Case report

Gastric gastrointestinal stromal tumor with incomplete duplication cyst – a case with possibility of neoplasia in fetal-period malformed tissues

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The coincidence of GIST and other gastric malignancies are documented well but arising GIST from congenital anomalies is still rarity in literature. To date, only a few papers have been concerned on the possibility of arising neoplasms from duplication cyst of gastrointestinal tract. There, are dominating usual cancers, neuroendocrine cancers or lymphomas but GIST has been noted only once. Here, we report a case of 73 years old female-patient with typical gastric stromal tumor comprised centrally locked an incomplete duplication cyst.

Key words: GIST, gastric duplication cyst.

Introduction

Coincidence of gastrointestinal stromal tumor (GIST) and other gastric malignancy has been documented in literature well, but GIST arising from or near to gastric congenital anomalies is still a rarity. Ectopic gastric tissues or duplications are often clinically asymptomatic. They are often diagnosed accidentally during upper endoscopy performed due to many different nonspecific clinical signs. Gastrointestinal duplication cyst (GDC) is a rare congenital malformation usually diagnosed in childhood. Gastrointestinal stromal tumor, generally driven by oncogenic KIT or PDGFRA mutations, is the most common mesenchymal tumor of the gastrointestinal tract (GI) [1]. Its occurrence affects people mostly after the fourth decade of life and is entirely different from GDC. Owing to the fact that molecular alterations in GISTs are completely different from usual epithelial malignancies of the GI, their simultaneous occurrence is rare and they are often are referred to as collision tumors or accidental findings. Similarly, a consideration of concomitance of GISTs and fetal-period malformed tissue in light of its great rarity is only an interesting observation yet.

Material and methods

This case description concerns a typical gastric submucosal stromal tumor of a 73-year-old female patient with a centrally located gastric duplication cyst. This paper is aimed at highlighting the possibility of involvement of fetal-period tissue malformation in neoplasia.

This study using human tissues was conducted in concordance with ethical standards of the Declaration of Helsinki with its latest revision in 2004. The patient was informed about the nature of this anonymous publication.

Clinical observations

The patient was admitted to hospital due to severe epigastric pain and severe gastrointestinal bleeding. Classical clinical signs such as coffee-ground vomiting and melena with signs of hemorrhagic shock were the dominant clinical problems. Urgent upper endoscopy revealed a stomach filled with blood clots and has shown polypoid ulcerated tumor in the subcardial region measuring 2.5 cm in diameter. A routine threatening procedure with fluid resuscitation, PPI (proton pump inhibitor), tranexamic acid and by a transfusion of concentrated packed erythrocytes was insufficient. Since endoscopic hemostasis was insufficient too, the patient underwent laparotomy and partial gastrectomy. The postoperative period was uncomplicated and the patient was discharged from hospital 7 days after the operation.

Pathological evaluation

The macroscopic evaluation of the specimen revealed a well-separated, polypoid gastric submucosal and an intramuscular tumor measuring 4 cm in diameter covered by focally ulcerated gastric mucosa. On the cut surface the tumor was whitish, fibrous, solid with focal edema and with a centrally located unilocular cyst measuring 1.2 cm in diameter filled with mucinous liquid (Fig. 1).

Histopathological procedures

The surgical specimen was fixed in 10% buffered formalin and then processed with routine histopathological procedures. Samples embedded in paraffin blocks were cut on 4 μm slides and were stained routinely by hematoxylin-eosin (HE), paS, mucicarmine, and alcian. The immunohistochemical analysis by Roche Benchmark Classic using monoclonal antibodies CD117, DOG1, CD34, SMA, S-100, HMB-45, PDGFR, CK AE1/3, CK 7, CK19, and CK20 has been performed using Ventana ultra View Universal DAB Detection Kit (Ventana Medical Systems; Roche Group, Tucson USA). As a positive control we used tissues recommended by the manufacturers.

Microscopic evaluation showed nonepithelial spindle cell proliferation with short fascicular texture without cellular atypia or necrosis and lacking mitotic activity (mitotic index 0/50 hpf) (Fig. 2B). There were observed focal stromal edema, extravasated erythrocytes, fibrosis and dispersed hemosiderin laden macrophages. Borders of tumor growth were the "pushing" type in nature without prominent infiltrative character (Fig. 2A).

An immunohistochemistry evaluation showed strong expression of CD117, DOG1, CD 34 (Fig. 3A, B), vimentin, desmin, smooth muscle actin (SMA), and lack of pan-keratin (CKAE1/3), HMB-45, S-100 and PDGFR. Another part of the tumor was centrally located cyst covered by tall, gastric like cylindrical and focal cuboidal epithelium without dysplastic changes. A histochemistry examination by paS demonstrated the presence of a substantial amount of cytoplasmic neutral glycopolysaccharides but alcian blue and mucicarmine stains were negative. This epithelial layer was positive for CK AE1/3 (Fig. 3D) and CK7 and negative for CK19 and CK20. Smooth muscle actin did not show the presence of a myoepithelial cell layer at the basis epithelial part (Fig. 3C). Since this appearance of epithelium is typical for gastric foveolar epithelium and we did not observe gastric glands or an invaginated muscular layer, the diagnosis was stated as incomplete noncommunicating duplication. A special, incomplete form of GDC in this case did not exhibit the existence of other gastric wall tissues besides superficial epithelium. At this point, a differential diagnosis has concerned mainly gastric epithelial inclusion cyst. Having regard to the possibility an existing and currently masking by tumor fibers of the muscular layer of a gastric duplication wall acts discus in range the nomenclature quite academic. Although these tumor components are common, each attempt to explain the mechanism of this composite tumor will be a speculation only. Noteworthy was the observation of an epithelial-stromal join. There, we did not demonstrate the existence of basement membrane and lack of a myoepithelial layer; therefore according to this the GDC – GIST join has been a continuum in nature (Fig. 2C, D). Finally, the histopathological pattern of this composite tumor has been stated as GIST growing around or from gastric incomplete duplication cyst, with categorization of this tumor to 2nd group of ESMO classification [2].

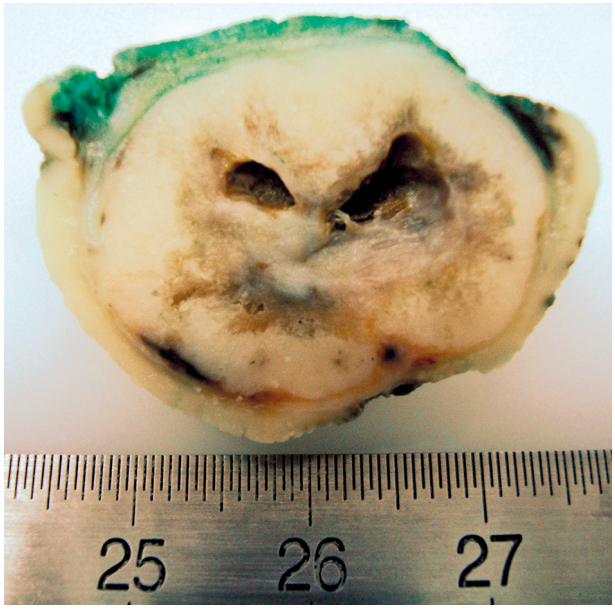

Fig. 1. Macroscopic view of the specimen – intramural gastric tumor with centrally locked cystic space filled muco-serous liquid

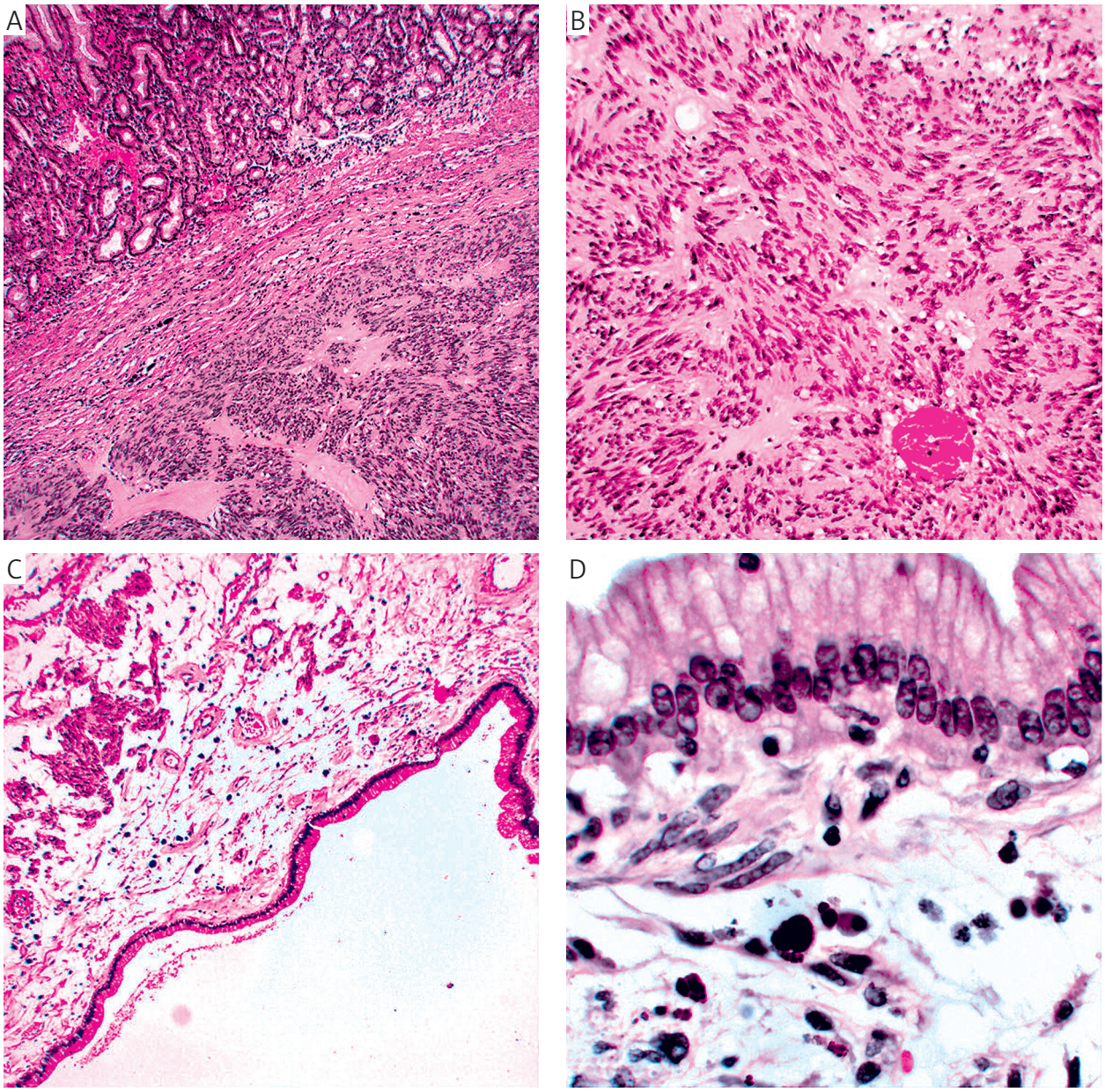

Fig. 2. A) Submucosal part of the tumor. Note, non-infiltrative borders of tumor (HE stain, original magnification 40×). B) Typical spindle cell GIST variant (HE stain, original magnification 100×). C) Cystic part of the tumor – one-layer tall gastric foveolar epithelium with presence GIST (HE stain, original magnification 100×). D) High power view of the subepithelial part of tumor. Note, epithelial and stromal continuum without a base membrane and myoepithelial layer (HE stain, original magnification 400×)

Discussion

Gastric duplications are usually located on the greater curvature and are twice as more common in females. A variety of mechanisms may affect their origin. The mostly noted in hypotheses ranging: the persistence of epithelial outpunching, fusion of embryologic longitudinal folds, endodermal-neurodermal adhesions, sequestration of embryologic tissues during embryonic movements, intestinal ischemia in early intrauterine life, impaired separation of the notochord from intestinal endoderm, the formation of neurenteric bands with embryonic growth, producing traction diverticula and failure of recanalization of the bowel lumen following the so-called solid-epithelial phase of the intestinal development, respectively [3-5].

Many publications have been written about complications of gastric duplications such as gastrorrhagia, complicated fistulas, pancreatitis and cholangitis, and the majority of these concern pediatric patients rather. Similar clinical symptoms can be caused by many different gastric tumors, especially usual cancers. In the experience of the Polish Gastrointestinal Tumor Working Group bleeding from ulcerated gastric GISTs or ruptured GISTs is a frequent and typical

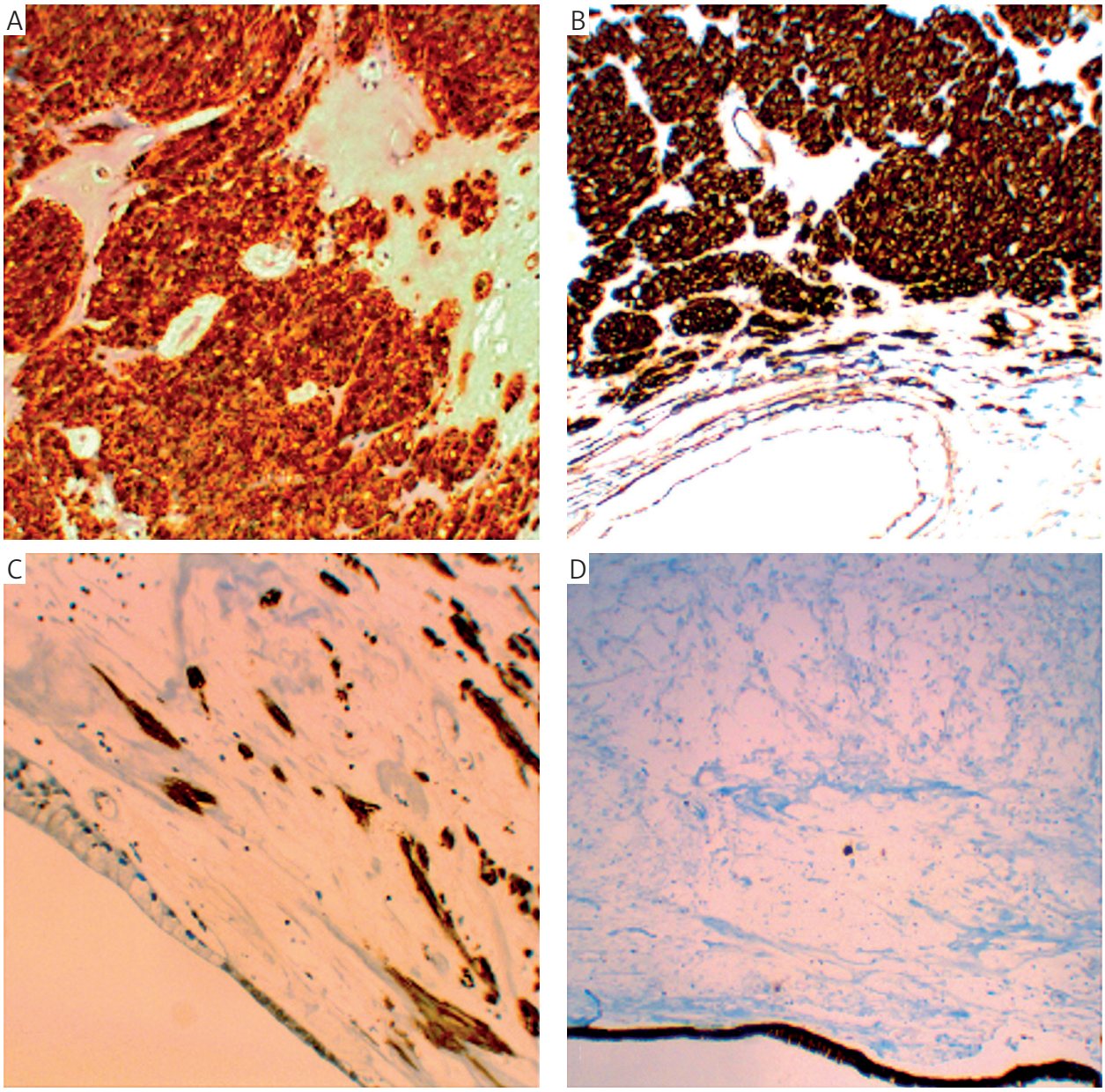

Fig. 3. A) GIST tissue – strong cytoplasmatic CD 117 expression (original magnification 100×). B) GIST tissue – strong cytoplasmatic CD34 expression (original magnification 100×). C) A border of GIST and GDC – prominent SMA expression in GIST and lack myoepithelial cell layer (original magnification 100×). D) Strong CK AE1/3 expression in duplication epithelium and lack expression in GIST (original magnification 100×)

complication in clinical outcomes [6, 7]. Like other past cases of GISTs, the present case proceeded with massive gastric bleeding and required an urgent laparotomy with local tumor resection. Rarely, described cases of gastric bleeding are complex and might be connected with another types of gastric tumors besides GISTs or GDC occurring incidentally, simultaneously also with other kind of cancer. The most frequently documented in the literature are simultaneous occurrence of GDC and cancer arising from epithelial parts of duplications. Currently, all published papers about it have a short report form as a case documentation of different cancer types with GDC. The lack of original papers indicates substantial rarity of the entity and greatly restricts the possibility of further studies. Barussaud *et al.* described usual gastric adenosquamous carcinoma with infiltration of wall GDC [8]. Kuraoka *et al.* described a similar case about coincidence of gastric adenocarcinoma with GDC [9]. Hata described a carcinoid tumor arising from the duodenal wall and retroperitoneal GDC. The authors indicated GDC epithelial changes such as dysplasia and an increased number of neuroendocrine cells, which were probably progenitors of carcinoid [10]. Similar observations were described by Horne *et al*. in a case of neuroendocrine carcinoma with gastric duplications [11]. These rare publications have noted very important findings such as dysplastic changes of epithelial cells in GDC

which caused development of cancer. This indicates the potential of progenitor cells for development of cancer. Another matter worth considering at this point of the discussion in the existence of mesenchymal tumors. Nonepithelial gastric neoplasms which are coincidental with other neoplasms concern predominantly GIST existing with some form of gastric cancers or lymphomas [12-19]. In daily practice this is observed fairly often and usually GISTs are findings incidental to the main malignancy and are often in a group with a "low recurrent percentage" often. Furthermore, the meaning existing GISTs is sometimes discussed in light of secondary tumors as derivate to chemical GIST therapy. Only a few works have described a potential connection of GIST with cancer in extra-gastric localization. Gonçalves *et al.* in a study on a group of 101 gastric GIST tumors observed 13% occurrence of another malignancy [20]. Coincidence of simultaneous GIST and another GI malignancy similiar to the above-mentioned one reported by Wronski *et al.* and Ruka *et al.* [21, 22].

Relatively few papers have described extra-gastric tissue within duplication. Here, the authors of the case reports once more have reported occurrence stratified bronchial epithelium, cartilage and pancreas tissue [23-27]. The meaning of these heterotopic tissues as a potential source of the carcinogenesis process remains unknown. Our case, as presented here, is a completely different problem. Illustrative documentation of tumors indicates, that they are not collisions in nature and GIST instead arise from GDC. To date, we have found only one publication with coincidence duplication cyst and GIST in the PubMed database. Namely, Van Rompuy *et al.* reported a case of colonic GIST with a duplication cyst in 2009 [28]. This indicates particular rarity of this form of malformation with GISTs. None of the publications have focused on a potential, mesenchymal component of duplication and its significance in potential course of the tumorigenesis. Opposite to epithelial dysplastic changes, the mesenchymal tumor does not have a defined intermediate stage between normal and malignant tissue. In our opinion, routine analysis by light microscope is an insufficient method in differential diagnosis between correct and invaginated muscle fibers, Cajal cells or other mesenchymal cells into the gastric wall. Assuming that some molecular or structural differences between these cells exist, we do not know yet the potential cellular antigens or molecular alterations, which are able to different invaginated cells during the fetal period. Finally, we suggest that similar to epithelial cancers in GDC, from nonepithelial components GDC can give rise to nonepithelial neoplasms too. Rarity of this entity and the consideration of interval time from fetal period to the beginning of tumor growth make the nature of discussion quite academic.

Conclusions

Duplication cysts are common pediatric pathological problems. Occurrence in adults is rare and is diagnosed accidentally during the diagnosis of malignancy or life-threatiening conditions. Epithelial components of GDC may trigger cancerogenesis in some instances. As mentioned above, the statement "nonepithelial components of GDC can give rise to nonepithelial gastric neoplasms" is in our opinion open to debate and it awaits further discussion.

The authors declare no conflict of interest.

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References

1. Guzińska-Ustymowicz K, Nasierowska-Guttmejer A. Gastrointestinal stromal tumors. Pol J Pathol 2013; 64 (4 Suppl 2): s47-s54.
2. The ESMO/European sarcoma networking group. Gastrointestinal stromal tumors: ESMO clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 (suppl. 7): vii49-vii55.
3. Falleti J, Vigliar E, Zeppa P, et al. Gastric duplication cyst: a rare congenital disease often misdiagnosed in adults. Case Rep Gastrointest Med 2013; 2013: 850967.
4. Keeling JW, Khong TY. Fetal and Neonatal Pathology. 4th edition. Springer, London 2007.
5. Fenoglio-Preiser C. Gastrointestinal Pathology. 3rd edition. Lippincot-Williams & Wilkins, Philadelphia 2008.
6. Rutkowski P, Bylina E, Wozniak A, et al. Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour – the impact of tumour rupture on patient outcomes. Eur J Surg Oncol 2011; 37: 890-896.
7. Rutkowski P, Nowecki ZI, Michej W, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Ann Surg Oncol 2007; 14: 2018-2027.
8. Barussaud ML, Meurette G, Cassagnau E, et al. Mixed adenocarcinoma and squamous cell carcinoma arising in a gastric duplication cyst. Gastroenterol Clin Biol 2008; 32: 188-191.
9. Kuraoka K, Nakayama H, Kagawa T, et al. Adenocarcinoma arising from a gastric duplication cyst with invasion to the stomach: a case report with literature review. J Clin Pathol 2004; 57: 428-431.
10. Hata H, Hiraoka N, Ojima H, et al. Carcinoid tumor arising in a duplication cyst of the duodenum. Pathol Int 2006; 56: 272-278.
11. Horne G, Ming-Lum C, Kirkpatrick AW, Parker RL. High-grade neuroendocrine carcinoma arising in a gastric duplication cyst: a case report with literature review. Int J Surg Pathol 2007; 15: 187-191.
12. Cai R, Ren G, Wang DB. Synchronous adenocarcinoma and gastrointestinal stromal tumors in the stomach. World J Gastroenterol 2013; 19: 3117-3123.
13. He JJ, Ding KF, Zheng L, et al. Adenosquamous carcinoma of the uncinate process of the pancreas with synchronous gastrointestinal stromal tumor of the stomach: Case report and review of the literature. Oncol Lett 2012; 4: 1191-1194.

14. Giuliani J, Marzola M, Indelli M, et al. Gastrointestinal stromal tumors and other malignancies: a case series. J Gastrointest Cancer 2012; 43: 634-637.
15. Samaras VD, Foukas PG, Triantafyllou K, et al. Synchronous well differentiated neuroendocrine tumour and gastrointestinal stromal tumour of the stomach: a case report. BMC Gastroenterol 2011; 11: 27.
16. Lin YL, Wei CK, Chiang JK, et al. Concomitant gastric carcinoid and gastrointestinal stromal tumors: a case report. World J Gastroenterol 2008; 14: 6100-6103.
17. Uchiyama S, Nagano M, Takahashi N, et al. Synchronous adenocarcinoma and gastrointestinal stromal tumors of the stomach treated laparoscopically. Int J Clin Oncol 2007; 12: 478-481.
18. Miehlke S, Morgner A, Ehninger G. Gastric MALT lymphoma and gastrointestinal stromal tumors (GIST). Praxis 2004; 93: 2143-2150.
19. Kleist B, Lasota J, Miettinen M. Gastrointestinal stromal tumor and gastric adenocarcinoma collision tumors. Hum Pathol 2010; 41: 1034-1039.
20. Gonçalves R, Linhares E, Albagli R, et al. Occurrence of other tumors in patients with GIST. Surg Oncol 2010; 19: e140-e143.
21. Wronski M, Ziarkiewicz-Wroblewska B, Gornicka B, et al. Synchronous occurrence of gastrointestinal stromal tumors and other primary gastrointestinal neoplasms. World J Gastroenterol 2006; 12: 5360-5362.
22. Ruka W, Rutkowski P, Nowecki Z, et al. Other malignant neoplasms in patients with gastrointestinal stromal tumors (GIST). Med Sci Monit 2004; 10: LE13-4.
23. Murakami S, Isozaki H, Shou T, et al. Foregut duplication cyst of the stomach with pseudostratified columnar ciliated epithelium. Pathol Int 2008; 58: 187-190.
24. Jiang W, Zhang B, Fu YB, et al. Gastric duplication cyst lined by pseudostratified columnar ciliated epithelium: a case report and literature review. J Zhejiang Univ Sci B 2011; 12: 28-31.
25. Montemurro S, Cartanese C, De Luca R, et al. Duplication cyst of the stomach with respiratory epithelium in adult: an uncommon finding. Report of case and review of literature. Ann Ital Chir 2011; 82: 487-491.
26. Napolitano V, Pezzullo AM, Zeppa P, et al. Foregut duplication of the stomach diagnosed by endoscopic ultrasound guided fine-needle aspiration cytology: case report and literature review. World J Surg Oncol 2013; 11: 33.
27. Falleti J, Vigliar E, Zeppa P, et al. Gastric duplication cyst: a rare congenital disease often misdiagnosed in adults. Case Rep Gastrointest Med 2013; 2013: 850967.
28. Van Rompuy AS, Lannoo M, D'hondt M, et al. Gastrointestinal stromal tumour (GIST) arising in a colonic duplication cyst: case report. Colorectal Dis 2010; 12: 1053.

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