Int J Clin Exp Pathol 2014;7(3):1206-1211
www.ijcep.com /ISSN:1936-2625/IJCEP1312077

Case Report

Collision tumor of the esophagus: report of a case with mixed squamous cell carcinoma and gastrointestinal stromal tumor

Ting Qian[1*], Feng Gao[2*], Mao-Zhen Chen[3], Fan-Hua Meng[1], Xiao-Jing Li[4], Yong-Juan Liu[4], Hua-Bin Yin[1]

Departments of [1]Radiology, [4]Pathology, The Fifth People's Hospital of Shanghai, Fudan University, Shanghai; [2]Department of Oncology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai; [3]Department of Interventional Radiology, The First People's Hospital of Huaian, Nanjing Medical University, Nanjing. [*]Equal contributors.

Received December 24, 2013; Accepted January 7, 2014; Epub February 15, 2014; Published March 1, 2014

Abstract: Esophageal cancer is mainly divided into squamous cell carcinoma and adenocarcinoma. Epidemiologically, the former contributes to 90% of worldwide esophageal cancer cases, while adenocarcinoma contributes to two-thirds of cases in developed countries. Although other rare types and collision with multiple histological types of tumors do occur in the esophagus, it is very rare for a gastrointestinal stromal tumor (GIST) to collide with an epithelial malignant tumor. To date, only three cases have been reported in the literature. The current study reported a 69-year-old male patient with squamous cell carcinoma and GIST in the middle esophagus. There was no merging of tissue components between these tumors. This study together with a literature review indicates that esophageal collision tumors have been increasingly reported in recent years. Histology and immunohistochemistry are needed to make a differential diagnosis. The exact oncogenic mechanism or the interaction of two independent neoplasms still remains to be determined, and further investigation, such as electron microscopy and genetic analysis, may help to elucidate the pathogenesis of the colliding tumors.

Keywords: Collision tumor, GIST, squamous cell carcinoma, esophagus

Introduction

Esophageal cancer is a significant health problem commonly associated with late diagnosis and a poor survival rate [1]. Histologically, esophageal cancer can be mainly divided into squamous cell carcinoma and adenocarcinoma. Epidemiologically, the former contributes to 90% of worldwide esophageal cancer cases, while adenocarcinoma contributes to two-thirds of cases in developed countries [1]. However, other rare types and collision with multiple histological types of tumors have been reported, especially in recent years [2-5]. The etiology of collision with multiple histological types of tumors remains to be determined, and diagnosis of a collision tumor is based on histology. There are two main theories for the etiology of collision. The first is the coexistence of two or more independent neoplasms that collide and expand into each other but with different tumorigenesis [6], and the second is a much stricter view that includes the following three features [3]: (i) two topographically separate sites of origin for the different tumor components; (ii) at least some separation of the two tumors, despite intimate mixing at points of juxtaposition, so that a dual origin can still be recognized; and (iii) at the sites of collision, in addition to intimate mixing of the two components, some transitional patterns may be acceptable, such as a mucoepidermoid appearance in the case of collision between squamous carcinoma and adenocarcinoma. The collision tumor localized in the esophagus is very uncommon, and collision of squamous cell carcinoma and gastrointestinal stromal tumor (GIST) in the esophagus is even more rare, and to date, only three cases have been reported in the literature [7, 8]. In this study, we report another case with an incidental and pathological identification. In this patient, the two tumor types were distinct

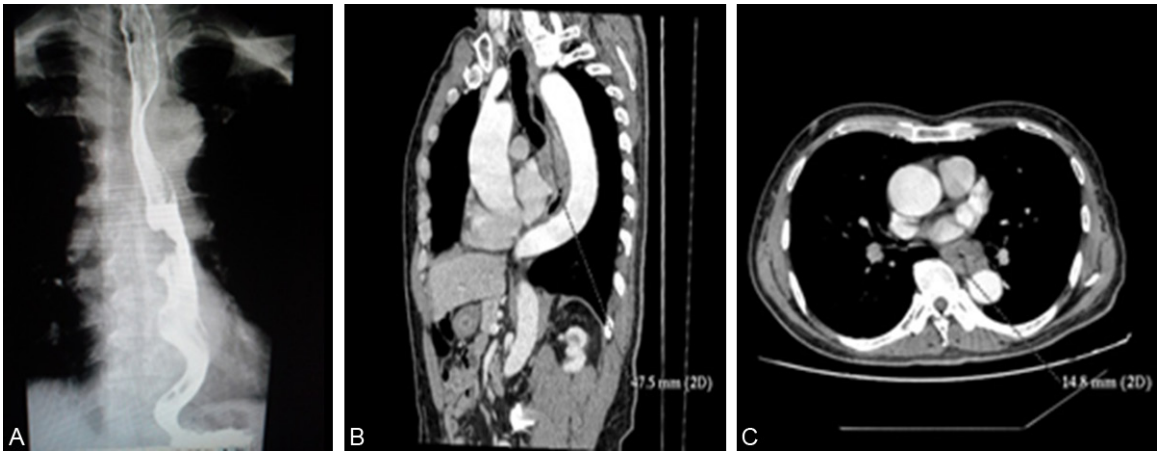

Figure 1. X-ray and CT images. A: Barium meal x-ray image showing a filling defect in the middle esophagus. B and C: CT images showing the thickened esophageal wall and the stenosis of the lumen in the middle esophagus.

without any histologically demonstrable morphological transition at the site of collision. This case satisfied the more strict criteria; thus, it can be considered a true collision tumor in the esophagus.

Case report

A 69-year-old-man was referred to our hospital with a 6-month history of retrosternal burning sensation after eating. His main complaint was retrosternal discomfort and occasional chest distress, nausea, and vomiting. He experience loss of appetite, but without loss of body weight. He smoked tobacco for 32 years at 2 packs per day, but did not consume alcohol. Physical examination displayed no obvious abnormalities and no palpable lymph nodes. Laboratory tests revealed that he had no anemia, and alpha fetal protein, carcinoembryonic antigen, and carbohydrate antigen-125 levels were all within the normal ranges. Barium meal revealed a filling defect area in the middle esophagus, and thus, recommended further examinations (**Figure 1A**). Computed tomography (CT) revealed a thickened esophageal wall and stenosis of the lumen in the middle esophagus. The lesion, which exited with a diameter of 47 mm and was 15 mm at the thickest point, was enhanced unevenly, when contrasted (**Figure 1B** and **1C**). No distant metastases or enlarged lymph nodes were seen on CT scan. Surgery was then recommended, and the patient underwent thoracotomy and partial esophagogastrectomy with Jejunostomy. During the surgery, a total of 37 periesophageal lymph nodes were dissected. Written informed consent was obtained from the patient for inclusion in this case report.

Pathologic findings

Grossly, a large tumor lesion with a size of 5 × 2 × 2 cm occupied the middle esophagus and appeared annulus, whitish-gray, and ulcerated. Additionally, an oval, whitish, and smooth small nodular mass was seen in the deep muscularis with a maximum diameter of 0.6 cm. This mass had a distinct border with the large lesion and the muscularis, indicating that there was no morphological transition between them (**Figure 2A**).

Histologically, routine hematoxylin-eosin staining showed that the large lesion was the moderately differentiated squamous cell carcinoma, whereas the small lesion was a GIST (**Figure 2B** and **2C**). It was also noted that carcinoma cells infiltrated into the deep muscularis and extensively invaded the lymph nodes, and tumor metastasis was found in 10 of the 37 removed lymph nodes. The resection margins were free of tumor cells. Furthermore, the GIST was localized in the muscularis with a surrounding pseudocapsule and showed mixed spindle-shaped and epithelioid cells. There was no merging of tissue components at the interface of tumor cells. Immunohistochemical analysis showed that carcinoma cells were positive for pan-cytokeratin (CK), CK5/6, and p63 (**Figure 3**), but were negative for p53 protein. The Ki67 staining index was 0.3, indicating moderate tumor

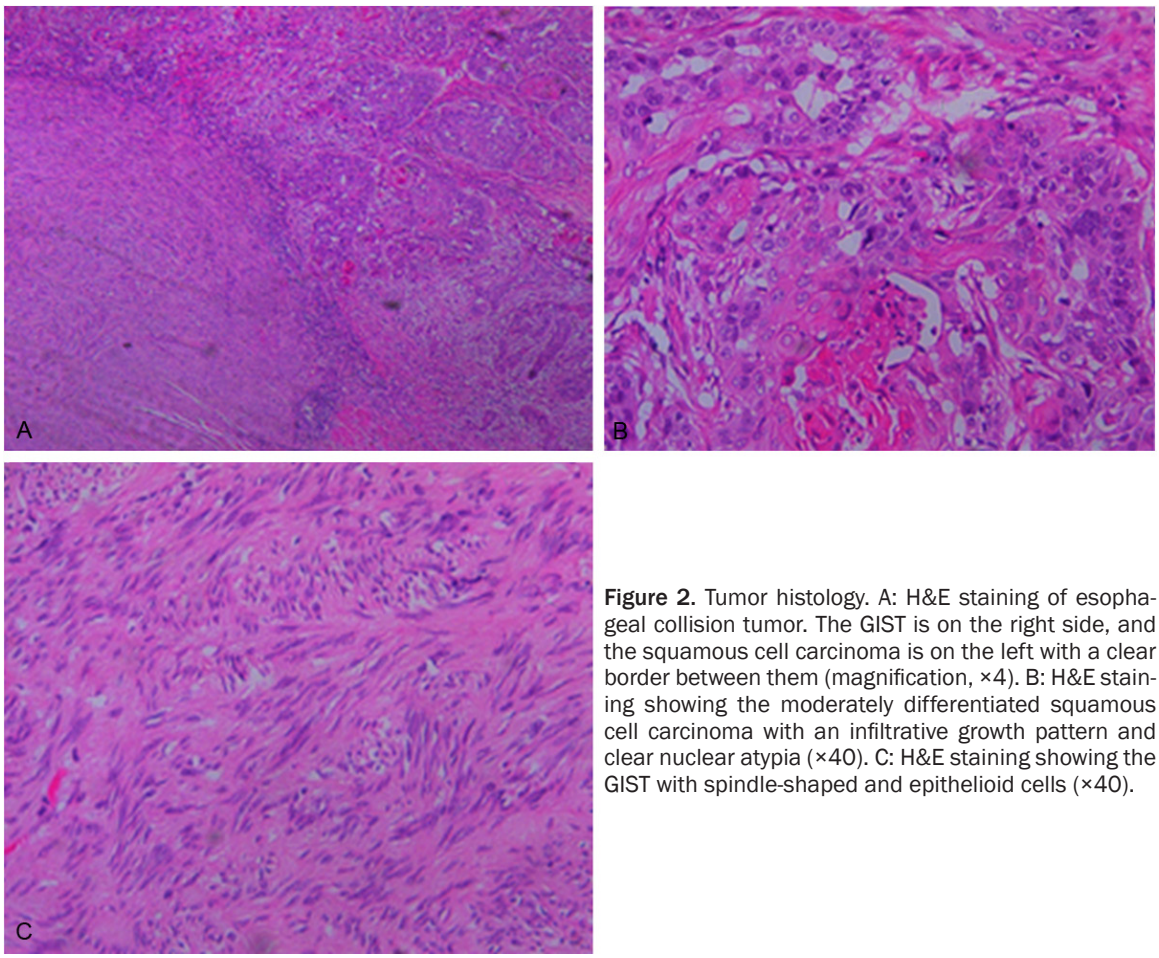

Figure 2. Tumor histology. A: H&E staining of esophageal collision tumor. The GIST is on the right side, and the squamous cell carcinoma is on the left with a clear border between them (magnification, ×4). B: H&E staining showing the moderately differentiated squamous cell carcinoma with an infiltrative growth pattern and clear nuclear atypia (×40). C: H&E staining showing the GIST with spindle-shaped and epithelioid cells (×40).

cell proliferation (**Figure 3**). In contrast, the GIST cells were positive for CD117 (**Figure 3**), CD34, and Vim, but were negative for smooth muscle actin (SMA), desmin, p53, and S100 proteins with a Ki67 staining index of 0.01 (**Figure 3**).

Discussion

The collision tumor is uncommon and often found randomly during pathological evaluation. Most collision tumors occur in the crania, lung, gastroesophageal junction, liver, rectum, bladder, uterus, and testis with two or more independent tumor components without transitional morphology. They are difficult to differentiate from composite tumors (characterized by two divergent lineages originating from the same neoplastic clonal proliferation) [9]. Purdy et al. [10] suggested that the collision tumor may result from a carcinogenic stimulus affecting two neighboring regions of mucosa or may simply be the chance apposition of two unrelated tumors. Gonzalez et al. [11] demonstrated a biclonal origin for both components of the collision tumor. Brahmania et al. [12] provided detailed descriptions of three possible mechanisms: (i) the rare occurrence that two primary tumors develop adjacent to each other at the same time; (ii) one tumor develops and changes local microenvironment to promote the development of the second tumor; and (iii) the two types of tumors share a common origin of pluripotent precursor stem cells that differentiate into the components of tumor cell types. The incidence of synchronous cancers in patients with esophageal cancer ranges from 3.6%-27.1% [13]. Many of these tumors are a combination of adenocarcinoma and sarcoma or of adenocarcinoma and lymphoma, and the coexistence of squamous cell carcinoma and GIST in the esophagus is uncommon [7]. The incidence of GIST is 14%-17.4% [8, 14] and these tumors mainly occur in the stomach and small intestine [8] and are rarely found in the esophagus. Esophageal squamous cell carci-

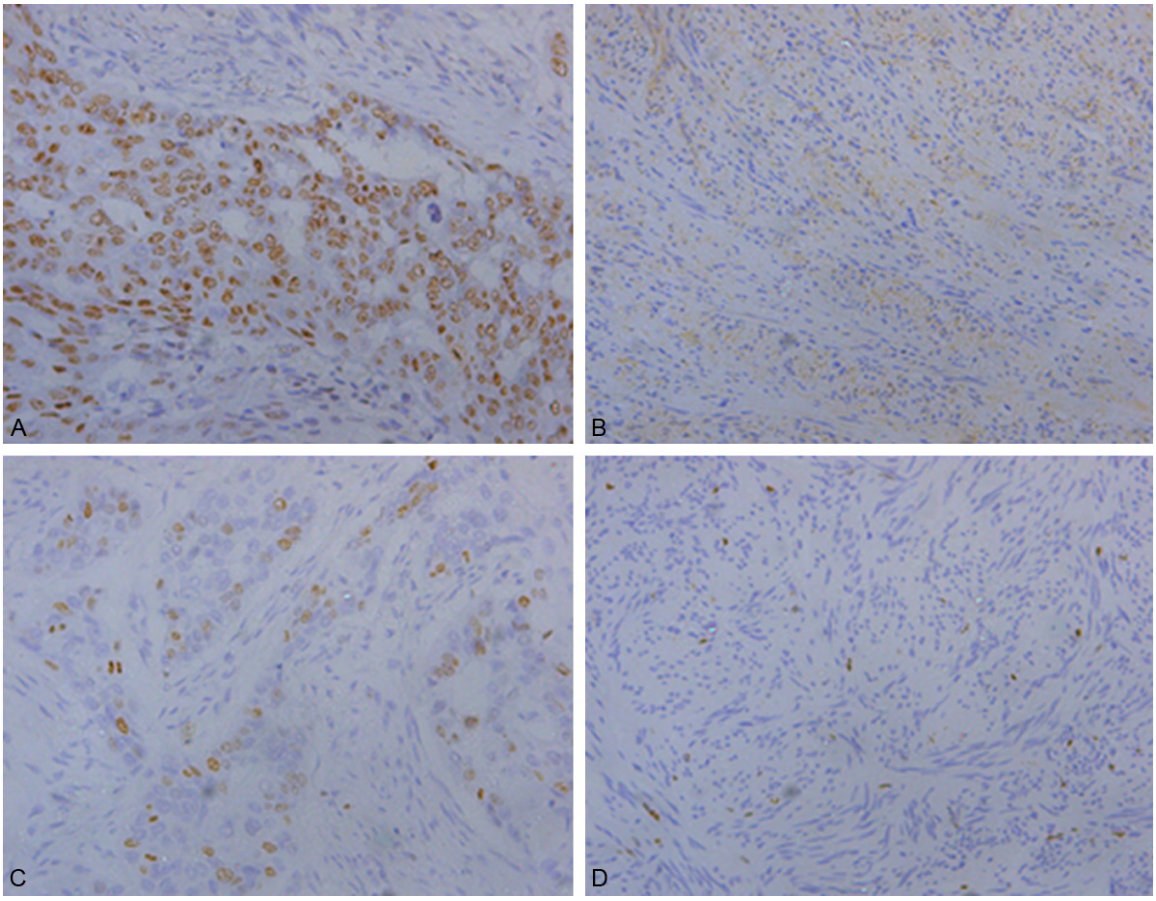

Figure 3. Immunohistochemical staining. (A) Strong positive staining for p63 in the squamous cell carcinoma cells (magnification, ×40). (B) Strong positive staining for CD117 in the GIST (×40). (C and D) Ki67 staining in squamous cell carcinoma cells (C) and the GIST (D).

noma is the most common malignancy originating in the esophageal mucosa. By contrast, the GIST is a mesenchymal tumor originating from the Cajal cells via directed differentiation of progenitor cells [15, 16]. To the best of our knowledge, to date, only three cases have been reported in the literature regarding the coexistence of esophageal squamous cell carcinoma and GIST [7, 8].

Spinelli et al. [7] described the first case of a 74-year-old male patient with a myeloproliferative syndrome, esophageal squamous cell carcinoma, and GIST. For their patient, CT scan did not show any other lesions, and surgery was conducted. The histology of the surgical tissue specimens confirmed the diagnosis of a collision tumor. The incidental GIST was small with a maximum diameter of 0.2 cm. Liu et al. [8] reported 54 cases of incidental GIST in 13804 cases of gastrointestinal epithelial malignant tumor (EMT) and 521 cases of pancreatic adenocarcinoma (PAC) between January 2000 and December 2007. Their patient population included two cases of the collision of esophageal squamous cell carcinoma and GIST. The collision with GIST occurred in older male patients, who often showed symptoms indistinguishable from those of EMT and surgery was the best treatment modality. The diagnosis was usually made by postoperative tissue specimen examination. Our current case was consistent with the data reported by these previous reports [7, 8]. Because there was no evidence to suggest that the tumor was a collision lesion before surgery [17], definite clinical diagnosis of the tumor could not be made before surgery. Imaging findings have little significance for the diagnosis of a collision tumor. Nevertheless, Van et al [4] showed that ^{18}F-FDG PET may be used to detect unexpected synchronous primary neoplasms in 5.5% of patients with esopha-

geal cancer, but ^{18}F-FDG is not a tumor-specific substance. Thus, false-positive results can occur as a result of increased glucose metabolism in benign lesions. Therefore, positive findings on ^{18}F-FDG must be confirmed by additional tests, preferably by percutaneous or ultrasound- or CT-guided tissue biopsy, or dedicated radiography. The coexistence of GIST with other tumors is rare, and they tend to be small, asymptomatic, located near the mucosal lesion but confined to the muscularis propria without invasion into the mucosa [18].

Histopathological and immunohistochemical analyses are helpful in making a differential diagnosis of collision tumors. Squamous cell carcinoma diagnosis is relative easy because tumor cells show an infiltrative growth pattern with clear nuclear atypia. In this report, tumor cells had infiltrated the deep muscularis, and immunohistochemical analysis showed positive CK and p63 expression. In contrast, the GIST contained spindle-shaped and epithelioid cells without infiltration. GISTs are distinguished from other mesenchymal tumors by their unique expression of c-kit protein (CD117) [18], which was positive in this case. Staining for CD34, a transmembrane glycoprotein that is mainly secreted by endothelial cells and bone marrow hematopoietic stem cells, also was positive in this case. Moreover, positive expression of vimentin (Vim) indicated that the GIST originated from the mesenchymal tissue. Positive staining for CD117, CD34, and Vim expression can aid GIST diagnosis. In addition, SMA and desmin as the myogenic markers, can be used to distinguish a GIST from leiomyoma. In contrast, S-100 is a neurogenic marker and can be used to distinguish the GIST from neurogenic tumors. Thus, negative results for S100, desmin, and SMA expression suggest that the GIST in the current case did not originate from myogenic or neurogenic tumor. The Ki67 proliferation index was only 1% with 4 mitoses per 50 HPF, and the p53 protein was negative in both carcinoma cells and the GIST, which may indicate a good prognosis.

To date, surgery remains the first-line treatment for both squamous and stromal neoplasms [7], and GISTs are often found accidently. After surgery, these patients need close follow-up [19]. Due to the infrequency of such collision tumors, the biological behavior of colliding tumors is difficult to ascertain [12]. Milne et al. [9] demonstrated that if two tumors arise independently and are associated by coincidence only, the genetic alterations present will differ from each other because of the different tumor origins. Further study is needed to discover their etiology and molecular mechanisms.

Acknowledgements

The study was supported in part by funds from the Radiology and Science and Education Departments of The Fifth People's Hospital of Shanghai, Fudan University. We thank Medjaden Bioscience Limited for assisting in the preparation of this manuscript.

Disclosure of conflict of interest

None.

Address correspondence to: Hua-Bin Yin or Ting Qian, Department of Radiology, The Fifth People's Hospital of Shanghai, Fudan University, Shanghai. Tel: 021-64308151; E-mail: hbyin1961@126.com (HBY); jnqc2003@126.com (TQ)

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011 Mar-Apr; 61: 69-90.

[2] Naritaka Y, Ogawa K, Shimakawa T, Wagatsuma Y, Isohata N, Asaka S, Miyaki A, Shiozawa S, Katsube T and Yoshimatsu K. Collision carcinoma of the residual cervical esophagus 27 years after esophageal cancer surgery. Anticancer Res 2007; 27: 505-511.

[3] Spagnolo D and Heenan P. Collision carcinoma at the esophagogastric junction: report of two cases. Cancer 1980; 46: 2702-2708.

[4] van Westreenen HL, Westerterp M, Jager PL, van Dullemen HM, Sloof GW, Comans EF, van Lanschot JJB, Wiggers T and Plukker JTM. Synchronous primary neoplasms detected on 18F-FDG PET in staging of patients with esophageal cancer. J Nucl Med 2005; 46: 1321-1325.

[5] Firat O, Yazici P, Makay O, Aydin A, Tuncyurek M, Ersin S and Guler A. Co-existence of gastrointestinal stromal tumors with malign epithelial tumors: a report of two cases. Acta Chir Belg 2009; 109: 629.

[6] Dodge O. Gastro-æsophageal carcinoma of mixed histological type. J Pathol Bacteriol 1961; 81: 459-471.

[7] Spinelli GP, Miele E, Tomao F, Rossi L, Pasciuti G, Zullo A, Zoratto F, Nunnari J, Pisanelli GC and Tomao S. The synchronous occurrence of squamous cell carcinoma and gastrointestinal

stromal tumor (GIST) at esophageal site. World J Surg Oncol 2008; 6: 116.
[8] Liu YJ, Yang Z, Hao LS, Xia L, Jia QB and Wu XT. Synchronous incidental gastrointestinal stromal and epithelial malignant tumors. World J Gastroenterol 2009; 15: 2027.
[9] Milne AN, Carvalho R, van Rees BP, van Lanschot JJ, Offerhaus GJA and Weterman MA. Do collision tumors of the gastroesophageal junction exist: a molecular analysis. Am J Surg Pathol 2004; 28: 1492-1498.
[10] Purdy S and Gaffney E. Ultrastructural and immunocytochemical definition of component neoplasms in an unusual gastrooesophageal collision tumour. Histopathology 1986; 10: 525-534.
[11] Gonzalez L, Sanz-Esponera J, Saez C, Alvarez T, Sierra E and Sanz-Ortega J. Case report: esophageal collision tumor (oat cell carcinoma and adenocarcinoma) in Barrett's esophagus: immunohistochemical, electron microscopy and LOH analysis. Histol Histopathol 2003; 18: 1-5.
[12] Brahmania M, Kanthan C and Kanthan R. Collision tumor of the colon-colonic adenocarcinoma and ovarian granulosa cell tumor. World J Surg Oncol 2007; 5: 118.
[13] Kagei K, Hosokawa M, Shirato H, Kusumi T, Shimizu Y, Watanabe A and Ueda M. Efficacy of intense screening and treatment for synchronous second primary cancers in patients with esophageal cancer. Jpn J Clin Oncol 2002; 32: 120-127.
[14] Wronski M, Ziarkiewicz-Wroblewska B, Gornicka B, Cebulski W, Slodkowski M, Wasiutynski A and Krasnodebski IW. Synchronous occurrence of gastrointestinal stromal tumors and other primary gastrointestinal neoplasms. World J Gastroenterol 2006; 12: 5360.
[15] Erlandson RA, Klimstra DS and Woodruff JM. Subclassification of gastrointestinal stromal tumors based on evaluation by electron microscopy and immunohistochemistry. Ultrastruct Pathol 1996; 20: 373-393.
[16] Miettinen M, Sarlomo-Rikala M and Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 1999; 30: 1213-1220.
[17] Ünal B, Elpek GÖ, Gelen T, Gürkan A and Yildirim B. Gastric collision tumor: Case report of a rare adenocarcinoma and a typical carcinoid tumor. Oncol Lett 2013; 6: 212-214.
[18] Hsiao HH, Yang SF, Liu YC, Yang MJ and Lin SF. Synchronous gastrointestinal stromal tumor and adenocarcinoma at the gastroesophageal junction. Kaohsiung J Med Sci 2009; 25: 338-341.
[19] Szumilo J, Dabrowski A, Skomra D and Chibowski D. Coexistence of esophageal granular cell tumor and squamous cell carcinoma: a case report. Dis Esophagus 2002; 15: 88-92.