HYPERTROPHIC GASTROPATHIES:
ALL THAT THICKENS...IS NOT MÉNÉTRIER 'S DISEASE

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The endoscopic observation of thickened gastric folds may reflect a variety of pathologies in the stomach, from common conditions to the very rare, such as Ménétrier's disease and poorly characterized polyposis syndromes. The pathophysiology and etiology of many of these conditions are not well understood, although many clinical associations have been made over the years. Because diagnosis of some of these disorders required examination of the full thickness of an often very thick gastric mucosa, standard forceps biopsies may not be adequate and the endoscopist should be encouraged to obtain full-thickness snare biopsies. For instance, superficial biopsies of hyperplastic foveolar epithelium may show similar findings in focal foveolar hyperplasia, hyperplastic polyp, hamartomatous polyps, Ménétrier's disease, in mucosa adjacent to gastric ulcers. Pathologic diagnosis therefore requires knowledge of the endoscopic findings including the location of the lesion in the stomach, adequate sampling, and careful clinical correlation.

<table>
<thead>
<tr>
<th>Hyperplastic Mucosal Compartment</th>
<th>Differential Diagnosis</th>
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<tr>
<td>Foveolar epithelium</td>
<td>Focal foveolar hyperplasia</td>
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<td></td>
<td>Hyperplastic polyp</td>
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<td></td>
<td>Hamartomatous polyp</td>
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<td></td>
<td>Ménétrier's disease</td>
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<tr>
<td>Parietal cells</td>
<td>Zollinger-Ellison syndrome</td>
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<tr>
<td>All layers</td>
<td>Hypertrophic Hypersecretory gastropathy</td>
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MÉNÉTRIER'S DISEASE

Clinical and demographic features. First described in 1888, Ménétrier’s disease is a rare acquired protein-losing gastropathy characterized by giant rugal folds with massive foveolar hyperplasia and loss of parietal cells. The classic clinical features are hypoalbuminemia with peripheral edema, abdominal pain, and nausea and vomiting. Two distinct forms occur: a chronic form with insidious onset seen in adults, and a spontaneously resolving form with abrupt onset associated with cytomegalovirus infection in children. The average age at diagnosis in adults is 55, and the disorder is more commonly reported in men. A number of patients with Ménétrier’s disease also have ulcerative colitis, although the association remains enigmatic. We have also seen a case associated with primary pulmonary hypertension. Ménétrier’ disease in adults is associated with an increased risk of gastric cancer, estimated at 2-15% lifetime risk.
**Endoscopic features.** Ménétrier’s disease primarily involves the gastric corpus and the antrum is often spared. At endoscopy, the enlarged gastric folds resemble cerebral convolutions. Gastric pH is neutral or alkaline due to decreased parietal cells, and copious thick mucus is often noted. Serum gastrin levels are usually normal or near-normal despite the hypoaclidity. Full-thickness snare biopsies are essential for evaluating the pathologic features.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location in stomach</th>
<th>Endoscopic Features</th>
<th>Clinical Findings</th>
<th>Pathologic Feature</th>
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<tbody>
<tr>
<td>Ménétrier’s disease</td>
<td>Corpus; may also involve antrum</td>
<td>Cerebriform thickened folds</td>
<td>Nausea, vomiting, peripheral edema</td>
<td>Massive foveolar hyperplasia</td>
</tr>
<tr>
<td>Zollinger-Ellison syndrome</td>
<td>Corpus</td>
<td>Folds thickened up to 8 mm</td>
<td>Refractory peptic ulcer disease</td>
<td>Parietal cell hyperplasia</td>
</tr>
<tr>
<td>Hypertrophic hyperplastic gastropathy</td>
<td>Corpus</td>
<td>Diffuse cobblestone nodularity</td>
<td>Peptic ulcer disease</td>
<td>Hyperplasia of all glandular elements</td>
</tr>
<tr>
<td>Hyperplastic polyp</td>
<td>Antrum; also in corpus and cardia</td>
<td>Polyp(s), single or multiple</td>
<td>Associated with chronic atrophic gastritis</td>
<td>Foveolar hyperplasia with architectural disarray</td>
</tr>
<tr>
<td>Polypoid gastritis</td>
<td>Antrum and corpus</td>
<td>Nodularity</td>
<td>Epigastric pain</td>
<td>Chronic active gastritis with <em>H. pylori</em></td>
</tr>
<tr>
<td>Polyposis syndrome</td>
<td>Antrum and corpus</td>
<td>Variable; diffuse nodular enlargement of gastric folds or discrete polyps</td>
<td>Juvenile polyposis, Peutz-Jaeger syndrome, other undefined polyposis syndrome</td>
<td>Features overlap with hyperplastic polyp</td>
</tr>
<tr>
<td>Gastritis cystica profunda/polyposa</td>
<td>Body &amp; antrum; gastric remnant in operated stomach</td>
<td>Usually localized</td>
<td>Usually found in operated stomach</td>
<td>Entrapped cystic glands in submucosa or deeper layers</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Antrum and corpus</td>
<td>Thickened folds</td>
<td>Variable</td>
<td>Effacement of gastric mucosal architecture by neoplastic lymphoid infiltrate</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Antrum and corpus</td>
<td>Thickened folds</td>
<td>Variable</td>
<td>Infiltrating carcinoma, non-cohesive type</td>
</tr>
</tbody>
</table>
Other rare causes of thickened gastric folds include metastatic carcinoma [1], eosinophilic gastroenteritis [2, 3], and gastric involvement by syphilis [4].

**Pathologic features of Ménétrier’s disease**

- Massive foveolar hyperplasia, with mucosal thickness of 1 cm or more
- Decreased or absent parietal cells
- Corkscrew morphology of foveolar epithelium, although overall linear architecture is primarily maintained
- Cystically dilated glands in deep mucosa
- Variable lamina propria inflammatory infiltrate, but often including eosinophils
- Smooth muscle strands in lamina propria

**Variants of Ménétrier’s disease**

Variants of Ménétrier’s disease reported include localized cases [5], spontaneously resolving forms and a form characterized by numerous intraepithelial lymphocytes and known as hypertrophic lymphocytic gastritis [6]. The latter condition may also present with giant folds in the body of the stomach sparing the antrum. The mucosal inflammation in hypertrophic lymphocytic gastritis is severe and diffuse, with a striking increase in intraepithelial lymphocytes. Uninflamed mucosa in a study of 13 cases did not show foveolar hyperplasia and loss of parietal cells was not seen [6]. In comparing these 13 cases with 10 cases of classic Ménétrier’s disease with massive foveolar hyperplasia and little inflammation, the investigators concluded that hypertrophic lymphocytic gastritis should be considered as part of the spectrum of lymphocytic gastritis and not a form of Ménétrier’s disease.

The spontaneously-remitting form of Ménétrier’s disease primarily occurs in the setting of cytomegalovirus (CMV) infection, but has also been reported in *H. pylori* gastritis. Spontaneous resolution generally occurs in children over 4 to 6 weeks [7]. CMV-associated Ménétrier’s disease may also be seen in adults [8].

Familial cases of Ménétrier’s disease have been reported; while some appear to represent Ménétrier’s disease, others likely represent polyposis syndromes involving the stomach. Inherited Ménétrier’s disease-like cases appear to be transmitted in an autosomal dominant fashion. In one reported family, affected individuals had anemia, not protein loss, and no increase in TGF-α was demonstrated by RT-PCR or immunohistochemistry [9].

**Pathophysiology.** TGF-α, one of the seven mammalian ligands that active the epidermal growth factor receptor (EGFR), stimulates gastric epithelial repair and renewal while inhibiting acid secretion. Twenty years ago, studies in MT- TGF-α overexpressing mice [10] showed a phenotype of foveolar hyperplasia with decreased parietal cells similar to Ménétrier’s disease, and increased levels of TGF-α were demonstrated in the hyperplastic foveolar epithelium in humans with this disorder [11]. While the cause of the sustained increase in gastric mucosal TGF-α has not been defined in Ménétrier’s disease, it is possible that subclinical gastric injury may trigger appropriate TGF-α release and activation of downstream EGFR signaling.

Ménétrier’s disease may result from failure of the normal feedback loop, which would also explain durable remission seen with cetuximab. CMV-dependent EGFR activation may explain the association of CMV infection with Ménétrier’s disease, as CMV infects human cells by interacting with EGFR. Similarly, *H. pylori* infection causes overexpression of amphiregulin and
heparin-binding EGF-like growth factor, other members of the EGFR ligand family, and may lead to a similar increase in EGFR signaling. Ruthenium red data suggests that defective tight junction barrier function may be related to protein loss in Ménétrier’s disease, although the signaling pathways responsible have not been defined.

**Clinicopathologic Decision-Making Tree for Diagnosis of Ménétrier's Disease**

*Treatment.* The mainstay of treatment for debilitating Ménétrier’s disease is gastrectomy. Evidence for the benefit of most medical treatments, including octreotide, which may modulate EGFR signaling, antibiotics, prednisone and non-steroidal anti-inflammatory agents, is inconsistent. Based on the observation of increased EGFR signaling as an underlying event in
Ménétrier’s disease, a clinical trial of cetuximab, a partially humanized antibody directed at EGFR that blocks ligand binding, was initiated in 1999 at Vanderbilt [12, 13]. All seven patients completing a one-month course of treatment showed improvement in clinical symptoms and gastric histology, with four showing near-total histologic remission [14]. However, the increased risk of gastric cancer remains a concern in this population, and four individuals elected to undergo gastrectomy despite durable response to therapy.

**Distinction from gastric involvement by polyposis.** Juvenile polyposis and other polyposis syndromes sometimes involve the stomach, and distinction from Ménétrier’s disease may be difficult on histologic grounds alone. Clinical features, such as anemia and protein loss, can also mimic Ménétrier’s disease, and it is likely that some cases reported in the literature as Ménétrier’s disease represent juvenile polyposis. In the Vanderbilt series of 48 patients evaluated for possible Ménétrier’s disease, 3 were diagnosed with juvenile polyposis, 1 with Cronkhite-Canada Syndrome, and 4 others with hamartomatous polyps or an uncharacterized polyposis syndrome [15]. Histologic features favoring juvenile polyp over Ménétrier’s disease are disorderly architecture and “cap-like” appearance of the hyperplastic foveolar epithelium, preservation of parietal cells, and lack of lamina propria smooth muscle.

**Gastric Polyposis Syndrome Mimics of Ménétrier’s Disease**

Juvenile polyposis syndrome (JPS) is an autosomal dominant disorder, manifested by hamartomatous polyps in the colon in 98% of patients; hamartomatous polyps are found in the stomach 14% and in small bowel in 7%. Roughly half of JPS cases are due to germline mutations in **SMAD4** or **BMPR1A**, with the remainder due to as-yet-uncharacterized genetic alterations. **SMAD4** mutations are associated with more severe gastric phenotypes [16], and an exclusively gastric form of JPS has been described [17], associated with a nonsense mutation resulting in a stop codon [c.1527 G>A] in exon 11 of **SMAD4** in one case, and a four base pair deletion in exon 9 at codon 415 in another. Such cases have been described as showing a mixed hyperplastic/polyoid gastropathy, mainly in the gastric corpus, with thick adherent mucus. Gastric juvenile polyps may be difficult to classify with certainty in the absence of a known diagnosis of JPS, and the morphology overlaps with hyperplastic polyps and that of other hamartomatous lesions [18]. In our experience, the non-polypoid background gastric body mucosa in JPS cases sometimes shows a subtle foveolar hyperplasia, and it has been speculated that disruption of the TGFβ/SMAD signaling pathway can lead to TGF α overexpression, especially in the setting of *H. pylori* infection [19], which could explain the similarities of gastric JPS polyps to Ménétrier’s disease in some cases.

Other polyposis syndromes that should be considered in the differential diagnosis include Peutz-Jaegers [18], Cronkhite-Canada, or Cowden’s syndrome [20, 21] and newly-described syndromes such as proximal polyposis of the stomach [22].

**Gastritis cystica profunda/polyposa**, an uncommon lesion more often found in previously operated stomachs, consists of displaced or herniated dilated glandular elements in the submucosa or deeper layers of the gastric wall. When the glands are primarily located deep in the gastric wall, the lesion is termed *profunda*; when an exophytic component is present, the term *polyposa* is used. It is often associated with chronic bile reflux and probably represents a reactive proliferation of entrapped herniated mucosal elements. While gastritis cystica profunda
may present as giant gastric folds [23], it more often presents as a localized lesion [24]. Cases of gastritis cystica profunda in the setting of Ménétrier’s disease [25] most likely represent herniation of cystically dilated mucosa often found in Ménétrier’s disease. The major significance of gastritis cystica profunda is the occasional difficulty in distinguishing the herniated glands from well differentiated adenocarcinoma [26].

Table 3. Diagnostic features of Ménétrier’s disease in patients with chronic symptoms

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Endoscopic</th>
<th>Histologic</th>
</tr>
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<tbody>
<tr>
<td>↓ serum albumin</td>
<td>Diffusely enlarged folds in corpus</td>
<td>Massive foveolar hyperplasia</td>
</tr>
<tr>
<td>peripheral edema</td>
<td>↓ gastric acidity</td>
<td>Decreased parietal cells</td>
</tr>
<tr>
<td>Normal serum gastrin</td>
<td>Increased mucin production</td>
<td>Maintenance of mucosal architecture</td>
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ZOLLINGER-ELLISON SYNDROME

Clinical features. The most severe gastric hypersecretory state is Zollinger-Ellison syndrome (ZES), characterized by refractory peptic ulcer disease due to ectopic release of gastrin by a neuroendocrine tumor. From 20% to 60% of patients with ZES have MEN-1 syndrome. Given that gastric acid secretion is increased up to five times normal in ZES, it is not surprising that the most common symptom is abdominal pain (83%). The gastrinoma is usually located in the duodenum (70 to 90% in recent studies) or pancreas in the gastrinoma triangle, but may be primary at many unusual sites, including lymph nodes, liver, heart, and ovaries [27]. Elevated serum gastrin is found in up to 99% of ZES patients, but it is important to measure gastric pH at the same time to rule out hypochlorhydric states. Because proton pump inhibitors (PPIs) can cause hypergastrinemia, fasting gastrin and secretin tests should be performed after stopping PPIs to avoid delay in diagnosis.

Endoscopy. Almost all patients with ZES (92%) have prominent gastric folds. Ulcers in esophagus (14%), stomach (18%), duodenum (6%) are now seen infrequently at baseline endoscopy but are routine-appearing when present.

Pathology. The mucosa of the gastric body is thickened, with measurements of up to 5-8 mm reported [28], due to parietal cell hyperplasia. In addition to expanding the mucosa, parietal cells also extend to the base of the glands, in zones normally occupied by chief cells. The foveolar compartment is not expanded. ECL cell hyperplasia is more common in the gastric body in MEN1/ZES patients compared to sporadic ZES cases.

Treatment and outcome. The peptic ulcer symptoms and complications of ZES respond well to PPI treatment [29]. Even patients with metastatic disease may have a relatively indolent course, although a subset have more aggressive disease, and the extent of liver metastases is an important factor influencing survival [30, 31]. Patients with sporadic gastrinomas may have a worse prognosis than those with MEN-1; median survival in one series was 7 years for non-syndromic patients [29].

Pseudo-Zollinger-Ellison Syndrome. Gastric acid hypersecretion may occur in the absence of gastrinomas and may be related to vagal hyperactivity. Such cases have been called ZES-like hypersecretion or pseudo-ZES, and are distinguished from ZES by negative secretin
stimulation testing. Most of the patients in one series were middle-aged white men with normal serum gastrin \[32\]. Some reported cases show primary G cell hyperplasia in the gastric antrum \[33, 34\]. Patients generally respond to treatment with proton pump inhibitors.

HYPERTROPHIC HYPERSECRETORY GASTROPATHY

This condition is defined as hyperplasia of all glandular compartments of the gastric body with hypersecretion of acid, pepsin, and mucoprotein. Many of the published reports predate recognition of \textit{H. pylori} gastritis, and it is possible that some cases represent polypoid gastritis. Most reported cases had duodenal or gastric ulcers, with 70% having documented peptic ulcer disease in one series \[35\]. The gastric body mucosa is described as diffusely nodular, with normal or atrophic antral mucosa on endoscopy \[36\]. In addition to parietal cell and foveolar hyperplasia, the gastric glands may be cystically dilated. As in Ménétrier’s disease, serum albumin levels are low and gastrin levels are normal.

HYPERPLASTIC POLYPS

One of the most commonly encountered lesions with foveolar hyperplasia is the gastric hyperplastic polyp. In a recent large survey, the prevalence of gastric polyps in a private practice setting was 6%, with 17% of polyps representing hyperplastic polyps or foveolar hyperplasia \[37\]. Some pathologists distinguish between focal or polypoid foveolar hyperplasia, defined as a sharply localized focus of superficial foveolar hyperplasia, without cystic change or architectural distortion, and hyperplastic polyps, characterized by marked elongation of the pit region, with a corkscrew appearance, branching and cystic dilatation of foveolar epithelium with architectural disarray, and lack of a glandular component \[38\]. These lesions may represent the continuum of a response to injury, supported by the observation that the surrounding mucosa is rarely normal, generally showing reactive or chemical gastropathy, or chronic gastritis with or without \textit{H. pylori}. While in older reports hyperplastic polyps are most commonly seen in the antrum \[39\], in some series they are also found in the gastric body \[38\]. They also tend to be associated with intestinal metaplasia in the surrounding mucosa and atrophic gastritis, and inversely associated with active \textit{H. pylori} infection, consistent with long-standing \textit{H. pylori}-induced atrophic gastritis. Hyperplastic polyps are found more proximally in atrophic mucosa in autoimmune gastritis. Risk of neoplastic transformation is proportional to polyp size, with resection recommended for those measuring over 1.5 cm.

Features of gastric hyperplastic polyps\[39\]:

- Most common in antrum, but may be found in body and cardia
- Variable in size, with polyps measuring up to 9 cm reported
- Multiple in 20% of patients
- Almost always associated with abnormal background mucosa, often atrophic gastritis
- Intestinal metaplasia is found in up to 16% of hyperplastic polyps, and is more common in the non-polypoid mucosa
- 1.5 to 4.5% contain neoplastic areas, either dysplasia or carcinoma. Overall risk of neoplasia is low and likely related to underlying condition.
DIFFERENTIAL DIAGNOSIS OF THICKENED GASTRIC FOLDS: NEOPLASIA

Two of the important causes of thickened gastric folds are neoplastic: lymphoma and diffuse gastric carcinoma.

*Gastric lymphomas*, especially marginal-zone B-cell lymphomas, affect the same population, older adults, as Ménétrier’s disease. Because the lesion is usually confined to the mucosa, the gastric folds may be diffusely thickened. Erosions and shallow ulcers may also be seen. However, the microscopic features of gastric lymphoma do not include epithelial hyperplasia, and while the condition may be confused with gastritis, it is not typically mistaken for the hypertrophic gastropathies. On microscopic examination, a diffuse of vaguely nodular infiltrate of B cells with infiltration and disruption of gastric glands (lymphoepithelial lesions) is seen. Prominent plasmacytid differentiation may also occur.

*Diffuse (non-cohesive) gastric carcinoma* may also cause generalized thickening of the gastric folds and may be missed with small forceps biopsies [40]. Clinical features such as anemia and abdominal pain may overlap with those of hypertrophic gastropathies, and a high index of suspicion must be maintained. Gastric carcinoma arising in Ménétrier’s disease may be particularly difficult to detect, given the difficulty in identifying localized lesions at endoscopy in a background of diffusely thickened mucosa.

REFERENCES


