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Does *Helicobacter pylori* eradication or proton pump inhibitor use benefit gastroesophageal reflux disease?

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We read with great interest the recently published article by Moschos *et al* [1]. They aimed to show the beneficial effect of *Helicobacter pylori (Hp)* eradication in gastroesophageal reflux disease (GERD) patients. They indicated in this study that *Hp* eradication may positively influence GERD symptoms. We commend Moschos *et al* for this study, but we think there are some controversial situations that need to be clarified.

They indicated that they found improvement in manometric pattern at 17% of patients and acid reduction in 3-h pH results at 82.8% of patients. But there are controversies of this procedure. Firstly, weak acid and non-acid reflux were not mentioned in this study. Ambulatory pH monitoring shows only acid reflux, and multichannel intraluminal 24-h pH-impedance (MII-pH) monitoring is needed to determine weak and non-acid reflux [2]. Thus, we think that to determine the exact beneficial results of *Hp* eradication, MII-pH monitoring may be done. Secondly, it has been shown that the intragastric and esophageal pH levels are affected postprandial according to the meal composition and mealtime. High-fat meals have been shown to elicit heartburn and increased acid exposure [3]; however, in this study, the patients' meal composition and type were not mentioned.

And thirdly, it is controversial whether the beneficial effect stems from proton pump inhibitor (PPI) use or from *Hp* eradication treatment. It is shown that PPI therapy aims to reduce the acidity of reflux episodes and conversely increases the exposure of the esophagus to non-acid and weakly acidic reflux [4]. Consistent with this study, Rinsma *et al* [5] showed improvement in distal baseline impedance and decrease in acid reflux in MII-pH monitoring, but they found an increase in non-acid reflux episodes in patients receiving PPIs after 6 months of therapy. In this study, the patients had taken rabeprazole for 10 days to eradicate *Hp*, followed by high-dose PPIs (4 times a day) for 30 days. Although there seems to be a 6-week without treatment period, it is a high acid suppressive dose that may affect acid secretion. Thus, we think that the beneficial effect observed during pH monitoring may be due to the long-term effect of PPI treatment. Based on the abovementioned data, we suggest that these controversies must be taken into account in future studies.

References

1. Moschos JM, Kouklakis G, Vradelis S, et al. Patients with established gastro-esophageal reflux disease might benefit from *Helicobacter pylori* eradication. *Ann Gastroenterol* 2014;**27**:352-356.
2. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastro esophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;**101**:1900-1920.
3. Simonian HP, Vo L, Doma S, Fisher RS, Parkman HP. Regional postprandial differences in pH within the stomach and gastro esophageal junction. *Dig Dis Sci* 2005;**50**:2276-2285.
4. Hemmink GJ, Bredenoord AJ, Weusten BL, Monkelbaan JF, Timmer R, Smout AJ. Esophageal pH-impedance monitoring in patients with therapy resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? *Am J Gastroenterol* 2008;**103**:2446-2453.
5. Rinsma NF, Farré R, Bouvy ND, Masclee AA, Conchillo JM. The effect of endoscopic fundoplication and proton pump inhibitors on baseline impedance and heartburn severity in GERD patients. *Neurogastroenterol Motil* 2014; doi: 10.1111/nmo.12468.

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Authors' reply

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Sakin *et al* [1] raised the following 3 concerns regarding our manometric and acid reduction in 3-h pH results: a) ambulatory pH monitoring shows only acid reflux; multichannel intraluminal 24-h pH-impedance (MII-pH) monitoring is needed to determine weak and non-acid reflux and also the exact beneficial results of *Helicobacter pylori* (*Hp*) eradication; b) high-fat meals have been shown to elicit heartburn and increased acid exposure, although, in our study, our patients' meal composition and meal type were not defined; and c) there was controversy whether proton pump inhibitor (PPI) use or *Hp* eradication benefited our patients.

However, as we initially mentioned [2], the main limitation of the 24-h pH monitoring is its low tolerability. Indeed, patients report that pH testing frequently induces unpleasant side effects lasting for the most part of the day,

and thus a shorter monitoring period is more tolerable. Moreover, it remains unidentified how weakly acidic or alkaline refluxate with a pH similar to a normal diet induces gastroesophageal symptoms. Most importantly, contrary to the previous studies mentioned by the authors [1], very recent data indicate that the 3-h postprandial recording provides an accurate prediction of absence or presence of gastroesophageal reflux disease (GERD) comparable to 24-h MII recording [3].

Regarding the second concern, it is known that, apart from high-fat meals and mealtime, mentioned by the authors [1], tomato products, alliums, sweets (chocolate), hot spicy food, citrus fruits and juices, peppermint tea, coffee, carbonated beverages, and/or alcohol are also contributors of GERD symptoms. However, instead of previous relative data mentioned by the authors [1], the role of diet as a risk factor for GERD has not as yet been clarified and recent relative studies are contradictory [4]. Nevertheless, our study patients had been advised to avoid consumption of such foods so as not to affect the study results.

With respect to the third concern, the authors misread our methods clearly stating that our patients had received rabeprazole once daily (q.d. means *quaque die* or once daily) and not 4 times daily after the initial 10-day *Hp* eradication therapy. Moreover, very recent data indicate that most GERD patients rendered asymptomatic on PPI therapy continue to experience abnormal esophageal and gastric acid exposure; the efficacy of acid suppression treatment, in certain patients, may be much lower than previously thought [5]. Therefore, since our patients received short-term (~40 days) PPI treatment and a second manometry and 3-h postprandial esophageal pH monitoring were introduced to assess the results of eradication therapy at 3-month post-treatment period, it is unlikely that the beneficial effect derives only from PPI use but rather by *Hp* eradication; rabeprazole has a half-life of less than 15 h, and rebound acid hypersecretion after administration of PPI has also been demonstrated in humans.

Finally, the references cited by the authors [1] to support their claims are irrelevant to the main aim of our study.

References

1. Sakin YS, Kekilli M, Uygun A, Bagci S. Controversies on *Helicobacter pylori* eradication in gastrointestinal reflux disease: is it benefit from eradication or PPI? *Ann Gastroenterol* 2015;**28:**294.
2. Moschos JM, Kouklakis G, Vradelis S, et al. Patients with established gastro-esophageal reflux disease might benefit from *Helicobacter pylori* eradication. *Ann Gastroenterol* 2014;**27:**352-356.
3. Gourcerol G, Verin E, Leroi AM, Ducrotté P. Can multichannel intraluminal pH-impedance monitoring be limited to 3 hours? Comparison between ambulatory 24-hour and post-prandial 3-hour recording. *Dis Esophagus* 2014;**27**:732-736.
4. Jarosz M, Taraszewska A. Risk factors for gastroesophageal reflux disease: the role of diet. *Prz Gastroenterol* 2014;**9**:297-301.
5. Lin D, Triadafilopoulos G. Dual ambulatory pH monitoring in patients with gastroesophageal reflux rendered asymptomatic with proton pump inhibitor therapy. *Dig Dis Sci* 2014 Aug 19. [Epub ahead of print].

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Giant esophageal gastrointestinal stromal tumor mimicking mediastinal tumor treated by thoracic approach

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Gastrointestinal (GI) stromal tumors (GISTs) are the most common mesenchymal tumors of the GI tract, but less than 2% of all GISTs are located at the esophagus. GISTs are classified as spindle cell, epithelioid, and pleomorphic mesenchymal tumors, usually express the KIT protein, and harbor mutation of a gene that encodes for a type III receptor tyrosine kinase. Debate exists regarding GIST nomenclature, diagnosis, and prognosis [1].

A 47-year-old female presented with progressively worsening dysphagia and epigastric tenderness dating since two years. A large hypodense elliptical mass occupying the left mid lung was identified initially on chest x-ray and computed tomography (CT) scan. The mass was contiguous with the esophagus, extending from the left atrium, through the hiatus to the pancreatic corpus and splenic vein (Fig. 1). Esophagogastroduodenoscopy showed no infiltration.

Thoracotomy and enucleation of the tumor at the cardio-esophageal junction were performed. The anterior esophageal wall was resected, leaving the posterior wall intact. The resected mass macroscopically resembled a benign tumor.

Intraoperative biopsy was suspicious of stromal tumor, but final reports suggested a GIST (positive for CD34, CD117, vimentin; partially positive for desmin; negative for SMA,

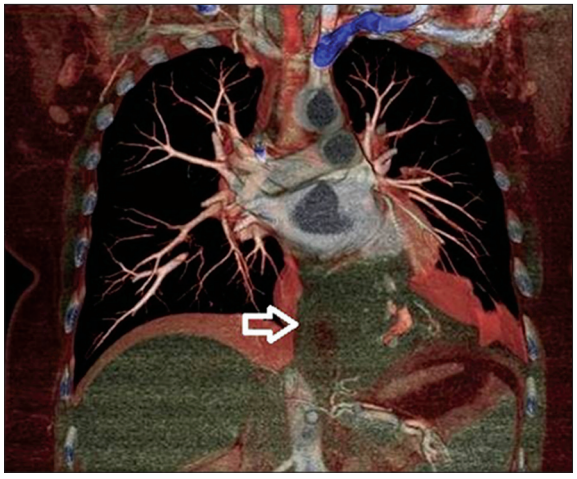

Figure 1 Coronal view of computed tomographic reconstruction showing the tumor in the left hemithorax (arrow indicates the tumor)

CK5/6, CK7; Ki67 index was 3-5%). Since discharge the patient remains free of symptoms.

GISTs originate from the interstitial cells of Cajal and are rare [2]. They typically present in adults 40-50 years old. GISTs of the GI tract are located: 60% in the stomach; 30% in the small intestine; and 10% in the esophagus, colon, and rectum [3]. Extraintestinal tumor locations are less frequent [4]. KIT or DOG 1 are expressed in the majority of GISTs and mutations in KIT or platelet-derived growth factor receptor-α (PDGFRA) polypeptide are very common [5]. Desmin and S-100 are rarely positive [5]. Existing literature shows that esophageal GISTs usually present with upper GI complaints (dysphagia, odynophagia, regurgitation, epigastric discomfort). The majority of published cases report tumors larger than 10 cm [6].

CT is the method of choice for primary evaluation and accurate staging of a suspected GIST. Magnetic resonance imaging has comparable diagnostic value, but may be preferred for rectum and liver GIST [7]. Positron emission tomography imaging detects smaller lesions and can dissolve diagnostic ambiguities. GI endoscopy findings may include a smooth protrusion of the wall, occasionally with signs of bleeding and ulceration. Either standard or endoscopic ultrasound-guided biopsies may not harvest enough tissue. A preoperative biopsy of a suspected resectable GIST is not recommended, but it is obligatory for metastatic disease.

The preferred method of treatment is surgical resection. If tumor size is less than 5 cm, lymph node resection is not necessary. Open surgery is indicated for large tumors, leaving laparoscopic resection for smaller tumors.

Molecular-targeted therapies, such as imatinib, may result in higher overall survival rates in high-risk patients, especially in unresectable and metastatic tumors [8]. PDGFRA mutation D842V, sporadic wild-type G, BRAF-mutated GIST, and mutations with succinate dehydrogenase rarely respond to imatinib. In patients with advanced disease in whom imatinib has failed, sunitinib is the best alternative choice [9].

References

1. Suster S. Gastrointestinal stromal tumors. *Sem Diag Pathol* 1996;**13**:297-313.
2. Burkill GJ, Badran M, Al-Muderis O, et al. Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. *Radiology* 2003;**226**:527-532.
3. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumor: recent advances in understanding of their biology. *Hum Pathol* 1999;**30**:1213-1220.
4. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000;**231**:51-58.
5. Bachet JB, Emile JF. Diagnostic criteria, specific mutations, and genetic predisposition in gastrointestinal stromal tumors. *Appl Clin Genet* 2010;**3**:85-101.
6. Blay JY, Bonvalot S, Casali P, et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. *Ann Oncol* 2005;**16**:566-578.
7. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic,immunohistochemical and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. *Am J Surg Pathol* 2000;**24**:211-222.
8. Scarpa M, Bertin M, Ruffolo C, Polese L, D'Amico DF, Angriman I. A systematic review on the clinical diagnosis of gastrointestinal stromal tumors. *J Surg Oncol* 2008;**98**:384-392.
9. Blay JY, Le Cesne A, Cassier PA, Ray-Coquard IL. Gastrointestinal stromal tumors (GIST): a rare entity, a tumor model for personalized therapy, and yet ten different molecular subtypes. *Discov Med* 2012;**13**:357-367.

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Epiploic appendagitis: a non-surgical cause of acute abdomen

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Two patients, a 53-year-old man and a 27-year-old woman, presented at the Emergency Department of our hospital with

symptoms of acute abdomen without concomitant fever. They both complained of severe acute abdominal pain localized at the right and left lower quadrants respectively, worsening during the last couple of hours, accompanied by moderate nausea. Rebound tenderness was present in the right and left lower abdominal quadrants respectively, with absence of other pathological findings on physical examination. In this setting our diagnostic thought was guided to the possibility of acute appendicitis in the first patient and acute diverticulitis, pelvic inflammatory disease or ruptured ovarian cyst in the second one. Laboratory tests were unremarkable. Both patients underwent contrast-enhanced abdominal computed tomography (CT) scan (Fig. 1A-D), which established the diagnosis of primary epiploic appendagitis (EA). Patients were administered a single dose of non-steroid anti-inflammatory drug intramuscularly with significant clinical improvement and were discharged from the Emergency Department with a short course of ibuprofen and advice to seek medical attention if symptoms worsened. Their clinical response was excellent and symptoms totally resolved three days later.

Primary EA is a benign, localized, sterile inflammation of the epiploic appendages, resulting from torsion or spontaneous venous thrombosis of a draining vein, usually involving the sigmoid colon or cecum. Secondary EA is associated with inflammation of adjacent organs (diverticulitis, appendicitis, cholecystitis) [1]. Patients present with acute abdominal pain mostly localized in the affected area with local tenderness on physical examination, while rebound tenderness may also exist, mimicking the clinical picture of acute abdomen, frequently leading to misdiagnoses such as acute appendicitis or diverticulitis. Notably, primary EA has been reported in 2-7% of patients in whom a clinical suspicion of diverticulitis was entertained and in 0.3-1% of patients suspected of having appendicitis [2-4]. However, in EA, fever, nausea, vomiting, decreased appetite and altered bowel function are usually absent, whilst inflammatory markers are usually normal or slightly elevated [1,5]. CT findings are virtually pathognomonic for EA, while excluding other causes of abdominal pain. The typical finding is a 2 to 3 cm, oval-shaped, fat density, paracolic mass with thickened peritoneal lining and peri-appendageal fat stranding. A high-attenuated central dot within the inflamed appendage that corresponds to a thrombosed draining appendageal vein is occasionally evident [6]. Magnetic resonance imaging findings of EA have not been well studied but appear to correlate with CT findings, while abdominal ultrasonography can be utilized in patients with a thin body habitus in experienced centers [7,8]. Patients can be managed conservatively with or without oral anti-inflammatory medications and occasionally with a short course of opiates. Complete resolution without surgical intervention usually occurs within 3 to 14 days. Complications are extremely uncommon, including

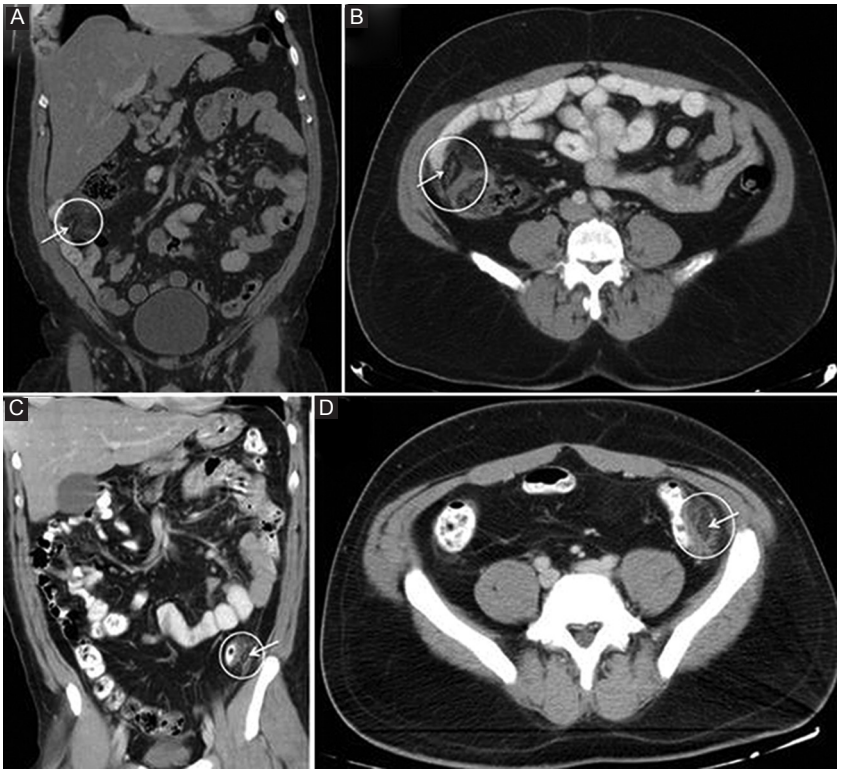

Figure 1 Contrast-enhanced abdominal computed tomography (CT) scans of the patient with right lower quadrant abdominal pain (A: coronal reformat, B: axial) and the patient with left lower quadrant abdominal pain (C: coronal reformat, D: axial). CT demonstrated the presence of oval-shaped, fat density paracolonic lesions (white circles) with a high-attenuation central "dot" (white arrow), located at the antimesenteric edge of the ascending colon for the first patient (A, B) and the descending colon for the second patient (C, D), respectively. Inflammatory changes of the adjacent pericolonic fat were also detected, more prominent in the second patient

intestinal obstruction and abscess formation; hence patients should be advised to seek medical attention if symptoms worsen [1,5].

Primary EA should be considered in the differential diagnosis of patients presenting with localized lower abdominal pain without fever or increased inflammatory markers. Inaccurate diagnosis can lead to unnecessary hospitalizations, antibiotic therapy and surgical intervention.

References

1. Schnedl WJ, Krause R, Tafeit E, Tillich M, Lipp RW, Wallner-Liebmann SJ. Insights into epiploic appendagitis. *Nat Rev Gastroenterol Hepatol* 2011;**8**:45-49.
2. Molla E, Ripolles T, Martinez MJ, Morote V, Rosello-Sastre E. Primary epiploic appendagitis: US and CT findings. *Eur Radiol* 1998;**8**:435-438.
3. Rao PM, Rhea JT, Novelline RA, Mostafavi AA, McCabe CJ. Effect of computed tomography of the appendix on treatment of patients and use of hospital resources. *N Engl J Med* 1998;**338**:141-146.
4. Rao PM, Rhea JT, Wittenberg J, Warshaw AL. Misdiagnosis of primary epiploic appendagitis. *Am J Surg* 1998;**176**:81-85.
5. Legome EL, Belton AL, Murray RE, Rao PM, Novelline RA. Epiploic appendagitis: the emergency department presentation. *J Emerg Med* 2002;**22**:9-13.
6. Singh AK, Gervais DA, Hahn PF, Sagar P, Mueller PR, Novelline RA. Acute epiploic appendagitis and its mimics. *Radiographics* 2005;**25**:1521-1534.
7. Danse EM, Van Beers BE, Baudrez V, Pauls C, Baudrez Y, Kartheuser A, Thys F, Pringot J. Epiploic appendagitis: color Doppler sonographic findings. *Eur Radiol* 2001;**11**:183-186.
8. Sirvanci M, Balci NC, Karaman K, Duran C, Karakas E. Primary epiploic appendagitis: MRI findings. *Magn Reson Imaging* 2002;**20**:137-139.AB

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