

CLINICAL NOTES

Large gastric folds arising in polyposis syndromes

Xiang-Yang Wang^{1,4}, Xin Wei³, Ying-Huan Dai², Yu Zhang¹ and Ji-Rong Huo¹

Department of ¹Gastroenterology and ²Pathology. The Second Xiangya Hospital. Central South University. Changsha, Hunan. China. ³Changsha Central Hospital. Changsha, Hunan. China. ⁴Department of Gastroenterology. Hunan Provincial People's Hospital. Hunan Normal University. Changsha, Hunan. China

ABSTRACT

Large gastric folds (LGF) can be caused by benign conditions as well as malignancies. Unfortunately, endoscopic features and biopsy results are often equivocal, making the diagnosis and management of large gastric folds difficult. Polyposis syndromes encompass a group of conditions in which multiple gastrointestinal polyps occur in the lumen of the gut. Large gastric folds are extremely rare in these syndromes. We present the case of a patient with polyposis who was found to have large gastric folds in the entire gastric fundus and body, mimicking malignancy. The patient's medical history and endoscopic ultrasonography (EUS) with mucosal resection confirmed the diagnosis of a pre-malignant disease. The lesion was monitored by serial endoscopic ultrasonography and biopsy, abdominal computed tomography (CT), and positron emission and computed tomography (PET-CT) for 6 years. The lesion remained stable, with the exception of abnormal fluorodeoxyglucose uptake on PET-CT in the gastric folds, which was determined to be a false-positive sign. To date, the patient remains healthy. We further discuss the mechanisms underlying the formation of large gastric folds caused by polyposis syndromes. *Helicobacter pylori* (*H. pylori*) or cytomegalovirus (CMV) is unnecessary for this progression. Immunohistochemistry (IHC) staining suggested that overexpression of transforming growth factor alpha (TGF- α) and down-regulation of myocyte enhancer-binding factor 2 (MEF2) may be involved in this case.

Key words: Large gastric folds. Polyposis syndromes. Ménétrier disease. Transforming growth factor α . Myocyte enhancer-binding factor 2.

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Correspondence: Ji-Rong Huo. Department of Gastroenterology. The Second Xiangya Hospital. Central South University. Changsha, Hunan. China
e-mail: HJR198@hotmail.com

INTRODUCTION

Large gastric folds (LGF) are usually suspected if the folds do not flatten on endoscopy or if folds of 15 mm or more in width are observed during a barium upper gastrointestinal series (UGI) or on CT (1). LGF can arise in benign and malignant diseases, such as Ménétrier disease (MD), anisakiasis, acute gastric mucosal lesion (AGML), gastric lymphoma, and scirrhous carcinoma (2,3). However, LGF in polyposis syndromes is extremely rare. Herein, we present a patient with polyposis syndromes found to have LGF and further investigate the possible pathophysiological mechanisms underlying this condition.

CASE REPORT

In January 2007, a 42-year-old man presented to our hospital with a 4-year history of abdominal distension and acid reflux. His past medical history was significant for polyposis syndromes and a subtotal colectomy for malignant polyps 10 years prior. Physical examination yielded unremarkable results, while laboratory investigations, including routine blood counts and assessment of albumin and CEA levels, yielded normal results. On colonoscopy, multiple polyps with diameters of 5-10 mm in the sigmoid colon and colonic anastomoses were observed and resected by high-frequency electric resection. Histopathology revealed adenomatous polyps. Four polyps with diameters of 2-10 mm in the gastric body and antrum were found on upper gastrointestinal endoscopy and resected. Histopathology suggested the presence of hyperplastic polyps. Furthermore, hypertrophy of the mucosal folds in the entire gastric fundus and body was noted, which was highly indicative of malignancies such as mucosa-associated lymphoid tissue (MALT) lymphoma and linitis plastica (Fig. 1). However, gastric distension was not impaired. Multiple biopsies of the lesion showed mucosal inflammation and no evidence

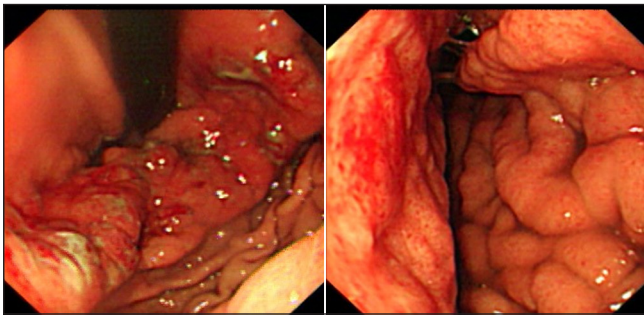


Fig. 1. Gastrointestinal endoscopy revealing large gastric folds in the gastric fundus and body.

of malignancy. Serological analysis for *cytomegalovirus* (CMV) and tests for *Helicobacter pylori* (*H. pylori*), including histologic evaluation, rapid urease test, and 14C-urea breath test (UBT), all yielded negative results.

To confirm the diagnosis, further examinations were performed. In addition to enlarged gastric folds, UGI also revealed weakened gastric peristalsis. Endoscopic ultrasonography (EUS) showed an extended thickening of the mucosa layer with preservation of layers as distinctive structures and no lymph node involvement around the gastric folds (Fig. 2). Pathological studies of the endoscopic mucosal resection (EMR) specimens taken from the lesion showed significant hyperplasia of the gastric glands with elongated, twisted foveolae, which were similar to those found in hyperplastic polyps and MD (Fig. 3). Hence, LGF caused by polyposis syndromes with gastric involvement was considered as the likely aetiology. Due to the lack of evidence suggestive of malignancy, the patient declined to undergo gastrectomy. Instead, expectant management was pursued and the patient was treated symptomatically, which included improvement of gastrointestinal motility and neutralisation of stomach acid. The patient showed

clinical improvement. During a 6-year follow-up period, he underwent gastroscopy or EUS with multiple biopsies at 6-month intervals to monitor any changes in the lesion. Last year, positron emission and computed tomography (PET-CT) was performed and showed abnormal fluoro-deoxyglucose uptake in the gastric folds. However, other subsequent investigations, including EUS and EMR specimen analysis, demonstrated no further progression of the disease and the PET-CT finding was considered to be false-positive. To date, the patient remains healthy.

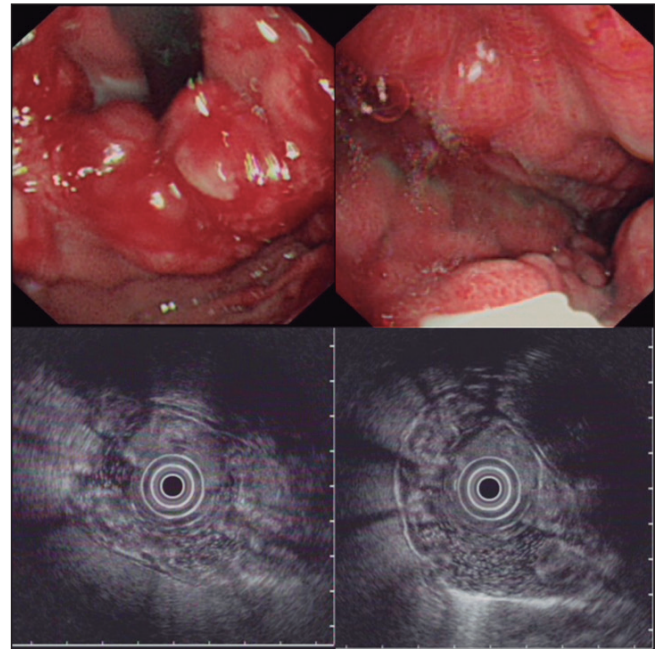


Fig. 2. Endoscopic ultrasonography showing enlargement of the mucous layer.

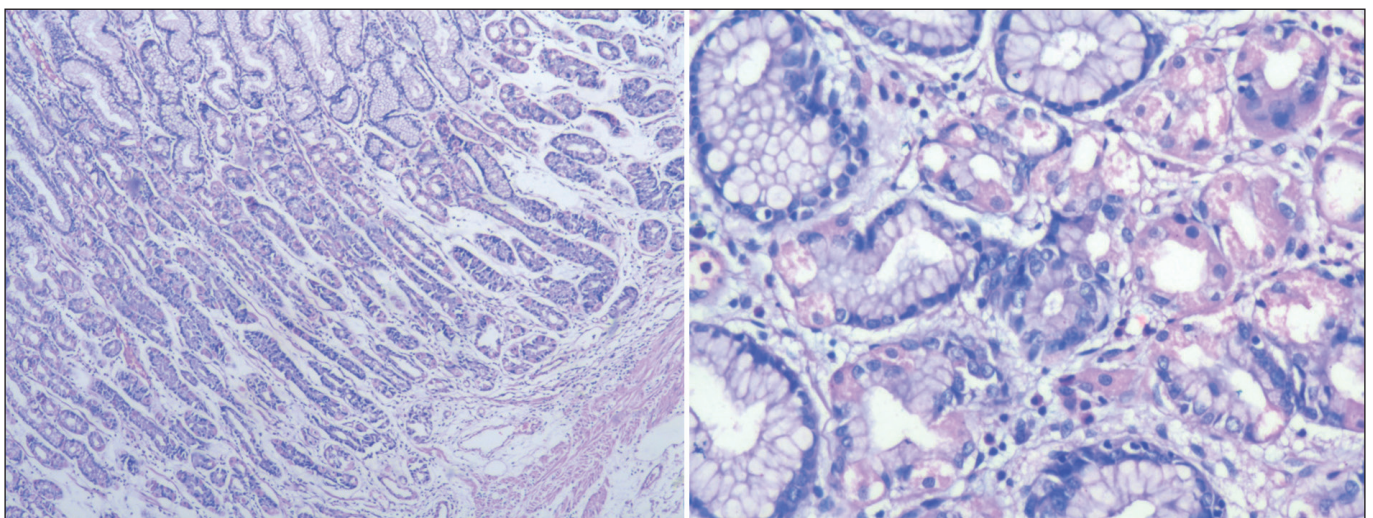


Fig. 3. Histology showing thickened mucosa with prominent foveolar hyperplasia as well as chief and parietal cells (Hematein and Eosin; left, 40 \times magnification; right, 200 \times magnification).

To explore the pathophysiological mechanism of LGF arising in polyposis syndromes, IHC was performed to investigate the expression levels of various proteins in full-thickness mucosal biopsies. In comparison with normal gastric mucosa taken from a patient with traumatic gastric perforation and a gastric hyperplastic polyp, the expanded foveolar epithelium of our patient was found to show overexpression of transforming growth factor alpha (TGF- α) and down-regulation of MEF2 (Fig. 4).

DISCUSSION

Various benign and malignant diseases can cause LGF. However, endoscopic characteristics are equivocal, and standard biopsy specimens usually contain only superficial mucosa while the specific histological features of these diseases are located in the deep part of the thickened mucosa. Therefore, EUS to detect any structural changes in the gastric wall layers and histopathologic examination of full-thickness mucosal biopsies are crucial to differentiate between diseases (1,4). In our case, the patient was in good health and showed no findings of oedema or anaemia. Furthermore, EUS showed localised thickening of the gastric wall in the mucosa layer, and multiple full-thickness mucosal biopsies revealed no evidence of gastric cancer or lymphoma. We reviewed all the biopsy results

and diagnosed thickened mucosa with prominent foveolar hyperplasia and a small degree of glandular distension, without cytologic atypia. Moreover, the chief and parietal cells were not reduced. Interstitial oedema and scattered lymphocytes were observed in some images (Fig. 3). The histological appearance partially resembled that of MD and hyperplastic gastric polyp. Polyposis syndromes are also considered to be the most common imitator of MD. However, the presence of chief and parietal cells as well as the absence of the clinical features of MD, such as excess mucus secretion and oedema (5), helped us distinguish between these conditions. In this case, physical examination showed no oedema, serum albumin level was normal, upper gastrointestinal endoscopy revealed no excess mucus secretion, and histological studies revealed chief and parietal cells. On the basis of these findings, the diagnosis of MD was ruled out.

Polyposis syndromes include familial adenomatous polyposis (FAP), *MYH* gene-associated polyposis (MAP), syndromes with hamartomatous polyps, and polyposis syndromes with neural polyp histology. The diagnostic criteria of FAP are as follows: characteristic clinical manifestations, specifically more than 100 colonic adenomas at any age; adenomas in a younger first-degree relative of a person with known FAP; or a disease-causing mutation in the *APC* gene in a person suspected of having FAP (6). We diagnosed our patient with FAP due to the presence of innumerable polyps in the colon prior to the subtotal colectomy. Histopathology revealed colonic adenomas. FAP is a genetic disorder resulting from a mutation in the adenomatous polyposis gene (*APC*) gene. Recently, a case of multiple aggressive intra- and extra-abdominal desmoid tumors in a patient with FAP caused by a novel germline *APC* mutation, the W421X mutation, has been reported (7). Currently, our patient's family is undergoing gastrointestinal endoscopy and *APC* gene sequencing to explore a possible genetic correlation of LGF in polyposis syndromes.

Gastric polyps occur in 23-100 % of FAP patients and are most often fundic gland polyps. Occasionally, the polyps can be so numerous that they coalesce, forming areas of irregular, matted surface mucosa (6). However, reports of LGF in polyposis syndromes are rare; cases of LGF in Peutz-Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS) have been described (8,9). The molecular mechanism underlying these manifestations remains unknown. *H. pylori* infection has been implicated in the development of LGF caused by MD (10) and MALT lymphoma (11). CMV infection has also been reported as an etiologic factor in LGF (12). Recently, Piepoli *et al.* reported that *H. pylori* infection induced hypertrophic gastropathy in patients with JPS carrying a *SMAD4* mutation (9). In our case, tests for *H. pylori* and CMV yielded negative results. Therefore, our case demonstrates that *H. pylori* or CMV is not required for LGF to occur in FAP.

Several studies suggest that overexpression of TGF- α may contribute to the pathogenesis of hypertrophic gastrop-

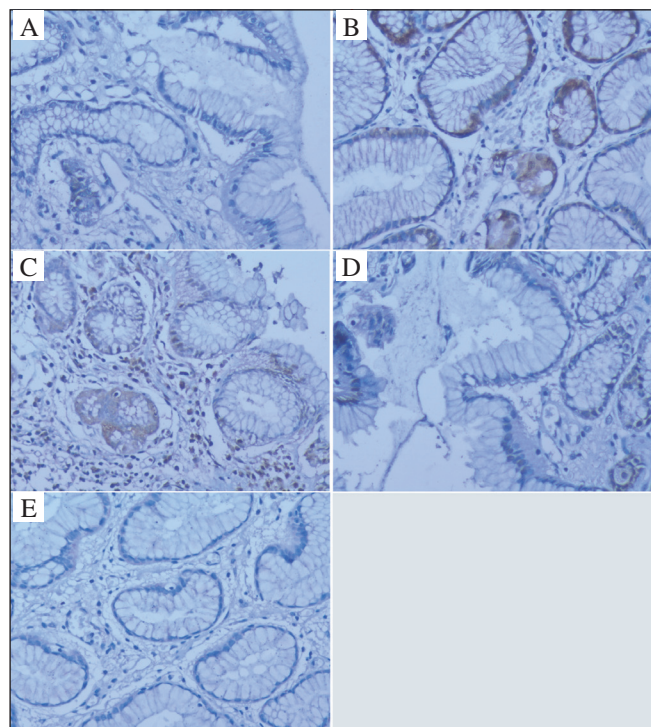


Fig. 4. Immunohistochemistry (IHC) revealing the following findings: A. No TGF- α in a gastric hyperplastic polyp. B. TGF- α in our patient. C. MEF2 in normal gastric mucosa. D. MEF2 in a gastric hyperplastic polyp; and E. No MEF2 in our patient.

athy in MD. Patients with MD exhibited overexpression of TGF- α in their expanded surface mucous cell compartment (13). Furthermore, transgenic mice with overexpression of TGF- α in the stomach were found to possess virtually all the features of MD, including massive expansion of surface mucous cells (14). In this study, we used a TGF- α antibody (ZA-0254; ZSGB-BIO) to detect the expression of TGF- α . IHC revealed that TGF- α was overexpressed in this patient's gastric mucosal biopsy samples, with reference to the expression levels in a gastric hyperplastic polyp (Fig. 4). Hence, TGF- α may be involved in hypertrophic gastropathy in polyposis syndromes.

MEF2 proteins belong to the evolutionarily ancient MADS (MCM1, agamous, deficiens, and SRF) family of transcription factors. There are 4 vertebrate MEF2 genes: MEF2A, MEF2B, MEF2C, and MEF2D. They participate in cell division, differentiation, and death (15,16). To our knowledge, MEF2 expression in LGF has not previously been reported. We used an antibody (sc-17785; Santa Cruz) raised against the highly conserved N-termini of MEF2 factors to detect a broad range of MEF-2 family members. Interestingly, MEF2 was absent in our patient, but present in the foveolar epithelium of normal gastric mucosa and gastric hyperplastic polyp (Fig. 4). MEF2 serves a pro-apoptotic function by stimulating expression of Nur77, which is a potent activator of cytochrome c-mediated apoptosis (15). We hypothesize that the down-regulation of MEF2 may help hyperplastic foveolar epithelium cells avoid apoptosis. However, further research is required to confirm this hypothesis.

LGF-related diseases such as MD have malignant potential (17). However, the malignant potential of LGF caused by polyposis syndromes is unknown. We suspect that this disease also has malignant potential. Although fundic gland polyps rarely progress to cancer, in FAP patients, dysplasia may occur in these polyps, occasionally becoming severe and progressing to gastric cancer (6). In our case, serial examinations performed during a 6-year follow-up period indicated that the patient's condition was stable. Similarly, a recent report showed that a female patient with more than 1,000 diffuse gastric polyposis underwent total gastrectomy, but there was no evidence of malignant progression found by immunohistochemical or molecular investigations (18). However, we are continuing to observe our patient and using EUS and EMR to monitor the lesion. Although PET-CT can present false-positive findings, we believe it is still a useful modality to screen for metastasis.

In conclusion, in patients with polyposis syndromes, hypertrophy of mucosal folds seen on endoscopy and the exclusion of other LGF diseases such as linitis plastica, gastric lymphoma, and MD are strongly suggestive of LGF caused by polyposis syndromes. *H. pylori* or CMV is unnecessary for LGF caused by FAP. Overexpression of TGF- α

and downregulation of MEF2 are likely involved in the development of hypertrophic gastropathy in polyposis syndromes. There is currently no gold standard treatment strategy for LGF arising in polyposis syndromes. We recommend close follow-up given the risk of progression to carcinoma.

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