

## Review Article

## Thickened Gastric Folds: Approach

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## ABSTRACT

Thickened gastric folds (TGF) are not an uncommon finding on radiological imaging or endoscopy. It is an enigmatic condition requiring a systematic approach with correlation between clinical, laboratory, radiological, endoscopic, and histological parameters to reach a final diagnosis. It has a varied number of differential diagnosis and reaching the final diagnosis is often challenging even to an astute clinician. Findings on endoscopy are similar and biopsy results often equivocal. Differentiating between benign and malignant conditions is challenging. Routine pinch biopsy usually does not sample deep enough to get an adequate tissue sample, and other methods of biopsy may be required. Newer modalities, such as endoscopic ultrasound (EUS) and EUS-guided sampling, are helpful in differentiating benign from malignant causes. At times, exploratory laparotomy and full-thickness biopsy may be required for final diagnosis. In this review, we discuss the various differentials of TGF, with special emphasis on how to approach a case of TGF.

**KEYWORDS:** *Large gastric folds, Menetrier's disease, thickened gastric folds*

## INTRODUCTION

Thickened gastric folds (TGF) are a common finding on radiological imaging or endoscopy, the etiological possibilities ranges from inflammatory to malignant conditions.<sup>[1-6]</sup> It often poses a diagnostic dilemma which needs resolution with further evaluation. In the last decade there has been addition of endoscopic ultrasound in evaluation of TGF. A systematic approach using combination of clinical, laboratory, radiological, endoscopic, and histological parameters to establish the diagnosis would avoid unnecessary laparotomy and facilitate rapid diagnosis. This review presents the etiological possibilities and outlines an algorithm based approach to a case with thickened gastric fold.

## DEFINITION OF LARGE GASTRIC FOLDS

Gastric folds measuring more than 10 mm in width on standard barium X-ray are considered as thickened gastric folds (TGF).<sup>[1]</sup> On endoscopy, large gastric folds are the ones that do not flatten with air insufflation.<sup>[2]</sup>

## CAUSES

TGF can be a manifestation of various diseases. The incidence or prevalence of TGF has not been studied

in detail. As such, there is not much literature in this regard. Tran *et al.*<sup>[3]</sup> studied 8325 consecutive upper gastrointestinal (GI) barium series and found isolated TGF in 182 patients out of the total cases. The causes are shown in Table 1.<sup>[2,4-6]</sup>

Ménétrier's disease (MD) is a rare acquired hypertrophic gastropathy characterized by thickened folds in the body and fundus of stomach, hypochlorhydria, increased gastric mucus production, and hypoalbuminemia due to secondary gastric protein loss.<sup>[7]</sup> Males typically between 30 and 60 years of age are more commonly affected. Nausea, vomiting, abdominal pain, weight loss, pedal edema, and malabsorption are the usual presentation of MD.<sup>[8]</sup> It usually is a progressive disease with an increased risk of gastric cancer. Cytomegalovirus infection has been associated with MD, especially in young patients.<sup>[9]</sup> *Helicobacter pylori* infection has also been associated with TGF and MD. Interestingly, eradication of

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**Table 1: Cause of thickened gastric folds**

Gastritis and gastropathies
Menetrier's disease
Hypertrophic lymphocytic gastritis
Hypertrophic hypersecretory gastropathy
Acute gastritis with G-cell hyperplasia
Polyposis
Juvenile polyposis with gastric involvement
Gastric hyperplastic polyps
Hamartomatous polyps or unclassified polyposis syndrome
CCS
Fundic gland polyps in the setting of familial adenomatous polyposis
Malignancy
Diffuse gastric carcinoma
Gastric adenocarcinoma
Lymphoma
Infiltrative disease
Amyloidosis
Sarcoidosis
Miscellaneous
Proton-pump inhibitor effect
Parietal cell hyperplasia
Gastric antral vascular ectasia
ZES

ZES=Zollinger–Ellison Syndrome, CCS=Cronkhite–Canada syndrome

*H. pylori* has shown to cause remission of symptoms in these patients.<sup>[10]</sup>

The usual presentation of polyposis syndrome is with anemia, bleeding per rectum, and evidence of polyps elsewhere. Malignant causes are usually found in elderly patients with symptoms of anemia, early satiety, weight loss, and anorexia. Long-term proton pump inhibitor therapy has also been linked to TGF.

## DIAGNOSTIC WORKUP OF THICKENED GASTRIC FOLDS

A systematic approach with correlation between clinical, laboratory, radiological, endoscopic, and histological parameters is needed to reach the etiological diagnosis of TGF.

## RADIOLOGICAL INVESTIGATIONS

TGF may be detected on computed tomography (CT) scan, upper GI barium series, or on endoscopy done for the evaluation of symptoms. The usual clinical manifestations for which radiological or endoscopic evaluation reveal TGF include nausea, vomiting, nonspecific upper abdominal pain, early satiety, weight loss, anorexia, anemia, malabsorption, etc. CT scan is a good noninvasive method to evaluate gastric

folds.<sup>[6,11]</sup> Adequate distension of stomach is important for analysis of gastric wall. Normal gastric wall is typically 7–10 mm in maximal thickness on CT scan. However, it should be kept in mind that gastric rugal folds in the proximal stomach are thicker than the distal stomach. Any gastric fold thickness above 10 mm is usually considered significant. Chen *et al.*<sup>[6]</sup> evaluated the efficacy of multidetector CT (MDCT) in diagnosis of TGF. They reported a good accuracy of MDCT in diagnosis of gastric cancer, lymphoma, MD, and acute gastric mucosal lesions. Gastric wall was thickest in lymphoma ( $26.6 \pm 9.0$  mm), followed by scirrhous carcinoma ( $15.8 \pm 4.5$  mm), MD ( $11.2 \pm 0.8$ ), and acute gastric mucosal lesion ( $4.4 \pm 1.0$ ). They found the Cramer phi-prime correlation coefficients of the criteria with the diseases investigated to be 0.577, 0.984, 0.500, and 0.711 for wall stratification, wall enhancement pattern, appearance of gastric folds, and abnormal perigastric condition, respectively. Cutoff values for the best diagnostic accuracy between diseases were 3.8, 5.8, and 7.9. The accuracy of MDCT based on consideration of all four parameters was 100% in the diagnosis of all four diseases. Furthermore, the absence of wall stratification on MDCT was found to be the best predictor of malignancy. However, false-negative results are common, and endoscopy, endoscopic ultrasound (EUS), and histology may be required for definitive diagnosis.<sup>[6,11]</sup>

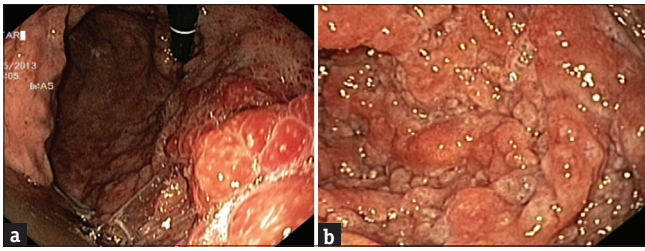
Positron-emission tomography has also been used to diagnose malignancy with good specificity. However, it has low sensitivity for gastric cancer, and more so for diffuse gastric cancers. As such, it has limited utility for the evaluation of TGF.<sup>[12]</sup>

## ENDOSCOPY

Endoscopy is important for direct visualization of the gastric mucosa and sampling from the mucosa. In MD, there will be diffuse involvement of stomach with markedly increased thickness of the gastric folds, often with erosions and thick mucus overlying these thickened folds.<sup>[7]</sup> It may be so thickened to resemble cerebral convolutions.

Polyposis syndrome with gastric polyps at times can mimic MD with TGF<sup>[13]</sup> [Figure 1]. These polyps can present as focal hypertrophic gastropathy and can be distributed so diffusely to mimic TGF. Hyperplastic polyps are most common in antrum; however, they can also occur in other areas of the stomach.<sup>[14]</sup>

In hypertrophic lymphocytic gastritis, similar to MD, there is the presence of giant folds in fundus with antral sparing. Hypertrophic hypersecretory gastropathy is a rare condition characterized by increased acid, pepsin,



**Figure 1:** (a) Thickened gastric folds in a patient with Cronkhite–Canada syndrome-fundus of stomach. (b) Thickened gastric folds in a patient with Cronkhite–Canada syndrome-body of stomach

**Table 2: Endoscopic ultrasound features suggestive of malignancy**

Increased gastric wall thickness (>9.8 mm)
Nonpreserved wall layer structure
Thickening of deep layer
Thickening of muscularis propria
Ascites and lymph node enlargement

and mucin secretion. On endoscopic examination, hypertrophic folds with cobblestoning of body and atrophy of antral mucosa are seen.<sup>[15]</sup>

Zollinger–Ellison Syndrome (ZES) also shows diffusely TGF, especially in the region of body and fundus. They are often associated with peptic ulcers.<sup>[16]</sup>

Obtaining a gastric pH during endoscopy may also be helpful. In MD, gastric pH is usually high.

## ENDOSCOPIC BIOPSY

Endoscopy-guided biopsy remains one of the most important investigations for the etiological diagnosis of TGF. However, routine tissue sampling with pinch biopsy forceps is usually inadequate for tissue sampling. The major disadvantage of pinch biopsy is that it samples only the superficial layers of the stomach (foveolar or pit compartment), which may be inadequate for the diagnosis, especially in cases of TGF.<sup>[17,18]</sup> As such, deep snare or jumbo biopsies are often required.<sup>[19]</sup> They provide full-thickness mucosal biopsies, which can provide details on pit-to-gland ratio and mucosal architecture. Deep snare biopsy is obtained by diathermic snare, which has an average width of 1 cm. The mucosa and superficial submucosa are elevated by injecting saline-adrenaline solution and then resected with electro-surgical snare. A deep specimen containing muscularis mucosa and occasionally submucosa is thus obtained. Jumbo biopsies are obtained using large-capacity forceps, which can provide larger sized specimen compared to standard forceps.<sup>[20,21]</sup>

## ENDOSCOPIC ULTRASOUND

EUS can accurately visualize the gastric wall structure, including thickened layers, degree of wall layer preservation, and internal echo patterns. Different diseases exhibit different levels of EUS infiltration in the gastric wall and characteristic echo patterns. Thus, EUS aids in the differential diagnosis of large gastric folds.

On EUS, gastric wall thickness >4 mm is considered as TGF.<sup>[22]</sup> EUS features that should be looked for in a case of TGF includes

- Gastric wall thickness
- Gastric wall architecture-preservation or distortion of the five-layered structure
- The layer which is thickened-superficial or deep. Superficial mucosa and deep mucosa on EUS are superficial, whereas submucosa, muscularis propria, and serosa are considered deep layers
- Ascites and lymph node enlargement
- Other EUS features such as round or sharp borders and echogenicity.

A study of 65 patients analyzed the EUS features that helped to make a differential diagnosis of TGF.<sup>[22]</sup> It was seen that gastric wall thickness and thickened muscularis propria were the EUS features of the gastric wall that were associated with malignant disease. Gastric wall thickness more than 9.8 mm predicted malignancy with an accuracy of 80.6%.

Ginès *et al.* in a study on patients with large gastric folds and negative biopsy results reported that a thickened deep layer on EUS is associated with malignant disease.<sup>[23]</sup> A nonpreserved wall layer structure is regarded as an important EUS finding predictive of malignant disease.<sup>[24]</sup> EUS also has the advantage of detecting and sampling ascites and lymph nodes which are important extraluminal features that can suggest malignant disease.

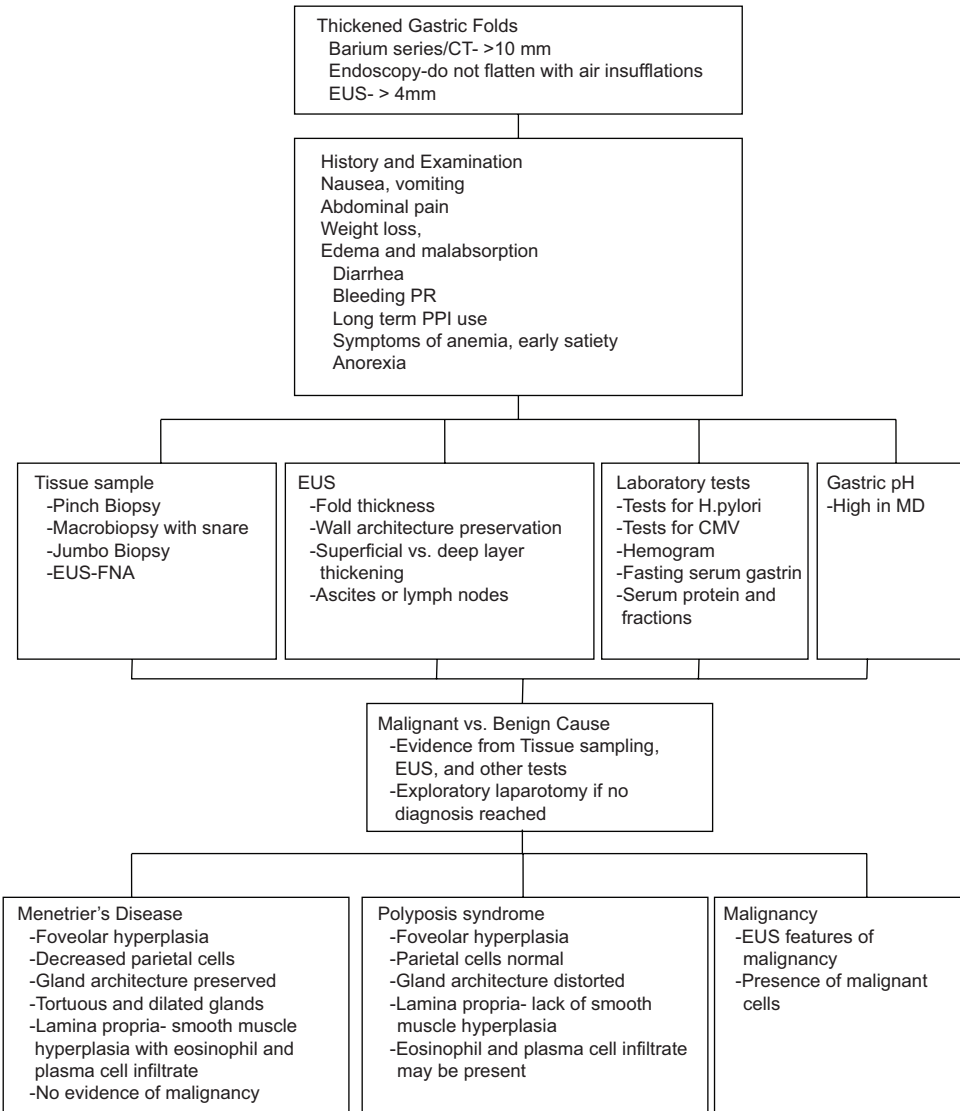
Although EUS is very useful for assessing the architecture of the gastric wall layer, operator dependency is a big demerit of EUS. However, the measurement of gastric wall thickness might be a semi-objective method because it may be a quantitative metric. Table 2 shows the EUS features suggestive of malignancy.<sup>[22]</sup>

## HISTOLOGY

Pathological evaluation can also help in diagnosis of TGF.<sup>[4,5,7]</sup> MD is characterized by foveolar hyperplasia which results in mucosal thickness and increased mucus production. The overall linear architecture is maintained, although corkscrew morphology of foveolar epithelium may be seen. There is oxyntic glands atrophy with decreased parietal cells and cystically dilated deep

glands. Chronic inflammatory cell infiltration with scattered eosinophils can be seen in lamina propria.

In hypertrophic lymphocytic gastritis, there is diffuse and severe inflammation of gastric mucosa with prominent



**Figure 2:** Diagnostic algorithm for thickened gastric folds. EUS-FNA=Endoscopic ultrasound-fine-needle aspiration, MD=Ménétrier’s disease, CT=Computed tomography, CMV=Cytomegalovirus

**Table 3: Features of major causes of thickened gastric folds**

Ménétrier’s disease	Polyposis syndrome	Gastric malignancy
Acquired hypertrophic gastropathy	Presents with polyps in GIT with some syndromes having extraintestinal manifestations	Usually presents with ulcer or mass in the stomach
Characterized by thickened folds, hypochlorhydria, hypoalbuminemia	Usually presents with anemia, bleeding per rectum, and evidence of polyps elsewhere	Diffuse gastric cancer and lymphoma may present with TGF
Affects males typically between 30 and 60 years	Sometimes polyps may be so confluent that differentiation from TGF’s may be difficult	Adenocarcinoma of stomach with proximal polyposis of the stomach has been described in families
Usually presents with nausea, vomiting, abdominal pain, weight loss, pedal edema, and malabsorption	Histologically, foveolar hyperplasia with architectural distortion	Usually presents in elderly
Association with CMV and <i>Helicobacter pylori</i>		Usual presentation is with symptoms of anemia, early satiety, weight loss, and anorexia
Histologically, massive foveolar hyperplasia with relatively preserved tissue architecture		Histologically, adenocarcinoma of the stomach with proximal polyposis shows fundic gland polyps with low- and high-grade dysplasia. Diffuse gastric carcinoma shows features of diffuse infiltrating carcinoma. Lymphoma shows infiltrating lymphoma cells

GIT=Gastrointestinal tract, CMV=Cytomegalovirus, TGF=Thickened gastric folds

intraepithelial lymphocytes, foveolar hyperplasia being limited to areas with inflammation.<sup>[25]</sup>

In hypertrophic hypersecretory gastropathy, hyperplasia is seen in both the foveolar epithelium and oxyntic glands. Cystic dilatation of gastric glands can also be present.<sup>[15]</sup>

ZES is characterized histologically by diffuse parietal cell hyperplasia and hypertrophy without foveolar hyperplasia. Enterochromaffin-like cell hyperplasia can also be often seen.<sup>[16]</sup>

Hyperplastic polyps are characterized microscopically by foveolar hyperplasia with dilated and tortuous glands.<sup>[26]</sup> Gastric polyps in juvenile polyposis syndrome are characterized by foveolar hyperplasia with distorted glandular architecture and edematous stroma. Gastric polyps in Cronkhite–Canada syndrome (CCS) [Figure 1] resemble juvenile polyps histologically. Eosinophilic inflammation with crypt abscesses is more predominant in CCS.<sup>[27]</sup> Peutz–Jeghers syndrome polyps in the stomach are characterized by hyperplastic epithelium with arborizing smooth muscle and dilated hyperplastic glands.<sup>[14]</sup>

Adenocarcinoma of the stomach with proximal polyposis of the stomach has been described in families.<sup>[28]</sup> They manifest as large number of gastric polyps in the stomach, predominantly fundus and body, with an increased risk of intestinal-type gastric adenocarcinoma.

## ENDOSCOPIC ULTRASOUND-GUIDED FINE-NEEDLE ASPIRATION

EUS-fine-needle aspiration (EUS-FNA) has been used to sample from TGF.<sup>[22]</sup> Under EUS guidance, the thickened layers can be aspirated using an EUS-FNA needle. This method can sample deeper layers and provide tissue sample for the analysis. It increases the diagnostic yield from TGF. Furthermore, EUS-FNA can be done from any enlarged lymph nodes if present.

## EXPLORATORY LAPAROTOMY/DIAGNOSTIC LAPAROSCOPY

Exploratory laparotomy/diagnostic laparoscopy and full-thickness gastric biopsy remain the last weapon in our armamentarium for the diagnosis of TGF.<sup>[1]</sup> When it is not possible to reach a diagnosis with the above-mentioned investigations, exploratory laparotomy or diagnostic laparoscopy can give us full-thickness tissue which could help reach the diagnosis and exclude malignancy with quiet certainty.

## DIAGNOSTIC ALGORITHM

Considering the above-mentioned facts about TGF, we propose a diagnostic algorithm to approach a patient with TGF [Figure 2]. Once TGF is diagnosed on the basis of either radiological or endoscopic methods, a multimodal systematic approach is needed to reach the final diagnosis. Adequate tissue acquisition is important, and various modalities such as pinch biopsy, snare biopsy, biopsy with jumbo forceps, or EUS-FNA may be required. Multiple modalities may be required at times. EUS can help to differentiate malignant from benign etiology. The final diagnosis is reached by histological examination of the tissue. When all the above tests are inconclusive, exploratory laparotomy and full-thickness biopsy are required. Table 3 summarizes the key features of the major causes of TGF.

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## Conflicts of interest

There are no conflicts of interest.

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