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Case Report

Triple Synchronous Tumors in a Patient: Gastric Adenocarcinoma, Omental Gastrointestinal Stromal Tumor and Renal Angiomyolipoma

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Abstract

Introduction: The presence of synchronous distinct tumors is uncommon in the literature, and the etiology of it is still unknown.

Presentation of Case: Herein, we report a 42 year-old-woman with synchronous triple tumors of gastric adenocarcinoma, renal angiomyolipoma (AML), and omental gastrointestinal stromal tumor (GIST). She underwent total gastrectomy after the diagnosis of adenocarcinoma by endoscopic biopsy. During macroscopic examination of gastrectomy specimen, an ulcerated tumor about 4.5 cm in diameter was observed in the fundus. Histopathologically, it was diagnosed as adenocarcinoma harboring some signet-ring features. While dissecting lymph nodes of the omentum of the lesser curvature, a nodular mass about 4.2 cm in diameter seemed to be a lymph node was detected macroscopically. However, it was diagnosed as GIST by histopathological and immunohistochemical features. Also, partial nephrectomy was performed during the same session due to a mass detected radiologically in the left kidney about 2.2 cm in diameter. It was indicated to be metastatic gastric adenocarcinoma clinically but AML was determined by histopathological and immunohistochemical findings.

Conclusion: To the best of our knowledge, our patient is the first case in the literature that has synchronous tumors of gastric adenocarcinoma, omental GIST and renal AML.

Keywords: Adenocarcinoma; angiomyolipoma; gastric; GIST; triple; synchronous

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Introduction

Gastric carcinomas, gastrointestinal stromal tumors (GISTs), renal angiomyolipomas (**AML**s) are distinct neoplasms originated from different cell layers [1]. Although carcinoma is the most common type of gastric tumors, synchronous development of GIST is extremely rare, documented as only single case reports in the literature [1-7]. Besides, the coexistence of gastric carcinoma, omental GIST, and renal AML has not been reported up to date in the literature, to the best of our knowledge. Herein, this combination of three distinct tumors in a patient is presented firstly in the literature.

Case Presentation

A 42-year-old female patient suffering from stomach pain and nausea was diagnosed as gastric carcinoma by endoscopic biopsy at a regional hospital and referred to our hospital for tertiary management. Her physical examination was unremarkable. Laboratory tests were normal. Abdominal computed tomography (CT) revealed a tumor surrounding the lumen of the stomach in the corpus causing polypoid irregular thickening of the wall of stomach measuring up to 3.1 cm. In the lesser curvature, many enlarged lymph nodes were monitored. In addition, a well-circumscribed hypodense lesion measuring about 4.2x3.5 cm was observed in the left upper quadrant comprising the left adrenal gland, upper pole of the left kidney, upper pole of the spleen, and fundus of the stomach. It was indicated to be a metastatic gastric carcinoma of adrenal or a primary renal tumor. Also, an exophytic, well-circumscribed lesion about 1.5x1.3 cm in size was detected in the mid-pole of the left kidney with a suspicion of primary or metastatic renal tumor. Subsequent chest tomography showed a right pulmonary nodule of 0.6 cm in diameter, and a left pulmonary nodule of 0.2 cm that indicated metastasis. The patient underwent a radical total gastrectomy with D2 lymphadenectomy and Roux-en-Y reconstruction. Also, partial nephrectomy was performed during the same session due to the mass detected radiologically in the left kidney.

At macroscopic examination Borrman type-3 tumor with the dimensions of 4.5x3.2x1 cm was observed in the corpus-fundus extending to the cardia of the gastrectomy specimen. The histopathological evaluation showed poorly differentiated adenocarcinoma harboring signet ring cells (mixed diffuse and intestinal type of Lauren classification) (Figure 1a and *inset*). This tumor was found to infiltrate the whole gastric wall including serosal adipose tissue. Extensive perineural, neural and angiolymphatic invasions were detected. Intestinal metaplasia and chronic active gastritis were observed in non-tumoral gastric mucosa. H. pylori was also encountered. Three of the 40 dissected lymph nodes in lesser and greater curvature were disclosed to be metastatic.

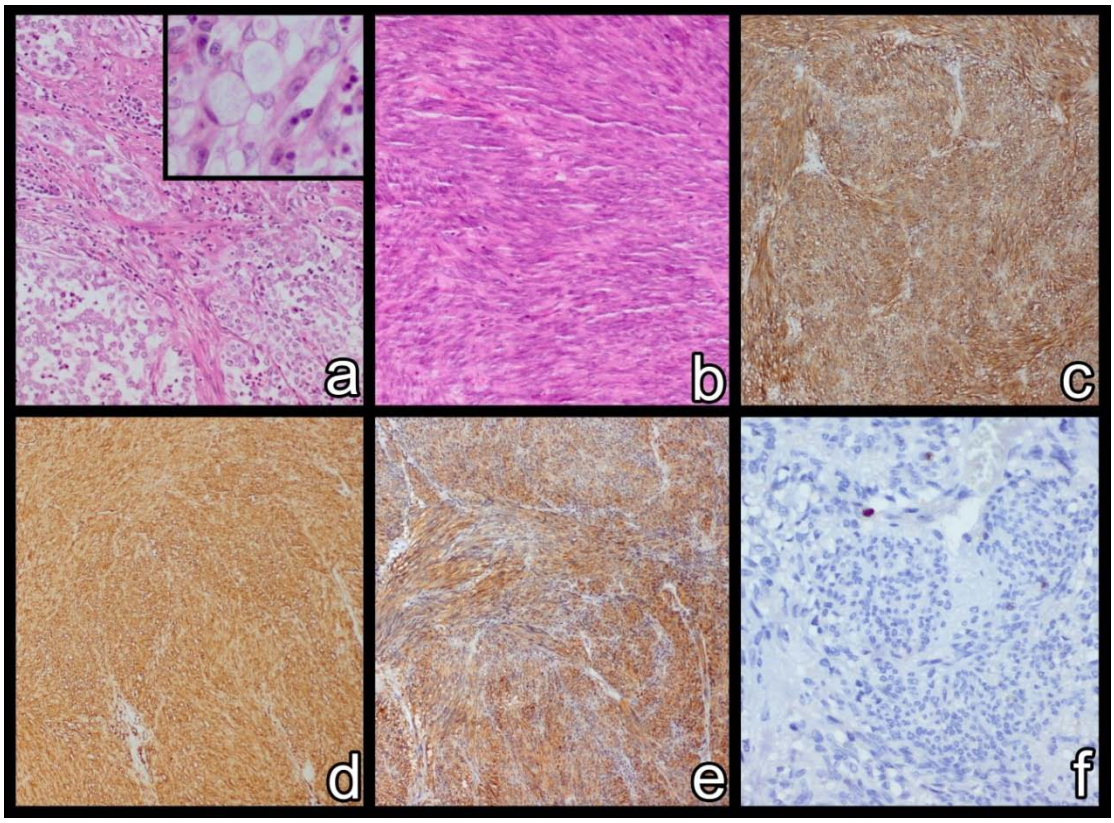

Figure 1 (a) Gastric adenocarcinoma harboring some signet-ring cells (*inset)*, (Hematoxylin and eosin, x200, *inset: x400*); (**b)** Cellular areas of omental GIST composed of interlacing fascicles of spindle cells, (Hematoxylin and eosin, x200); (**c-e)** CD117, CD34, and DOG-1 positivity of GIST, respectively (Avidin-biotin-peroxidase method, x100, each); (**f)** Low Ki-67 proliferation index of GIST, (Avidin-biotin-peroxidase method, x400).

During macroscopic evaluation of lymph nodes of lesser curvature, a well-circumscribed mass about 4.2x3.8x3.5 cm in size seemed to be a metastatic lymph node in the fat tissue without any relation with gastric wall was sampled. Under light microscope, a different lesion other than a metastatic lymph node was detected. Histopathologically, this lesion exhibited high cellularity with interlacing fascicles of spindle cells showing mild cytological atypia (Figure 1b). It had an expansive growth pattern and showed focal areas of hemorrhage. Necrosis or ulceration were absent. Three mitotic figures were detected in 50 high power fields (HPFs). Immunohistochemically, the tumor cells were intensely reacted with CD117 (Figure 1c), CD34 (Figure 1d), and DOG-1 (Figure 1e). S100, α-smooth muscle actin (SMA), desmin, HMB-45, Melan A and pancytokeratin were negative. Ki-67 proliferation index was low (less than 1%) (Figure 1f), Then, it was diagnosed as GIST-low risk category. This lesion was thought to be consistent with the lesion mentioned in the left upper quadrant in the abdominal CT.

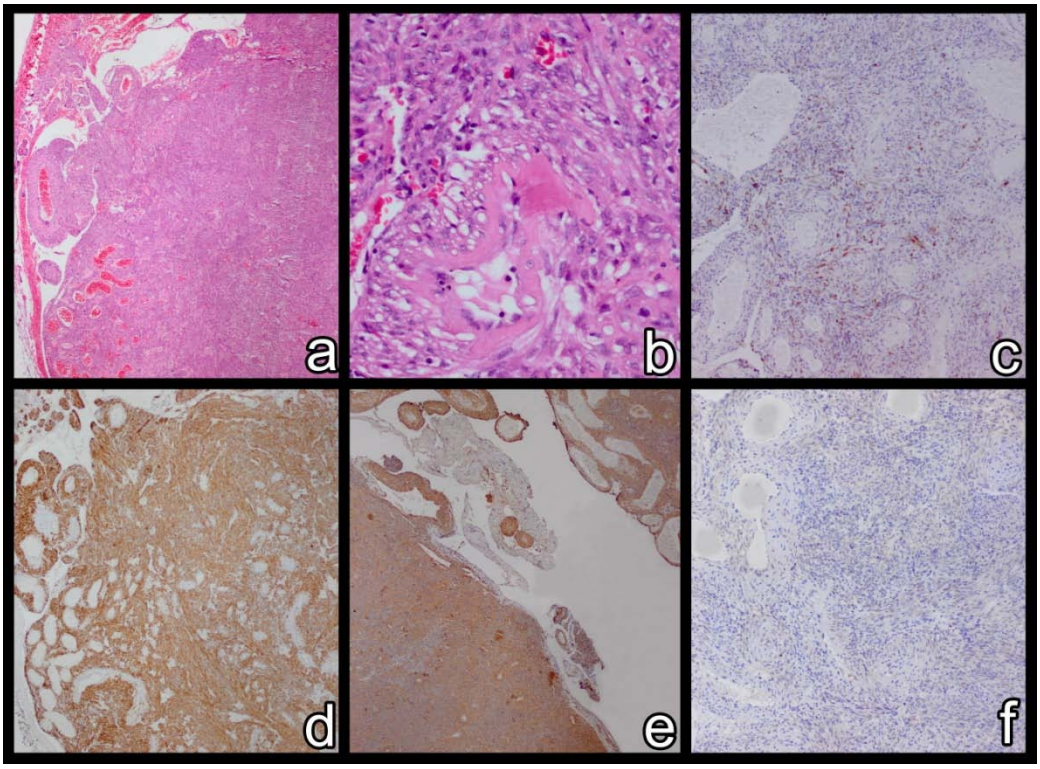

Figure 2 Photomicrographs of renal AML; **(a)** Cellular areas containing thick-walled blood vessels and fascicles of spindle cells, (Hematoxylin and eosin, x40); **(b)** Higher magnification of the tumor with scattered adipocytes, (Hematoxylin and eosin, x400); **(c-e)** Positivity for HMB-45, desmin, and SMA, (Avidin-biotin-peroxidase method, x100, x40, x40), respectively; **(f)** Negativity for CD117, (Avidin-biotin-peroxidase method, x100).

The specimen of partial nephrectomy was of 2.2x1.7x1.3 cm and it seemed to comprise the lesion detected by abdominal CT. It was sampled totally at macroscopic examination. Under light microscopy, the lesion was cellular and composed of thick-walled blood vessels, and fascicles of spindle cells (Figure 2a). In additional serial sections, scant mature adipose tissue was detected (Figure 2b). Significant cellular atypia, high mitotic activity or necrosis were absent. Immunohistochemically, the spindle cells were positive for HMB-45 (Figure 2c), desmin (Figure 2d) and SMA (Figure 2e). CD34 was positive in the blood vessels. Adipocytes in the lesion immunoreacted with S100. CD117 (Figure 2f), DOG-1, pancytokeratin and Melan-A were entirely negative in the lesion. Ki-67 proliferation index was low (less than 1%)]. Histopathological and immunohistochemical findings were compatible with AML, although the lesion was indicated to be metastatic gastric adenocarcinoma clinically. The postoperative course was uneventful, and the patient was discharged at postoperative third day. No further information about the clinical course of the patient was achieved because she did not attend the clinical follow-up in our institute.

Discussion

GIST was initially described in 1983 by Mazur and Clark [3]. It is a rare entity that constitutes 0.1%-3% of all gastrointestinal malignancies, however it is the most common non-epithelial neoplasia in the gastrointestinal tract [2]. These tumors are considered to be originated either from the stem cells that differentiate towards interstitial cells of Cajal, or directly from interstitial cell of Cajal, a pace-maker cell that regulates the autonomic motor function of digestive tract [3, 8]. Most of GISTs [90%] have mutation of c-Kit proto-oncogene that encodes the c-Kit protein [CD117], a transmembrane tyrosine kinase receptor [2, 3]. However, approximately 10% miss this mutation [3]. These CD117-negative GISTs often show a mutation in the platelet-derived growth factor receptor alpha [PDGFRa] gene [3].

Primary GISTs arise most commonly in the stomach (50%-70%), followed by the small intestine (25%-35%), colon and rectum (5%-10%) and esophagus (<5%) through the digestive tract [2]. In addition, GISTs may occur primarily in extragastrointestinal sites (<5%), such as mesentery, omentum, peritoneum, etc. [9]. Hence, the name “extra-gastrointestinal stromal tumors (EGISTs)” is used. The present case is an omental EGIST. As an explanation of EGISTs development theoretically, Sakurai et al. have reported the presence of some mesencymal cells in normal omentum that have expressed CD117 similar to interstitial cells of Cajal [9, 10]. However, the origin of EGIST is still controversial. Similar to most of classical GISTs, omental EGISTs are usually asymptomatic and mostly detected incidentally during the operation for other purposes as in our case.

The histopatological and immunohistochemical features of EGISTs are identical to those of classical GISTs in digestive tract. GISTs may resemble smooth muscle tumors both macroscopically and histopathologically, thus historically most of GISTs were misdiagnosed as leiomyosarcoma. GISTs are composed of spindle cells, epithelioid cells or occasionally pleomorphic cells. Marked cytological atypia is unusual. Most GISTs are positive for CD117, however CD117 may be negative in some cases [8, 9]. Many GISTs (70-80%) exhibit immunopositivity for CD34, 30-40% are focally or diffusely positive for SMA. Desmin and S100 are usually negative, but less than 5% of the tumor cells might demonstrate positivity (usually weak) [8]. Many mesenchymal tumors (leiomyoma, leiomyosarcoma, schwannoma, neurofibroma, desmoid tumor, solitary fibrous tumor, etc.) should be considered in the differential diagnosis of GISTs [11]. Immunohistochemistry for CD117 alone is not sufficient for GIST diagnosis because it may be positive in some non-GIST tumors [11]. Thus, a basic panel of immunohistochemistry containing CD117, CD34, S100 and desmin should be performed to exclude those tumors and achieve an exact diagnosis of GIST [11]. Although it is rare, the diagnosis of CD117-negative GISTs may be problematic. Therefore, some molecules alternative for CD117 such as DOG-1 have been reported recently to be positive in GISTs, especially in CD117-negative GISTs [12]. Our case was positive for both CD117 and DOG-1.

Histological assessment of biological behaviour and prognosis is essentially based on the size of the tumor and mitotic figures [3, 8, 13]. According to the classification of the Fletcher et al. GISTs are divided into 4 risk groups as very low-risk, low-risk, intermediate-risk and high-risk categories [9, 13]. The tumor of the present case was compatible with low-risk category with the diameter of 4.2 cm and 3 mitoses in 50 HPFs. Also, DNA-aneuploidy and proliferative index of more than 10% are implicated to show higher malignant potential [8]. Ki-67 proliferation index of our case was lower than %1 that indicated low malignant potential.

Primary treatment for GIST is surgical resection. Five-year survival is only 50%, because of the tendency of the GIST to metastasize or to recur [3]. Recurrence, metastatic disease or unresectable tumors could be treated with imatinib (a small-molecule, tyrosine-kinase inhibitor) [2]. Recently, imatinib resistance has developed and nearly 50% of patients do not respond after two years of treatment [3].

AML is a mesenchymal neoplasm that is composed of thick-walled blood vessels, smooth muscle, and mature adipose tissue in variable proportions [14]. It is a member of PECOMAs, a group of neoplasms derived from perivascular epithelioid cells [14, 15]. It constitutes about 1% of all renal tumors. It is mostly sporadic (80%), but it may occur with the syndrome of tuberous sclerosis (TS) [14, 15]. The present case showed no signs of TS. **AMLs** develop in the cases with TS (mean age: 25-35 years) earlier than the sporadic (mean age: 40 to 45 years) cases. It is more common in female patients than males (female/male: 4/1). **AMLs** are usually asymptomatic and detected incidentally by imaging studies or may rarely show some symptoms such as hematuria, flank pain, or a palpable mass. Intraabdominal bleeding due to rupture might be seen.

AMLs are typically well circumscribed lesions. Gross appearance depends on the relative amount of three components. Histopathologically, three components as blood vessels, spindle to epithelioid cells, and mature adipose tissue are detected in various proportions. Tumor has an elaborate vasculature ranging from capillary sized to large hyalinized blood vessels [14, 15]. There are mostly spindle-shaped cells with blunt-ended elongated nuclei and eosinophilic cytoplasms similar to smooth muscle cells accompanying epithelioid cells with or without clear cytoplasm. Some bizarre cells with degenerative nuclear atypia may be seen. Adipocytes might have cytologic atypia. It should be noted that focal nuclear pleomorphism and/or increased cellularity are often seen. In addition to these findings, the presence of **AML** components in lymph nodes should not be considered as signs of malignancy [14]. **AML** has three subtypes according to the morphology of the cells in the tumor. Monomorphic [spindle cell] variant is predominantly consisted of spindle cells with little or no vascular and adipose components. Cystic variant is composed of cystic spaces lined by benign cuboidal epithelial cells accompanying the characteristic components. Epithelioid variant contains significant amount of epithelioid cells, that are round- or oval-shaped cells with clear or granular cytoplasm and prominent nuclei. Multinucleated pleomorfic cells are not uncommon in epithelioid variant. Although most of the renal **AMLs** are benign and are cured by surgical resection, 25% to 33% of epithelioid **AMLs** are reported to exhibit malignant behavior

[17]. Large tumor size, tumor necrosis, atypical mitosis, and diffuse nuclear atypia are considered as the features of malignant **AMLs**. Immunohistochemically, **AMLs** usually show at least focal reactivity for melanocytic markers, including HMB45, Melan-A, and tyrosinase. SMA and muscle-specific actin are positive. Also, it should be noted that estrogen and progesterone receptors, S100, desmin, cytokeratins, CD34, and CD117 may be expressed in **AMLs**, rarely [15]. The diagnosis of **AML** is straightforward when those three components mentioned before coexist. However, the absence of one or more component or hypercellularity might cause difficulty in the differential diagnosis. Renal cell carcinoma (RCC) with eosinophilic cytoplasm containing intratumoral fat, true smooth muscle tumors, myelolipoma, and metastatic malignant melanoma and GIST should be considered particularly in the differential diagnosis of renal **AMLs** [14, 15]. The present mass in the kidney was highly cellular and adipose tissue-poor, thus additional serial sections were performed in order to find out fat component and immunohistochemical studies were carried out to achieve the exact diagnosis of **AML**. Negativity for CD117 and CD34, and positivity for SMA, desmin and HMB-45 in the spindle cells of renal mass in our case ruled out primary or metastatic GIST derived from omentum.

Gastric cancer comprises %7.8 of cancers worldwide [8]. Gastric adenocarcinoma is the second most common cancer in the world that accounts for 80% of all stomach cancers [2]. Various synchronous tumors, particularly benign, are detected incidentally during the operation, gross and/or histopathological examination of the surgical materials from stomach [1-7]. The higher incidence of simultaneous distinct primary tumors with gastric carcinoma may be attributed to the higher frequency of gastric carcinoma and the performed operations for it.

Synchronous multiple tumors of the same or different organs that are unrelated with a syndrome (e.g., neurofibromatosis type 1, Carney triad and familial GIST) are rare. The incidence of synchronous GISTs with other primary tumors varies from 4.5% to 33% as case reports in the literature [16]. The etiology and pathogenesis of synchronous distinct tumors are still obscure [1-7, 16]. Some hypotheses, such as gene mutation, expression of metallothioneins, adjacent tissues being influenced by the same carcinogens have been suggested regarding the coexistence of GIST and other cancers [2]. For instance, the stem cell is stated as a responsible factor for coexistence of tumors from different lineages, and the overexpression of CD34, a well-known marker of precursor cells in patients with synchronous GIST might be considered as a support for this hypothesis [17]. Helicobacter pylori infection has been suggested as a causative factor for the development of simultaneous GIST and gastric carcinoma but no definite association has been found [6]. It has been suggested in the literature that the combination of some agents may cause synchronous distinct tumors. For instance, the development of gastric adenocarcinoma in rats has been demonstrated when exposed to nitrosoguanidine by Cohen et al. [16]. When this compound has been combined with agents such as aspirin, the emergence of leiomyosarcoma was detected accompanying gastric adenocarcinomas [16]. Shitkov has stated that the exposure to dimethyl-1,2-enzanthracene inducted gastric adenocarcinomas in rats and after the additional treatment with cellophane plate gastric sarcomas

has arised [16]. However, none of these hypotheses about the occurrence of synchronous tumors has been proved up to date.

In the literature, GISTs have been reported to occur synchronously mostly with intestinal type gastric adenocarcinoma as in our case. In addition, the coexistence of diffuse type gastric carcinoma, lymphoma and carcinoid tumor of stomach, pancreatic adenocarcinoma, cholangiocellular carcinoma, lung adenocarcinoma, RCC, esophageal squamous cell carcinoma, breast carcinoma, prostatic adenocarcinoma, endometrial adenocarcinoma, ovarian adenocarcinoma have been presented in the literature rarely [4, 5, 7, 16]. Also, non-epithelial tumors such as osteosarcoma, Burkitt's lymphoma, plasmacytoma, neuroblastoma, somatostatinoma, chronic lymphocytic leukemia, lipoma have been reported with GIST simultaneously in the literature [7].

It has been documented that GISTs have been detected incidentally in 0.2% of all autopsies [7]. Therefore, the incidental GIST may occur synchronously with other diseases more frequently than expected clinically [7].

In the literature, the coexistence of renal **AML** with RCC and oncocytoma has been reported more frequently, but also single case reports of coexistence with cystic nephroma and retroperitoneal schwannoma have been presented [18-20]. A case of simultaneous early gastric carcinoma and retroperitoneal **AML** has been reported by Mogi et al. [21]. A case of concomittant hepatic PECOMA-compatible with epithelioid **AML** and GIST of lesser curvature has been presented by Paiva et al. [22].

Conclusion

The coexistence of different primary tumors in a patient is a rare event. In this report, concomittant triple distinct tumors in a patient including gastric carcinoma, omental GIST, and renal AML have been presented. To the best of our knowledge, this is the first report that has this combination of synchronous triple distinct tumors in a patient. The etiology and pathogenesis are still debated in the literature whether it is a coincidence or has some unknown common causative factors [2]. Further studies are crutial to clarify the pathogenesis of synchronous tumors.

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References

1. Firat Ö, Çalışkan C, Karaca C, Sezak M, Özütemiz Ö, Ersin S, Güler A. Coexistence of gastric cancer and gastrointestinal stromal tumor: report of two cases. ***Turk J Gastroenterol.*** 2010, 21: 302-4
2. Zhou Y, Wu XD, Shi Q, Jia J. Coexistence of gastrointestinal stromal tumor, esophageal and gastric cardia carcinomas. ***World J Gastroenterol.*** 2013, 19:2005-8

3. Idema DL, Daryanani D, Sterk LM, Klaase JM.Collision tumor of the stomach: a case of an adenocarcinoma and a gastrointestinal stromal tumor. ***Case Rep Gastroenterol.*** 2008, 2: 456-60
4. Sema B, Özden C, Şerife A, Şirin B, Mahmut B, Nilgün K, Nermin K, Metin Ç. Synchronous primary adenocarcinoma and gastrointestinal stromal tumor in the stomach: A report of two cases. ***Turk J Gastroenterol***. 2004, 15: 187-191
5. Vogel Y, Müller C, Uhl W, Tannapfel A. Coexistence of multifocal gastric adenocarcinoma with signet-ring cell morphology and a gastrointestinal stromal tumour in a stomach with hp-associated gastritis. ***Z Gastroenterol.*** 2011, 49: 201-6
6. Salemis NS, Gourgiotis S, Tsiambas E, Karameris A, Tsohataris E. Synchronous occurrence of advanced adenocarcinoma with a stromal tumor in the stomach: a case report. ***J Gastrointestin Liver Dis.*** 2008, 17: 213
7. Liu YJ, Yang Z, Hao LS, Xia L, Jia QB, Wu XT. Synchronous incidental gastrointestinal stromal and epithelial malignant tumors. ***World J Gastroenterol.*** 2009, 15: 2027-31
8. Bosman FT, Carneiro F, Hruban RH, Theise ND (eds): *WHO Classification of Tumours of the Digestive System*. Lyon: **IARC Press**; 2010
9. Fagkrezos D, Touloumis Z, Giannila M, Penlidis C, Papaparaskeva K, Triantopoulou C. Extra-gastrointestinal stromal tumor of the omentum: a rare case report and review of the literature. ***Rare Tumors.*** 2012, 4: 44
10. Sakurai S, Hishima T, Takazawa Y, Sano T, Nakajima T, Saito K, Morinaga S, Fukayama M. Gastrointestinal stromal tumors and KIT positive mesenchymal cells in the omentum. ***Pathol Int***. 2001, 51: 524-31
11. Abraham SC. Distinguishing gastrointestinal stromal tumors from their mimics: an update. ***Adv Anat Pathol.*** 2007, 14: 178-88
12. Kang GH, Srivastava A, Kim YE, Park HJ, Park CK, Sohn TS, Kim S, Kang DY, Kim KM. DOG1 and PKC-θ are useful in the diagnosis of KIT-negative gastrointestinal stromal tumors. ***Mod Pathol.*** 2011, 24: 866-75
13. Miettinen M, Lasota J. Gastrointestinal stromal tumors. Review on morphology, molecular pathology, prognosis and differential diagnosis. ***Arch Pathol Lab Med.*** 2006, 130: 1466–78
14. Zhou M, Netto GJ, Epstein JI. *Uropathology: High-Yield pathology*. Philadelphia: **Elsevier/Saunders;** 2012
15. Folpe AL, Inwards CY. *Bone and soft tissue pathology*. Philadelphia: **Saunders/Elsevier;** 2010
16. Gonçalves R, Linhares E, Albagli R, Valadão M, Vilhena B, Romano S, Ferreira CG. Occurrence of other tumors in patients with GIST. ***Surg Oncol.*** 2010, 19: 140-3
17. Ferreira SS, Werutsky G, Toneto MG, Alves JM, Pianta CD, Breunig RC, Brondani da Rocha A, Grivicich I, Garicochea B. Synchronous gastrointestinal stromal tumors (GIST) and other primary cancers: case series of a single institution experience. ***Int J Surg.*** 2010, 8: 314-7
18. Radopoulos D, Tahmatzopoulos A, Kalinderis N, Dimitriadis G. Bilateral synchronous occurrence of three different histological types of renal tumor: a case report. ***J Med Case Rep.*** 2009, 3: 6798
19. Val-Bernal JF, Hernandez-Nieto E, Garijo MF. Association of cystic nephroma with angiomyolipoma in the same kidney. ***Pathol Res Pract.*** 2000, 196: 583-8

20. Dong A, Wang Y, Zuo C. Synchronous pure epithelioid angiomyolipoma of the kidney and retroperitoneal schwannoma in the same patient on 18F-FDG PET/CT imaging. ***Clin Nucl Med.*** 2013, 38: 98-100
21. Mogi Y, Takimoto R, Kura T, Tamakawa M, Sakamaki S, Niitsu Y. Retroperitoneal extrarenal angiomyolipoma with early gastric carcinoma. ***J Gastroenterol.*** 1998, 33: 86-90
22. Carlos Eduardo Paiva, Francisco Alves Moraes Neto, Abbas Agaimy, Maria Aparecida Custódio Domingues, Silvia Regina Rogatto. Perivascular epithelioid cell tumor of the liver coexisting with a gastrointestinal stromal tumor. ***World J Gastroenterol***. 2008, 14: 800-802