurring in the setting of MD, which is considered to have malignant potential at an unknown incidence.[37–40] Of note, 4 MD patients enrolled in the cetuximab clinical trial also had ulcerative colitis; these disease states have been previously reported to coexist, but the pathogenesis underlying this association remains unclear.[41,42]

In addition to clinical presentation, a careful family history and documentation of extra-gastric signs and symptoms can help distinguish MD from some of its mimics, especially the polyposis syndromes. We are currently evaluating several familial cases of MD, including a father and son in this report. Therefore, a positive family history of enlarged gastric folds, or a suspicion of a heritable cause for disease, may not exclude a diagnosis of MD. JPS patients will typically have a history or presence of colonic polyps at time of diagnosis and/or a family history of JPS, although a significant proportion of JPS cases are thought to arise from *de novo* mutations.[43] Genetically, JPS has been linked to mutations in two genes, *SMAD4* and *BMPRIA*, and it has been found that patients with *SMAD4* mutations have a higher likelihood of upper gastrointestinal polyps and massive gastric polyposis.[44] Thus, JPS should be suspected in cases with diffuse involvement of the stomach by gastric polyps in a younger individual, since hyperplastic gastric polyps are usually found in older patients with atrophic gastritis. An additional patient, who did not meet inclusion criteria for this study, had JPS polyps in the stomach and colon, along with hereditary hemorrhagic telangiectasia (HHT); this patient also had a germline *SMAD4* mutation as has been previously reported for patients with this compound phenotype.[45] Other polyposis syndromes represented in our cohort include Cronkhite-Canada syndrome, characterised by hair and nail changes in addition to multiple hamartomatous polyps throughout the gastrointestinal tract, and familial adenomatous polyposis (FAP). Nail and hair loss and/or hyperpigmentation in Cronkhite-Canada syndrome may lag behind gastrointestinal symptoms in presentation, as they did in our patient, further confounding the diagnosis. Fundic gland polyps seen in FAP are unlikely to be confused with MD because of lack of foveolar hyperplasia. Other polyposis syndromes not represented in this study that could also mimic MD include Peutz-Jeghers syndrome and Cowden's syndrome.

While clinical presentation, patient characteristics and family history may favour one diagnosis over another, laboratory tests are also helpful in establishing the diagnosis of MD. Although one would expect low serum albumin, high gastric pH and normal to slightly elevated serum gastrin values in MD patients, a range of laboratory values may occur. However, we recommend that patients be screened for anaemia, and have both serum albumin and serum gastrin measured in the setting of enlarged gastric folds of uncertain etiology. This data must be interpreted in the setting of clinical and histological data. Gastric pH should be measured at the time of EGD, which can be easily determined with colorimetric paper, since hypochlorhydria will further support a diagnosis of MD. PPI therapy should be discontinued for at least one week before measuring gastric pH to ensure an accurate measurement. An additional test to assess stool protein loss, stool α -1-antitrypsin, was employed with mixed results that may be attributable to acquisition of the sample and/or laboratory variance. Due to the variability in results and the infrequency with which α -1-antitrypsin is obtained in clinical practice, we did not include this value in our analysis. Overall, a range of laboratory values is seen in MD and a single laboratory test cannot confirm or refute the diagnosis.

It is advisable to obtain CMV serology regardless of patient age; one of our adult immunocompetent patients was confirmed to have a CMV-associated form of MD. Cases of abrupt onset, spontaneously remitting MD have been previously described, usually associated with CMV infection and predominantly in children, but may also be seen in adults.[4–8] There have been isolated reports that *H. pylori* eradication caused remission of symptoms in patients with MD; therefore, we recommend eradication of *H. pylori* if the patient has positive serology before seeking other therapy.

Another challenge to proper diagnosis of MD is the endoscopist's experience in evaluating enlarged gastric folds. An enlarged gastric fold is defined by Bjork et al. as a fold measuring greater than 1.0 cm by radiographic studies that persists after air insufflation on endoscopy. [46,47] Initial investigation of abdominal symptoms often includes CT scan of the abdomen, which may show a thickened gastric wall; we recommend administration of oral VoLumen to distend the stomach and intravenous contrast. EGD must be employed for direct visualisation and biopsy sampling. EGD will show markedly increased thickness of the gastric rugal folds, which may fill the lumen, and have been compared to cerebral convolutions (Figure 5A). These folds often have surface erosions, and are accompanied by copious amounts of thick mucus that may form bridges across the gastric lumen and obscure visualisation (Figure 5B). Gastric pH, which should be procured during EGD, is often high. These endoscopic findings are distinct from polyposis syndromes, such as JPS, which may have diffuse gastric involvement similar to MD. However, instead of giant rugal folds, JPS is characterised by protuberant, translucent polyps that have been compared to a cluster of grapes (Figure 5C, D).

Deep snare biopsies, rather than pinch biopsies or large capacity ("jumbo") biopsies, are essential for proper histological evaluation of suspected MD. These full mucosal thickness biopsies allow assessment of the mucosal architecture and the pit to gland ratio. In contrast to snare biopsies, pinch biopsies may only sample the foveolar or pit compartment, especially when sampling a thickened mucosa. Martin biopsy forceps, a standard forceps size, can obtain biopsy specimens from large gastric folds that average 3 to 4 mm in width and 2 mm in depth, whereas the electrosurgical snare averages 10 mm in width, always includes muscularis mucosae and occasionally includes submucosae.[47,48] "Jumbo" biopsies, which can encompass 2 to 3 times the surface area of standard forceps, do not reliably yield deeper specimens.[48] Deep snare may be performed, with or without electrocautery, to obtain full thickness biopsies without an increased risk of bleeding. In our experience, enlarged gastric folds can be difficult to sample using cold snare (without

electrocautery), but hot snare can be more easily implemented, and does not interfere significantly with the histological diagnosis.

Twenty-two of 40 subjects from this study with slides available for review had MD (55%). Foveolar hyperplasia, tortuosity or “corkscrewing” of the glands, dilatation of the glands, and significant parietal cell loss were present in all patients with MD. Other features include deep lateral branching, lamina propria oedema, surface erosion and smooth muscle hyperplasia. Two distinct forms of MD have been reported in the literature - HLG and massive foveolar hyperplasia (MFH) with minimal inflammation.[49,50] HLG is characterised by a large number of intraepithelial lymphocytes and highly increased inflammation in the lamina propria, whereas inflammation is not a prominent feature of MFH and intraepithelial lymphocytes are rarely seen. MFH has also been reported to exhibit a more striking increase in mucosal thickness than HLG, and is more likely to show the classic reversal of the pit-gland ratio of 3:1 or greater.[50] Conversely, HLG shows a maximum pit-gland ratio of 3:1, with no variance from normal in uninflamed mucosa for those patients with patchy inflammation, and may represent an unusual form of lymphocytic gastritis.[50] This study does not include any patients with HLG; all MD patients were confirmed as MFH without prominent inflammation with the exception of eosinophils and/or clusters of plasma cells in the lamina propria, which we consider a heretofore underappreciated histological feature of MD that is rarely associated with peripheral eosinophilia (1/25, 4%).

Polyps and polyposis syndromes, the most common mimics of MD in this study, are best-differentiated one from another and from MD by family history, manifestations outside of the stomach, genetic testing, appearance at endoscopy, and histological presentation. On pathological examination, MD can be distinguished from hyperplastic polyps and juvenile polyps by the preservation of tissue architecture and parallelism of gastric glands, and the presence of prominent lamina propria smooth muscle fibres. Hyperplastic polyps and juvenile polyps will appear more disorganised and oedematous, as they show a lower gland-to-stroma ratio.

While special stains can be employed, routine haematoxylin and eosin (H&E)-stained slides are sufficient for pathologic evaluation of MD and its mimics. Surface mucous cells stain positive with PAS, MUC5AC, gastrosine and TFF1. Reduction in number of parietal cells and chief cells can be visualised with reduced expression of H⁺/K⁺ATPase and pepsinogen, respectively, by immunohistochemical staining. Additionally, Ki67 may show an increase in the number of proliferating cells in the expanded, downwardly displaced progenitor zone, a characteristic feature of MD.[27]

In this study, there were also a group of non-polyposis, non-MD patients (10/23), as listed above. Lymphoma, gastric cancer, gastrointestinal stromal tumours (GIST), tuberculosis, or other infiltrative disease also must be on the differential for thickened gastric wall. A recent review from our group discusses molecular and clinical insights on GIST and MD.[3] Two individuals in this study were found to have cancer - linitis plastica with carcinomatosis and diffuse signet cell gastric cancer - upon further evaluation for possible MD. We recently have identified two cases of linitis plastica due to metastatic breast cancer.

PPI effect can also thicken the gastric mucosa and mimic MD clinically, but is differentiated from MD histologically by the abundance of parietal cells. The oxyntic glands may be slightly dilated, and parietal cells will sporadically exhibit snouting, in which the apical portion of the parietal cell extends like a process into the glandular lumen (Figure 3F). This will also be accompanied by a history of long-term PPI use. Parietal cell hyperplasia can be associated with Zollinger-Ellison (ZE) syndrome, which will be accompanied by gastrin-

producing tumours in the pancreas or duodenum and ulcers in the stomach and/or duodenum. Parietal cell hyperplasia is easily distinguishable from MD histologically, since MD usually has a marked reduction in parietal cell mass.

The greatest challenge to the diagnosis of MD is the lack of standardised criteria for diagnosis. Establishing this clinicopathological diagnosis requires a high level of cooperation between gastroenterologists and pathologists, as the disease is difficult to identify based upon symptomatology, imaging or pathology alone. Based upon our experience, we suggest the following algorithm for approaching patients with suspected MD (Figure 6):

- Endoscopic evaluation:
 - Obtain a full thickness mucosal biopsy of involved mucosa via deep snare technique.
 - Obtain gastric pH at the time of endoscopy.
 - Assess for thick, copious mucus.
- Laboratory evaluation:
 - Complete blood count, serum albumin, serum gastrin, *H. pylori* and CMV serology upon diagnosis of enlarged gastric folds.
- Pathologic evaluation:
 - Assess overall mucosal architecture for parallelism of glands and foveolar compartment for hyperplasia of surface mucous cells.
 - Look for relative reduction in parietal cells, dilatation of glands, increased eosinophilis and plasma cells in the lamina propria, oedema and smooth muscle hyperplasia.
- Clinical evaluation
 - Correlate clinical information with histopathological diagnosis, including but not limited to information obtained via CT scan, EGD, family history, patient presentation and extra-gastrointestinal symptoms.

Summary Box

What is already known about this subject

- Ménétrier's disease (MD) is a rare form of acquired gastropathy characterised by giant rugal folds in the gastric body, foveolar hyperplasia and markedly decreased or absent oxyntic glands.
- The average age of onset for MD is 55, and there is a male predominance.
- The classic constellation of symptoms for MD includes abdominal pain, nausea, vomiting and oedema secondary to protein loss across the gastric mucosa with resultant low serum albumin.
- Cetuximab, a monoclonal antibody to the epidermal growth factor receptor, has recently been reported as an effective therapy for the treatment of MD.

What are the new findings

- MD is most commonly confused with gastric polyps or gastric involvement by polyposis syndromes.

- MD is more likely to cause vomiting and oedema, whereas polyps are more likely to cause bleeding; other clinical features present at similar frequencies.
- MD is most accurately diagnosed by clinicohistopathological analysis including esophagoduodenoscopy with gastric pH, appropriate laboratory tests and full thickness mucosal biopsy.

How might it impact on clinical practice in the foreseeable future?

- Based upon our experience, we propose a diagnostic algorithm to use when MD is suspected.
- Recommendations for how gastroenterologists and pathologists can best evaluate patients with enlarged gastric folds will lead to accurate diagnosis of MD and its mimics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

MD	Ménétrier's disease
CMV	cytomegalovirus
EGFR	epidermal growth factor receptor
TGF-α	transforming growth factor- α
VUMC	Vanderbilt University Medical Center
EGD	esophagogastroduodenoscopy
PPI	proton pump inhibitor
JPS	Juvenile Polyposis syndrome
HLG	hypertrophic lymphocytic gastritis
HHT	hereditary hemorrhagic telangiectasia
FAP	familial adenomatous polyposis
MFH	massive foveolar hyperplasia
H&E	haematoxylin and eosin
GIST	gastrointestinal stromal tumours
ZE	Zollinger-Ellison

References

1. Ménétrier P. Des polyadenomes gastriques et leur rapport avec le cancer de l'estomac. Arch Physiol Norm Pathol 1888;1:236–62.
2. Scharschmidt B. The natural history of hypertrophic gastrophy (Ménétrier's disease). Report of a case with 16 year follow-up and review of 120 cases from the literature. Am J Med 1977;63:644–62. [PubMed: 199063]
3. Coffey RJ, Washington MK, Corless CL, et al. Menetrier disease and gastrointestinal stromal tumors: hyperproliferative disorders of the stomach. J Clin Invest 2007;117:70–80. [PubMed: 17200708]

4. Drut RM, Gomez MA, Lojo MM, et al. Cytomegalovirus-associated Menetrier's disease in adults. Demonstration by polymerase chain reaction (PCR). *Medicina (B Aires)* 1995;55:659–64. [PubMed: 8731575]
5. Eisenstat DD, Griffiths AM, Cutz E, et al. Acute cytomegalovirus infection in a child with Ménétrier's disease. *Gastroenterology* 1995;109:592–95. [PubMed: 7615210]
6. Hoffer V, Finkelstein Y, Balter J, et al. Ganciclovir treatment in Menetrier's disease. *Acta Paediatr* 2003;92:983–5. [PubMed: 12948079]
7. Pederiva C, Ruscitto A, Brunetti I, et al. Cytomegalovirus-induced protein-losing gastropathy: a case report. *Pediatr Med Chir* 2006;28:42–7. [PubMed: 17533897]
8. Setakhr V, Muller G, Hoang P, et al. Cytomegalovirus-associated protein losing gastropathy in an immunocompetent adult: A case report. *Acta Gastroenterol Belg* 2007;70:296–99. [PubMed: 18074741]
9. Badov D, Lambert JR, Finlay M, et al. *Helicobacter pylori* as a pathogenic factor in Ménétrier's disease. *Am J Gastroenterol* 1998;93:1976–79. [PubMed: 9772069]
10. Davis GE, O'Rourke MC, Metz RJ, et al. Hypertrophic gastropathy symptoms responsive to prednisone. A case report and a review of the literature. *J Clin Gastroenterol* 1991;13:436–41. [PubMed: 1918850]
11. Dournovo P, Midnon M, Favriel JM, et al. Menetrier's disease: long-term treatment with cimetidine. *Nouv Presse Med* 1980;9:1241. [PubMed: 7454558]
12. Frederiksen HJ, Olsen N, Krag E. Cimetidine treatment of Menetrier's syndrome. *Ugeskr Laeger* 1978;140:298–9. [PubMed: 636061]
13. Gadour MO, Salman AH, El Samman el Tel W, et al. Menetrier's disease: an excellent response to octreotide. A case report from the Middle East. *Trop Gastroenterol* 2005;26:129–31. [PubMed: 16512461]
14. Green BT, Branch MS. Menetrier's disease treated with octreotide long-acting release. *Gastrointest Endosc* 2004;60:1028–9. [PubMed: 15605031]
15. Jun DW, Kim DH, Kim SH, et al. Menetrier's disease associated with herpes infection: response to treatment with acyclovir. *Gastrointest Endosc* 2007;65:1092–5. [PubMed: 17531647]
16. Kawasaki M, Hizawa K, Aoyagi K, et al. Menetrier's disease associated with *Helicobacter pylori* infection: resolution of enlarged gastric folds and hypoproteinemia after antibacterial treatment. *Am J Gastroenterol* 1997;92:1909–12. [PubMed: 9382064]
17. Krag E, Frederiksen HJ, Olsen N, et al. Cimetidine treatment of protein-losing gastropathy (Menetrier's disease). A clinical and pathophysiological study. *Scand J Gastroenterol* 1978;13:636–9. [PubMed: 705259]
18. Krol TC, Isenberg JI. Remission in a patient with Menetrier's disease: spontaneous or induced by treatment? *J Clin Gastroenterol* 1985;7:161–8. [PubMed: 3924991]
19. Maunoury V, Wacrenier A, Malamut G, et al. Results of treatment with COX-2 inhibitors and lanreotide in a patient with Menetrier's hypertrophic gastropathy. *Gastroenterol Clin Biol* 2004;28:407–8. [PubMed: 15146161]
20. Plottin F, Capony P, Meullenet J, et al. Treatment of Menetrier's disease with pirenzepine. *Gastroenterol Clin Biol* 1983;7:1046–7. [PubMed: 6689306]
21. Raderer M, Oberhuber G, Templ E, et al. Successful symptomatic management of a patient with Menetrier's disease with long-term antibiotic treatment. *Digestion* 1999;60:358–62. [PubMed: 10394031]
22. Rothenberg M, Pai R, Stuart K. Successful use of octreotide to treat Menetrier's disease: a rare cause of abdominal pain, weight loss, edema, and hypoalbuminemia. *Dig Dis Sci* 2009;54:1403–7. [PubMed: 19255847]
23. Smith RL, Powell DW. Prolonged treatment of Menetrier's disease with an oral anticholinergic drug. *Gastroenterology* 1978;74:903–6. [PubMed: 640345]
24. Jung JH, Hong SJ, Lee MS. Resolution of Menetrier's disease after *Helicobacter pylori* eradication. *Korean J Gastroenterol* 2006;48:1–3. [PubMed: 16861874]
25. Madsen LG, Taskiran M, Bytzer P. Menetrier's disease: Another *Helicobacter pylori* associated disease? *Ugeskr Laeger* 2000;162:4250–3. [PubMed: 10962941]

26. Yoshimura M, Hirai M, Tanaka N, et al. Remission of severe anaemia persisting for over 20 years after eradication of *Helicobacter pylori* in cases of Menetrier's disease and atrophic gastritis: *Helicobacter pylori* as a pathogenic factor in iron-deficiency anaemia. *Intern Med* 2003;42:971–7. [PubMed: 14606710]
27. Fiske WH, Tanksley J, Nam KT, et al. Efficacy of cetuximab in the treatment of Menetrier's disease. *Sci Transl Med* 2009;1:8ra18.
28. Nomura S, Settle SH, Leys CM, et al. Evidence for repatterning of the gastric fundic epithelium associated with Menetrier's disease and TGF- α overexpression. *Gastroenterology* 2005;128:1292–305. [PubMed: 15887112]
29. Settle SH, Washington K, Lind C, et al. Chronic treatment of Menetrier's disease with Erbitux: clinical efficacy and insight into pathophysiology. *Clin Gastroenterol Hepatol* 2005;3:654–9. [PubMed: 16206497]
30. Bluth RF, Carpenter HA, Pittelkow MR, et al. Immunolocalization of transforming growth factor- α in normal and diseased human gastric mucosa. *Hum Pathol* 1995;26:1333–40. [PubMed: 8522306]
31. Bockman DE, Sharp R, Merlino G. Regulation of terminal differentiation of zymogenic cells by transforming growth factor α in transgenic mice. *Gastroenterology* 1995;108:447–54. [PubMed: 7835587]
32. Coffey RJ, Romano M, Goldenring J. Roles for transforming growth factor- α in the stomach. *J Clin Gastroenterol* 1995;21 (suppl 1):S36–9. [PubMed: 8774988]
33. Coffey RJ, Romano M, Polk WH, et al. Roles for transforming growth factor- α in gastric physiology and pathophysiology. *Yale J Biol Med* 1992;65:693–704. discussion 621–3. [PubMed: 1341072]
34. Goldenring JR, Ray GS, Soroka CJ, et al. Overexpression of transforming growth factor- α alters differentiation of gastric cell lineages. *Dig Dis Sci* 1996;41:773–84. [PubMed: 8674399]
35. Burdick JS, Chung E, Tanner G, et al. Treatment of Ménétrier's disease with a monoclonal antibody against the epidermal growth factor receptor. *N Engl J Med* 2000;343:1697–701. [PubMed: 11106719]
36. Campbell I. Chi-squared and Fisher-Irwin tests of two-by-two tables with small sample recommendations. *Stat Med* 2007;26:3661–75. [PubMed: 17315184]
37. Hsu CT, Ito M, Kawase Y, et al. Early gastric cancer arising from localized Ménétrier's disease. *Gastroenterology Japan* 1991;26:213–17.
38. Choi SB, Park SS, Oh SY, et al. Primary squamous cell carcinoma of the stomach that developed with Menetrier's disease. *Dig Dis Sci* 2007;52:1722–24. [PubMed: 17443414]
39. Johnson MI, Spark JI, Ambrose NS, et al. Early gastric cancer in a patient with Menetrier's disease, lymphocytic gastritis and *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 1995;7:187–90. [PubMed: 7712313]
40. Wood MG, Bates C, Brown RC, et al. Intramucosal carcinoma of the gastric antrum complicating Menetrier's disease. *Journal of Clinical Pathology* 1983;36:1071–75. [PubMed: 6886023]
41. Hemmings CT. Menetrier's disease in a patient with ulcerative colitis: a case report and review of the literature. *Pathology* 2007;39:282–3. [PubMed: 17454767]
42. Hatemi I, Caglar E, Aksoy D, et al. Menetrier's disease coexisting with ulcerative colitis and sclerosing cholangitis. *Dig Liver Dis* 2008;40:78–9. [PubMed: 18037066]
43. Gammon A, Jaspersion K, Kohlmann W, et al. Hamartomatous polyposis syndromes. *Best Pract Res Clin Gastroenterol* 2009;23:219–31. [PubMed: 19414148]
44. Chow E, Macrae F. A review of juvenile polyposis syndrome. *J Gastroenterol Hepatol* 2005;20:1634–40. [PubMed: 16246179]
45. Gallione CJ, Repetto GM, Legius E, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet* 2004;363:852–9. [PubMed: 15031030]
46. Bjork JT, Geenen JE, Komorowski RA, et al. Menetrier's disease diagnosed by electrosurgical snare biopsy. *Jama* 1977;238:1755–6. [PubMed: 578274]
47. Bjork JT, Geenen JE, Soergel KH, et al. Endoscopic evaluation of large gastric folds: a comparison of biopsy techniques. *Gastrointest Endosc* 1977;24:22–3. [PubMed: 892391]

48. Faigel DO, Eisen GM, Baron TH, et al. Tissue sampling and analysis. *Gastrointest Endosc* 2003;57:811–6. [PubMed: 12776025]
49. Haot J, Bogomoletz WV, Jouret A, et al. Menetrier's disease with lymphocytic gastritis: an unusual association with possible pathogenic implications. *Hum Pathol* 1991;22:379–86. [PubMed: 2050372]
50. Wolfsen HC, Carpenter HA, Talley NJ. Menetrier's disease: a form of hypertrophic gastropathy or gastritis? *Gastroenterology* 1993;104:1310–9. [PubMed: 8482445]

Figure 1.

The most common clinical complaints associated with MD (blue), total non-MD (red) and non-MD with polyps (yellow). * $p = 0.01$; p value for difference in vomiting between MD and non-MD with polyps was 0.051. ** $p = 0.016$. Dotted lines represent range of normal values.

Figure 2. Comparison of relevant lab values. A. Serum albumin; B. Gastric pH; Serum gastrin. Dotted lines signify normal range. Median values are designated with a bar for each group.

Figure 3.

Histological features of MD and its mimics. A. Low power H&E of MD showing relative preservation of mucosal architecture with foveolar hyperplasia, tortuosity and dilatation of the glands, smooth muscle hyperplasia and decreased numbers of parietal cells. B. High power view of MD showing clusters of eosinophils (arrows). C. Low power H&E of JPS polyp. D. High power view of JPS polyp showing oedematous stroma and lack of smooth muscle hyperplasia. E. Hyperplastic polyp. F. PPI effect (arrow points to parietal cell snouting). Size bar = 50µm.

Figure 4. Cancer in the setting of MD. A. Low power view showing typical features of MD with arrow pointing to a focus of cancer. B. Multiple small foci of cancer seen in the lymphovascular space. Size bar = 50 μ m.

Figure 5. Endoscopic views of MD (A&B) versus a polyposis syndrome (C&D). A. Giant rugal folds with surface erosions and overlying mucus in MD. B. Mucus bridge across the lumen upon retroflex view of the fundus in MD. C. Translucent cluster of polyps lacking thick mucus accumulation in polyposis syndrome. D. Translucent polyps covering the mucosal surface in polyposis syndrome.

Figure 6.
Clinicopathological decision-making tree for the diagnosis of MD.

Table 1

Diagnoses of study patients

Disease state	Number
Ménétrier's disease	25
Juvenile Polyposis syndrome with gastric involvement	3
Gastric hyperplastic polyps	4
Hamartomatous polyp or unclassified polyposis syndrome	4
Cronkhite-Canada syndrome	1
Fundic gland polyps in setting of familial adenomatous polyposis	1
Proton pump inhibitor effect	2
Parietal cell hyperplasia	2
Chronic gastritis	2
Acute gastritis with G-cell hyperplasia	1
Gastric antral vascular ectasia	1
Linitis plastica with carcinomatosis	1
Diffuse signet cell gastric cancer	1

Table 2**Patient characteristics and clinical complaints**

Summary of the clinical comparisons made among MD patients, total non-MD patients, and non-MD patients with polyps

Variable	MD (n=25)	Total non-MD (n=23)	Non-MD with polyps (n=13)
Age at diagnosis ^{1,2}	40 (16 to 79)	57 (39 to 73)	52 (39 to 73)
Male:Female ^{3,4}	18:7	9:14	5:8
Nausea	10 (40%)	9 (39%)	4 (31%)
Vomiting ³	12 (48%)	3 (13%)	2 (15%)
Peripheral oedema ⁵	11 (44%)	5 (22%)	3 (23%)
Pain	12 (48%)	13 (56%)	5 (38%)
Weight loss	8 (32%)	7 (30%)	3 (23%)
Anaemia ⁴	7 (28%)	9 (39%)	9 (69%)
Anaemia requiring transfusion	2 (8%)	4 (17%)	4 (31%)
Early satiety	1 (4%)	3 (13%)	1 (8%)
Diarrhea	3 (12%)	3 (13%)	2 (15%)
Supplemental nutrition required	3 (12%)	0	0
GERD-like symptoms	3 (12%)	2 (15%)	2 (15%)

¹ Wilcoxon rank sum test p<0.05 comparing MD to total non-MD.

² Wilcoxon rank sum test p<0.05 comparing MD to non-MD with polyps.

³ Chi-square p<0.05 comparing MD to total non-MD.

⁴ Chi-square p< 0.05 comparing MD to non-MD with polyps.

⁵ Chi-square p=0.11 comparing MD to total non-MD.