

Duodenal plexiform fibromyxoma as a cause of obscure upper gastrointestinal bleeding

A case report

Demetrios Moris, MD, MSc, PhD, MACS^{a,c,*}, Evangelia Spanou, MD^b, Stavros Sougioultzis, MD, PhD^b, Nikolaos Dimitrokallos, MD, MSc^a, Polyxeni Kalisperati, MD^b, Ioanna Delladetsima, MD, PhD^d, Evangelos Felekouras, MD, PhD^a

Abstract

Rationale: We are reporting the first-to our knowledge-case of duodenal Plexiform Fibromyxoma causing obscure upper gastrointestinal bleeding.

Patient concerns: Plexiform fibromyxoma triggered recurrent upper gastrointestinal bleeding episodes in a 63-year-old man who remained undiagnosed, despite multiple hospitalizations, extensive diagnostic workups and surgical interventions (including gastrectomies), for almost 17 years.

Diagnoses-Interventions: During hospitalization for the last bleeding episode, an upper gastrointestinal endoscopy revealed an intestinal hemorrhagic nodule. The lesion was deemed unresectable by endoscopic means. An abdominal computerized tomography disclosed no further lesions and surgery was decided. The lesion at operation was found near the edge of the duodenal stump and treated with pancreas-preserving duodenectomy (1st and 2nd portion).

Outcomes: Postoperative recovery was mainly uneventful and a 20-month follow-up finds the patient in good health with no need for blood transfusions.

Plexiform fibromyxomas stand for a rare and widely unknown mesenchymal entity. Despite the fact that they closely resemble other gastrointestinal tumors, they distinctly vary in clinical management as well as the histopathology. Clinical awareness and further research are compulsory to elucidate its clinical course and prognosis.

Abbreviations: CT = computerized tomography, GI = gastrointestinal, GIST = gastrointestinal stromal tumors, H&E = hematoxylin and eosin, *H pylori* = helicobacter pylori, MRI = magnetic resonance imaging, PAMT = plexiform angiomyxoid myofibroblastic tumor.

Keywords: case report, plexiform fibromyxoma, tumor, upper GI bleeding

Editor: Mahmoud Abdelwahab Ali.

Authorship: MD, SE, DN, and KP designed the report; SE, DN, and KP collected the patient's clinical data; MD, SE, DN, and KP analyzed the data and wrote the paper; DI performed the pathological analysis; SS performed the endoscopic approach; and FE supervised the manuscript.

Informed consent statement: All involved persons (subjects or legally authorized representative) gave their informed consent (written or verbal, as appropriate) prior to study inclusion.

Contributors: All authors equally contributed to patient care and writing of the report. Written consent to publication was obtained.

The authors have no funding and conflicts of interest to disclose.

^a First Department of Surgery, ^b Department of Pathophysiology, "Laikon" General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece, ^c Department of Immunology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, ^d Department of Pathology, Medical School, National and Kapodistrian University of Athens, Athens, Greece.

* Correspondence: Demetrios Moris, Department of Immunology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH (e-mail: dimmoris@yahoo.com).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution-No Derivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2017) 96:1(e5883)

Received: 30 August 2016 / Received in final form: 30 November 2016 /

Accepted: 17 December 2016

<http://dx.doi.org/10.1097/MD.0000000000005883>

1. Introduction

Obscure gastrointestinal bleeding is defined as recurrent or persistent bleeding of unknown origin after a negative initial study of the small intestine.^[1] Diagnostic evaluation normally includes an upper gastrointestinal (GI) endoscopy, a lower GI endoscopy to the terminal ileum, and contrast imaging modalities.^[1,2]

Twenty-five percent of the lesions associated with obscure GI bleeding are located in the esophagus, stomach, duodenum, and colon^[3] and cannot be documented during initial endoscopic evaluations^[4] obviously due to diverse reasons such as intermittent or slow bleeding and/or the absence of visible clot. Nevertheless, the small intestine is the source of hemorrhage in about 75% of obscure GI bleeding cases^[3]; common incited lesions include inflammatory bowel disease, angiodysplasia (especially in older patients),^[5] nonsteroidal anti-inflammatory drug enteropathy,^[6,7] Meckel's diverticulum-associated ulceration (especially in younger patients),^[8] radiation enteropathy,^[9] Dieulafoy's lesions,^[10] hemosuccus pancreaticus,^[11] small-bowel varices,^[12] and tumors.^[7,13]

In particular, tumors, such as leiomyomas, carcinoids, lymphomas, and adenocarcinomas of the small intestine, are considered the most common source of obscure GI bleeding in patients around 50 years of age.^[13] Moreover, stromal tumors such as gastrointestinal stromal tumors (GISTs)^[14,15] and the uncommon entirety plexiform fibromyxoma^[14,16] should be

considered in patients around 50 years old presenting with obscure GI bleeding.

We report here a case of duodenal plexiform fibromyxoma that triggered recurrent upper GI bleeding episodes in a 60-year-old man who remained undiagnosed, despite multiple hospitalizations, extensive diagnostic workups, and surgical interventions for almost 17 years.

2. Case report

A 63-year-old man presented to the emergency department with anemia and a 2-day history of melena confirmed by digital rectal examination. His blood pressure was 100/55 mm Hg, heart rate of 75 bpm, and his lab values were as follows: white blood count of $7.27 \times 10^9/L$ (neutrophils=82.9%), hemoglobin of 6.6 g/dL, hematocrit of 23.5%, platelets of $204 \times 10^9/L$, normal liver function tests, total protein=5.1 g/dL, and albumin=3.2 g/dL.

The patient had a history of recurrent upper gastrointestinal (GI) bleeding of almost 17 years. He was diagnosed with *Helicobacter pylori* positive duodenal ulcer of the posterior bulb at age of 25, resistant to numerous anti-helicobacter pylori treatment regimens. The ulcer was repeatedly bleeding at age of 45, and after failure of medical and endoscopic treatments, he underwent an antrectomy with gastro-entero-anastomosis (Hoffmeister–Finsterer and Brown) with bleeding cessation. Despite the surgical treatment of his ulcer, he experienced multiple upper GI bleedings in the following years and underwent several procedures. Among them, he had 6 gastroscopies, 3 colonoscopies, 5 angiographies, 2 scintigraphies with labelled red blood cells, 4 computerized tomographies with contrast (CTs) of the upper and lower abdomen, magnetic resonance (MR) enterography, and 2 capsule endoscopies of the small intestine during the diagnostic work-up to reveal the bleeding source. All investigations were nondiagnostic.

In the attempt to contain bleeding, for all these years at various hospitals, he received 3 consequent enterectomies with resection of a long part of the jejunum, a subtotal gastrectomy with a Roux-en-Y anastomosis, and an appendectomy. A carcinoid of the appendix, with maximum diameter of 2 cm, was incidentally found. Repeated serum gastrin levels and an octreoscan were normal; serologic tests for vasculitis, connective tissue diseases, and antiphospholipid syndrome were negative. It should be mentioned that 2 intraoperative endoscopies were also performed and failed to disclose the bleeding source.

All these years, he was transfused with more than 100 units of red blood cells and intravenous iron transfusions almost every 4 to 5 months with small effect on his hematocrit and ferritin levels that remained ~24% and <5 ng/mL, respectively.

During hospitalization for the last bleeding episode in our hospital, an upper GI endoscopy with a pediatric colonoscope revealed an intestinal hemorrhagic 3 × 3 cm reddish mucosal nodule extending to the submucosa (Fig. 1). The lesion was deemed unresectable by endoscopic means; it was marked with permanent ink and biopsies were taken. The results were compatible with a neoplasm of mesenchymal origin. An abdominal CT disclosed no further lesions and surgery was decided.

After laborious adhesiolysis, the surgical team explored every part of the small bowel and failed to discover the marked lesion. Thus, an intraoperative endoscopy with push enteroscopy was decided. The endoscopy failed to identify the lesion in the Roux limb. Upon entering the biliopancreatic limb, the lesion was finally discovered near the edge of the duodenal stump, where the

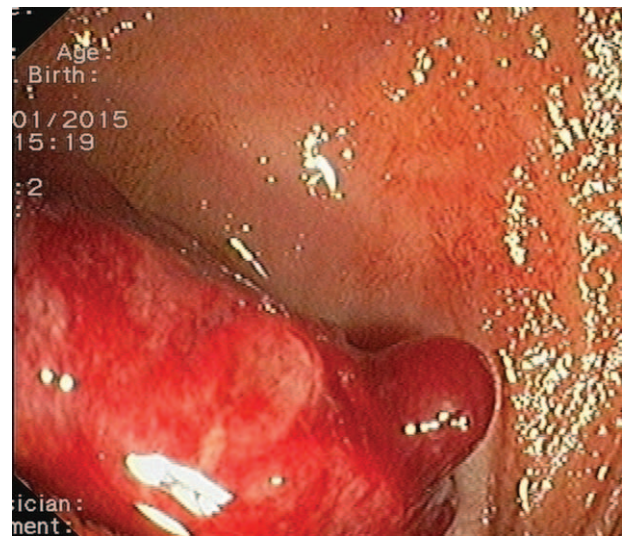


Figure 1. Endoscopic image of the tumor: reddish mucosal nodule located in the duodenal remnant after Roux-en-Y anastomosis with small active bleeding.

endoscopists also found the tattooing. Kocher maneuver was performed followed by a duodenotomy that delineated the lesion between the ampulla of Vater and the edge of the duodenum (Fig. 2). Thus, a pancreas-preserving duodenectomy of the first 2 portions of the duodenum was performed resulting into R0 resection (Fig. 3).

Pathologic examination of the surgical specimen confirmed the mesenchymal origin of the lesion that was further classified as plexiform fibromyxoma. The lesion was characterized by the presence of extensive hemorrhagic areas (Fig. 4) and thrombosed vessels (Fig. 5) as well as by paucicellular nodules with blunt spindle cells, myxoid stroma, and well-formed capillary network (Fig. 6). Remnants of muscle fibers were visible, whereas areas of pyloric metaplasia were encountered on the tumor surface. On immunochemical staining the lesion was characterized as SMA (+), S-100 protein(–), c-kit(–), DOG1.6(–), CD34(–), keratin 8/18(–), desmin(–). Molecular genetic analysis revealed no mutations in exons 9, 11, 13, and 17 of KIT and exons 12, 14, and 18 of platelet-derived growth factor receptor, alpha polypeptide (PDGFRA) genes.

Postoperative recovery was mainly uneventful complicated only by a low output pancreatic-skin fistula totally drained after 4

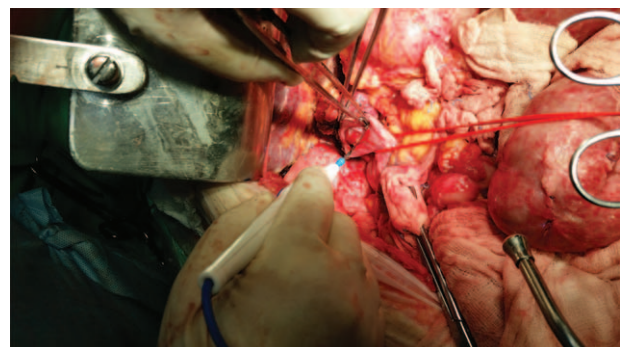


Figure 2. Intraoperative imaging showing partial duodenectomy delineated the lesion between the ampulla of Vater and the edge of the duodenum.

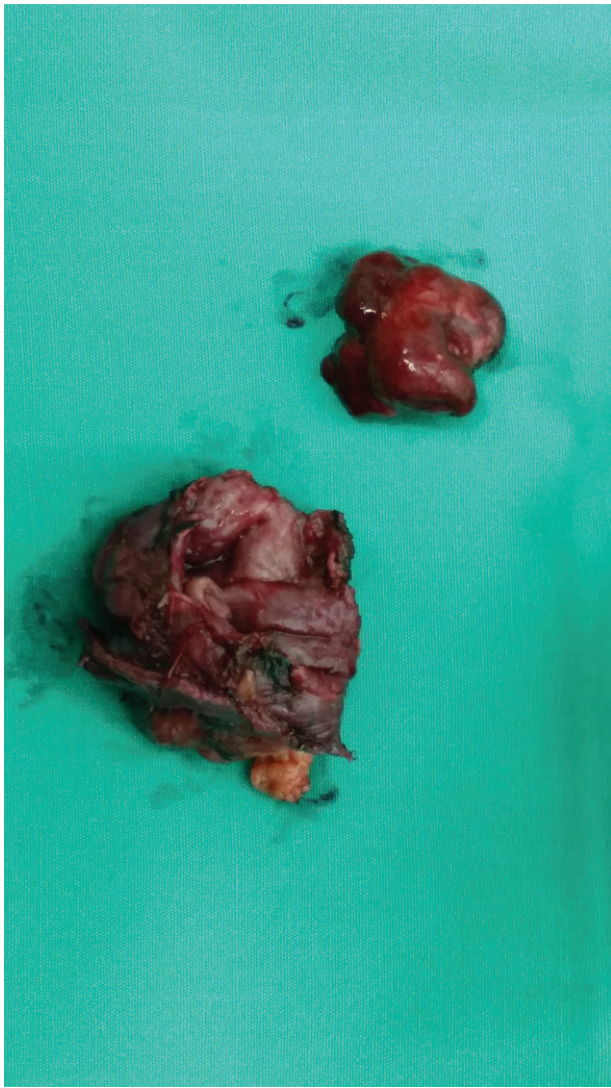


Figure 3. Resected specimen after pancreas-preserving duodenectomy of the first 2 portions of the duodenum. Note the mass on the left side of the figure, indicating a mucosal lesion.

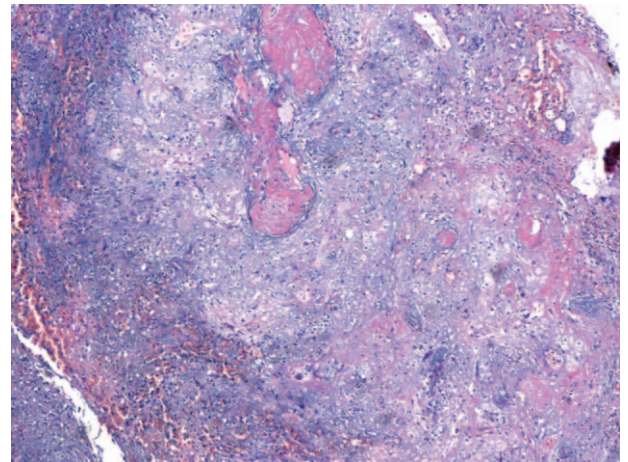


Figure 5. Area of extensive vessel thrombosis (H&E, $\times 100$). H&E = hematoxylin and eosin.

months. Twenty months after surgery, the patient is in good health with no need for further blood transfusions and a steady hematocrit of 39.9%.

3. Discussion

Plexiform fibromyxomas are recently identified mesenchymal tumors of the GI tract, almost always found in the stomach^[17–20] with few reports of its development in other tissues or organs.^[21,22] To date, no case of duodenal origin and only 5 cases of duodenal bulb involvement were published.^[16] They closely resemble other gastric tumors but vary distinctly in clinical management as well as the histopathology. These rare tumors were first described in 2007 by Takahashi et al^[23] who classified them as mesenchymal in origin and coined the term Gastric Plexiform Angiomyxoid Myofibroblastic Tumor (PAMT). Miettinen et al^[14] in 2009 reported a series of similar tumors and named them “plexiform fibromyxoma.” They even suggested that this tumor was specific to stomach, possibly related to an anatomically restricted progenitor cell population.^[14] Thus, our case makes their theory improbable. Although the name of this

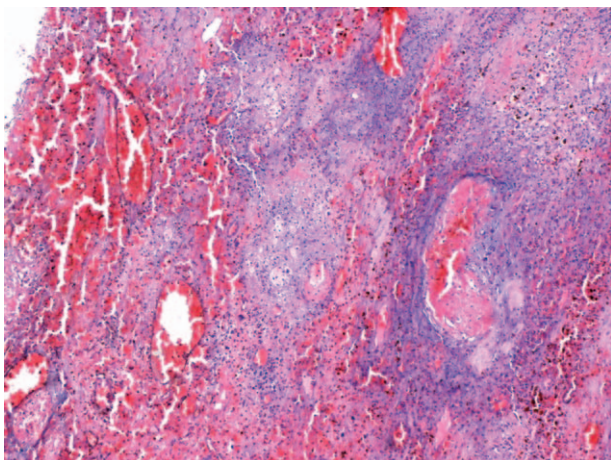


Figure 4. Myxoid nodules with extensive hemorrhagic areas and thrombosed vessels (H&E, $\times 100$). H&E = hematoxylin and eosin.

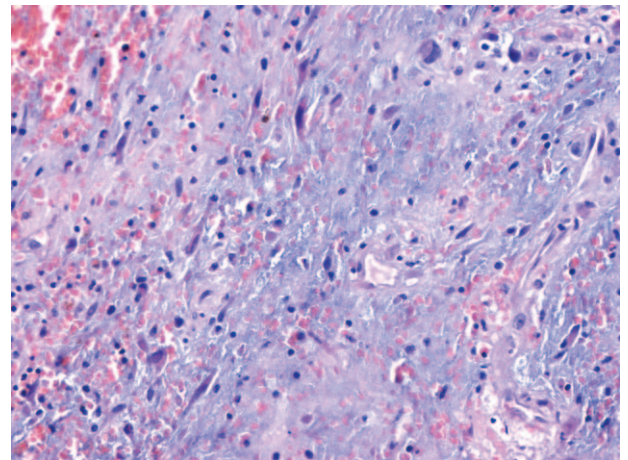


Figure 6. Paucicellular nodule with blunt spindle cells and myxoid stroma (H&E, $\times 200$). H&E = hematoxylin and eosin.

entity is still controversial, and PAMT is used by most researchers, the WHO classification of tumors of the digestive system has designated “plexiform fibromyxoma” as the diagnostic term instead of PAMT.^[24]

These tumors are located mainly in the gastric antrum, but cases have been described in the gastric fundus^[25] and gallbladder.^[21] They are mainly submucosal but may extend from mucosa to serosa and exhibit unique histologic features. In particular, they appear as a plexiform intramural growth pattern of ovoid or spindle cells in a myxoid extracellular matrix, limited cytologic atypia, and low mitotic activity, a myxoid stroma rich in small and thin-walled blood vessels^[16] and myofibroblastic differentiation with expression of SMA. They may also express vimentin and α -smooth muscle actin but they are immunohistochemically negative for c-kit, CD34, desmin, DOG 1.6, s100 protein, cytokeratin, neurofilament, and β -catenin with the variable expression of CD10. It should be mentioned that only about 40 isolated cases have been reported in the English-language medical literature^[26] up to date. It should be also noted that Takahashi et al^[16] have also described 6 cases of plexiform fibromyxomas in the pyloric region with extension into the duodenal wall.

According to previous reports, plexiform fibromyxomas can occur at any age (range, 7–75 years) with an equal gender distribution. The clinical symptoms may be nonspecific such as abdominal discomfort or distention. However, in most cases, the tumors are manifested by melena, hematemesis, or iron deficiency anemia as a result of ulceration of the underlying mucosa.^[19] A case of perforation has also been described.^[16] According to the limited data thus far, plexiform fibromyxomas have benign biological behavior and surgical excision is considered curative. Although extragastric extension and vascular invasion could sometimes be observed, there have been no reported cases of local recurrence or distant metastases after resection.

To the best of our knowledge, this is the first case of duodenal plexiform fibromyxoma ever reported. Furthermore, it is the first to manifest as obscure upper GI bleeding in a patient with undiagnosed, chronic upper GI bleeding episodes despite multiple hospitalizations, extensive diagnostic workups, and surgical interventions. Little is known about the natural history of plexiform fibromyxoma, but we feel that the perennial and rather peculiar history of our patient can contribute to that. Placed in the distal stump of the biliopancreatic limb of a Roux-en-Y restoration of the continuity of the GI tract after a subtotal gastrectomy, the tumor failed to present with symptoms associated with gastric outlet obstruction or obstruction of the ampulla of Vater.

The hypervascular nature of plexiform fibromyxoma produces a distinct image on contrast enhanced CT and MRI scan consisting of a gradually enhanced mass starting from the periphery to include the entire mass in the delayed phase.^[27] Moreover, it has been reported to present as a heterogeneously enhancing mass with both solid and cystic components, a result that is attributed to the fibromyxoid stroma.^[16,18,23] In our case, consecutive contrast enhanced CT-scans as well as the contrast enhanced MRI enterography failed to reveal the mass probably due to the multiple laparotomies and the consequent distortions as well as due to the location of this small mass near the duodenal stump neighboring the pancreatic head, the colon, and the hepatoduodenal ligament. After the diagnosis being set, the review of the imaging studies failed to reveal new findings.

In addition to that, various endoscopies and laparotomies failed to reveal the mass prior to admission to our hospital. The first laparotomy of our patient resulted in a vagotomy, an

antrectomy, and a gastro-entero-anastomosis following the diagnosis of *H pylori* resistant infection and a bleeding ulcer located on the duodenal bulb. This was decided following the long history or resistant *H pylori* infection for over 20 years, since the age of 25 and his hospitalization for acute upper GI bleeding. Reviewing previous surgical reports, an antrectomy with a Billroth II reconstruction was described without any further investigation of the duodenum during the surgery. A stapled resection of the antrum and the duodenal bulb 2 cm distal to the vein of Mayo and proximal to the angularis incisura was performed and a retrocolic gastro-entero-anastomosis ensured continuation of the GI tract. Pathology report from that specimen established the diagnosis of *H pylori* infection, gastritis, and duodenal ulceration with areas of gastric metaplasia, all typical findings of chronic active duodenitis and ulceration following resistant *H pylori* infection without any other specific findings.

The patient did well for 3 more years when he presented with a new acute upper GI bleeding that was treated with a subtotal gastrectomy and a Roux-en-Y reconstruction accompanied by a truncal vagotomy following the findings of *H pylori* infection, gastritis, and possible anastomotic ulceration during the endoscopy performed on the acute setting. Unfortunately, we could not trace the pathology reports for this or the following laparotomies that our patient underwent for recurrent upper GI bleeding episodes that bared equivocal findings preoperatively and resulted in a number of enterectomies that ultimately failed to resolve our patient’s symptoms in the long term. It is only natural that the complex and long surgical history of our patient made it difficult to conceive the various surgical interventions and the continuity of the GI tract and, as a result, the surgical interventions designed to match the needs of the emergency setting of a massive GI bleeding were not sufficient.

Furthermore, the various adhesions made it difficult for the endoscopists to find the way into the biliopancreatic limb and check the proximal end of the duodenal stump. Even in our hospital, the discovery of the mass required a rather exhaustive and laborious endoscopy with the use of a pediatric colonoscope. What is more, the endoscopy report was inconclusive regarding the exact location of the lesion and thus it was stained with ink to help the surgical team identify it. On top of that, during our laparotomy the vast amount of adhesions made it seemingly impossible for the operating surgeons to discover the tattooed lesion and an intraoperative endoscopy with push enteroscopy was required.

The immediate ceasing of the ongoing clinical symptoms and laboratory findings of obscure GI bleeding after the resection of the lesion can lead us to the safe assumption that the tumor had been present for all these years and remained intraluminal without causing disruption of the duodenum while, in the meantime, it retained its benign characteristics.

4. Conclusions

Plexiform fibromyxomas stand for a rare and widely unknown mesenchymal entity. Despite the fact that they closely resemble other GI tumors, they distinctly vary in clinical management as well as the histopathology. Clinical awareness and further research are compulsory to elucidate its clinical course and prognosis.

References

- [1] Gerson LB, Fidler JL, Cave DR, et al. ACG Clinical Guideline: diagnosis and management of small bowel bleeding. *Am J Gastroenterol* 2015; 110:1265–87. quiz 1288.

- [2] Rondonotti E, Marmo R, Petracchini M, et al. The American Society for Gastrointestinal Endoscopy (ASGE) diagnostic algorithm for obscure gastrointestinal bleeding: eight burning questions from everyday clinical practice. *Dig Liver Dis* 2013;45:179–85.
- [3] Bollinger E, Raines D, Saitta P. Distribution of bleeding gastrointestinal angioectasias in a Western population. *World J Gastroenterol* 2012;18:6235–9.
- [4] Raju GS, Gerson L, Das A, et al. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. *Gastroenterology* 2007;133:1697–717.
- [5] Foutch PG. Angiodysplasia of the gastrointestinal tract. *Am J Gastroenterol* 1993;88:807–18.
- [6] Frye JM, Hansel SL, Dolan SG, et al. NSAID enteropathy: appearance at CT and MR enterography in the age of multi-modality imaging and treatment. *Abdom Imaging* 2015;40:1011–25.
- [7] Ohmiya N, Nakagawa Y, Nagasaka M, et al. Obscure gastrointestinal bleeding: diagnosis and treatment. *Digestive Endosc* 2015;27:285–94.
- [8] Diamond T, Russell CF. Meckel's diverticulum in the adult. *Brit J Surg* 1985;72:480–2.
- [9] Taverner D, Talbot IC, Carr-Locke DL, et al. Massive bleeding from the ileum: a late complication of pelvic radiotherapy. *Am J Gastroenterol* 1982;77:29–31.
- [10] Blecker D, Bansal M, Zimmerman RL, et al. Dieulafoy's lesion of the small bowel causing massive gastrointestinal bleeding: two case reports and literature review. *Am J Gastroenterol* 2001;96:902–5.
- [11] Risti B, Marincek B, Jost R, et al. Hemosuccus pancreaticus as a source of obscure upper gastrointestinal bleeding: three cases and literature review. *Am J Gastroenterol* 1995;90:1878–80.
- [12] Traina M, Tarantino I, Barresi L, et al. Variceal bleeding from ileum identified and treated by single balloon enteroscopy. *World J Gastroenterol* 2009;15:1904–5.
- [13] Pourmand K, Itzkowitz SH. Small bowel neoplasms and polyps. *Current Gastroenterol Rep* 2016;18:23.
- [14] Miettinen M, Makhoulouf HR, Sobin LH, et al. Plexiform fibromyxoma: a distinctive benign gastric antral neoplasm not to be confused with a myxoid GIST. *Am J Surg Pathol* 2009;33:1624–32.
- [15] Miettinen M, Lasota J. Gastrointestinal stromal tumors. *Gastroenterol Clin N Am* 2013;42:399–415.
- [16] Takahashi Y, Suzuki M, Fukusato T. Plexiform angiomyxoid myofibroblastic tumor of the stomach. *World J Gastroenterol* 2010;16:2835–40.
- [17] Dixit JD, Sharief SA, Goyal MK, et al. Plexiform angiomyxoid myofibroblastic tumor (PAMT) of stomach with synchronous bilateral cystic ovarian neoplasms, a rare case presentation. *Ind J Surg Oncol* 2016;7:82–5.
- [18] Kane JR, Lewis N, Lin R, et al. Plexiform fibromyxoma with cotyledon-like serosal growth: a case report of a rare gastric tumor and review of the literature. *Oncol Lett* 2016;11:2189–94.
- [19] Li B, Zhang QF, Han YN, et al. Plexiform myxoid gastrointestinal stromal tumor: a potential diagnostic pitfall in pathological findings. *Int J Clin Exp Pathol* 2015;8:13613–8.
- [20] Lu B, Ye W, Liu H. A rare gastric tumor in a young woman. Gastric plexiform angiomyxoid myofibroblastic tumor. *Gastroenterology* 2015;149:294–5.
- [21] Fassan M, Salmaso R, Saraggi D, et al. Plexiform fibromyxoma of the gallbladder. *Pathologica* 2015;107:181–4.
- [22] Duckworth LV, Gonzalez RS, Martelli M, et al. Plexiform fibromyxoma: report of two pediatric cases and review of the literature. *Pediatr Dev Pathol* 2014;17:21–7.
- [23] Takahashi Y, Shimizu S, Ishida T, et al. Plexiform angiomyxoid myofibroblastic tumor of the stomach. *Am J Surg Pathol* 2007;31:724–8.
- [24] Flejou JF. WHO Classification of digestive tumors: the fourth edition. *Annales Pathol* 2011;31(5 suppl):S27–31.
- [25] Wang WY, Li JN, Li GD. Plexiform angiomyxoid myofibroblastic tumour of the gastric fundus: successful diagnosis and treatment by endoscopy. *J Clin Pathol* 2010;63:569–70.
- [26] Kang Y, Jung W, Do IG, et al. Plexiform angiomyxoid myofibroblastic tumor of the stomach: report of two cases and review of the literature. *Kor J Pathol* 2012;46:292–6.
- [27] Sakamoto K, Hirakawa M, Atsumi K, et al. A case of gastric plexiform fibromyxoma: radiological and pathological findings. *Jpn J Radiol* 2014;32:431–6.