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Coexistence of papillary renal cell carcinoma and gastrointestinal stromal tumor in a case

Papiller renal hücreli kanser ve gastrointestinal stromal tümör birlikteliği

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Gastrointestinal stromal tumors are rare causes of gastrointestinal bleeding. In most cases, these tumors are localized in the stomach and small intestine, more rarely in the esophagus and colon. Papillary renal cell carcinoma and gastrointestinal stromal tumor may occur as recurrent familial tumors related to mutations in the protooncogenes, c-MET and c-KIT, both of which are tyrosine kinase receptor molecules. However, these two tumors can sometimes occur simultaneously in sporadic cases. Some authors blame imatinib mesylate (Gleevec), which is traditionally used in gastrointestinal stromal tumor therapy, as the etiological factor in certain secondary tumors, especially papillary renal cell cancer. In this paper, we present the appearance and growth of papillary renal cell carcinoma in a patient receiving Gleevec therapy for gastrointestinal stromal tumor.

Key words: Gastrointestinal stromal tumor, papillary renal cell carcinoma, protooncogene, receptor tyrosine kinase

Gastrointestinal stromal tümörler sindirim sisteminin nadir görülen tümörleridir ve sıklıkla mide veya incebarsaktan, nadiren ise özefagus ve kolondan köken alırlar. Bu tümörler birer reseptör tirozin kinaz molekülü olan c-MET ve c-KIT protoonkogenlerinde meydana gelen mutasyonlar sonucu papiller renal hücreli kanser ile birlikte ailesel kanserler şeklinde karşımıza çıkabilmektedirler. Ancak bazen bu iki tümör sporadik vakalar olarak bir arada bulunabilmektedir ve bu durum bazı yazarlarca gastrointestinal stromal tümör tedavisinde kullanılan imatinib mesylate (gleveec)'ın sekonder tümörlere özellikle de papiller renal hücreli kansere yol açma potansiyeline bağlanmıştır. Biz bu yazımızda metastatik gastrointestinal tümörü olan bir hastanın bu dönemde ortaya çıkıp gleevec tedavisi sırasında ilerleme gösteren papiller renal hücreli kanser ile birlikteliğini sunmaktayız.

Anahtar kelimeler: Gastrointestinal stromal tümör, papiller renal hücreli karsinom, protoonkogenler, reseptör tirozin kinaz

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) constitute an important group of mesenchymal tumors of the gastrointestinal tract. It is thought that GISTs originate from the interstitial cells of Cajal, which control gastrointestinal peristalsis. GISTs arise from any portion of the gastrointestinal tract, most commonly from the stomach (39%), small intestine (32%), and colorectal regions (15%) (3). It is known that 85% of GISTs have c-KIT mutations and 35% of GISTs with normal c-KIT contain platelet derived growth factor receptor– α mutations (4). These genes encode receptor proteins which have tyrosine kinase activity and their mutations lead to ligand independent activation of the tyrosine kinase signaling pathway, promoting cell proliferation and inhibiting apoptosis. Overexpression of c-KIT can be detected by immunohistochemistry, which is a very useful tool for the confirmation of the diagnosis of GIST. There has been a remarkable development in the treatment of c-KIT-positive GISTs with the discovery of efficacy of imatinib mesylate (Gleevec), a tyrosine kinase inhibitor (5).

C-MET protooncogene also encodes protein belonging to the tyrosine kinase receptor family, and some cases of papillary renal cell carcinoma (RCC) have been found to be associated with germline mutations of the c-MET oncogene (6). We present here a case of concurrent papillary RCC and GIST.

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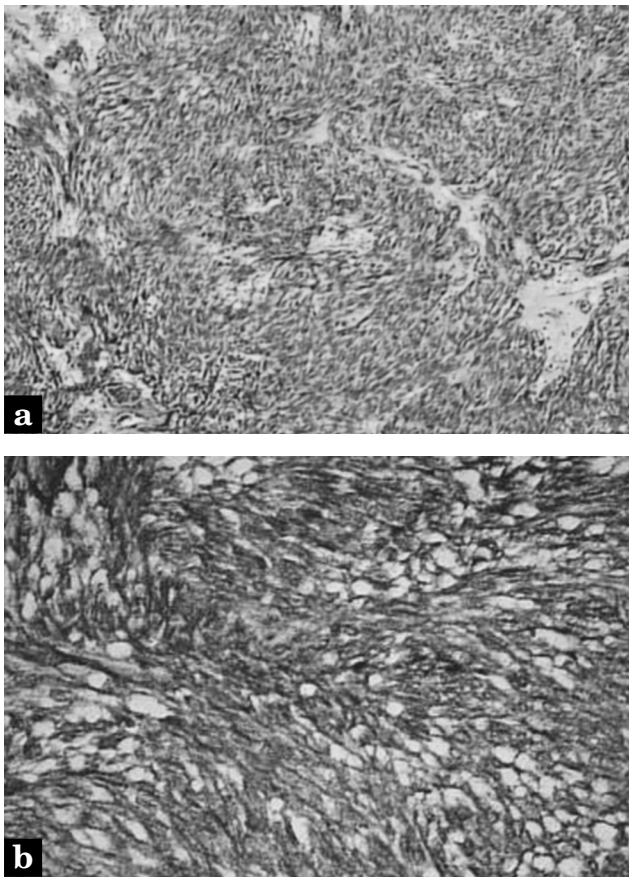

Figure 1. Gastrointestinal stromal tumor **a)** HEx10, **b)** c-kitx10

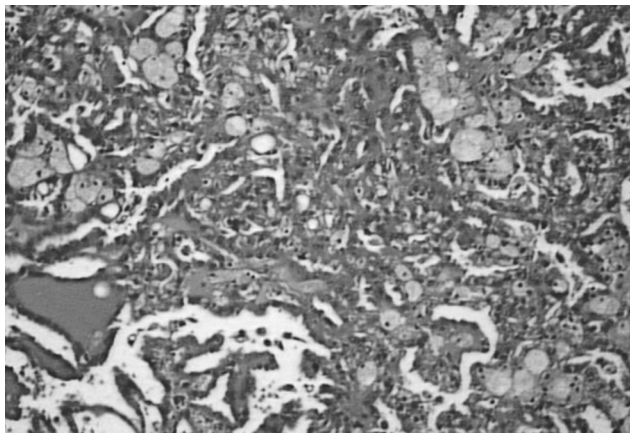

Figure 2. Papillary renal cell carcinoma (HEx20)

CASE REPORT

A 58-year-old man presented with a six-month history of anorexia, upper abdominal discomfort, and weight loss of 5 kg, initially suggesting the diagnosis of gastric ulcer. Upper gastrointestinal endoscopy revealed a friable, exophytic mass in the major curvature of the stomach. Spiral computed tomography (CT) scanning of the abdomen demonstrated the presence of a 12 x 20 cm gastric mass. The patient underwent surgical resection with partial gastrectomy and colectomy. A tumor, 20 cm in length, located in the muscularis propria and serosa of stomach and colon was detected. The tumor was encapsulated and composed of spindle cells growing in the form of fascicles. Twenty-two mitoses were counted on 50 HPF. Immunohistochemistry was performed by streptavidin biotin peroxidase method and tumor cells were positive for c-KIT, CD34 and vimentin, but they were negative for S-100 and SMA. It was diagnosed as malignant gastrointestinal stromal tumor (Figures 1a, 1b). Fourteen months later, the patient had tumor relapse, with intra-abdominal metastases and 2.5 x 2.5 cm right renal mass. Imatinib had become available, and the patient was treated with this drug at a dosage of 400 mg/day. Five months later, abdominal CT showed regression of all abdominal metastatic lesions, but the renal mass had increased in size (3.5 x 3 cm) and was noted to be enhancing in nature. Right partial nephrectomy was performed and it was in papillary configuration and consisted of pleomorphic cells with prominent nucleoli and clear or granular cytoplasm. The patient was diagnosed as papillary RCC with a histopathological grade of 3 (Figure 2). Immunohistochemistry was performed and tumor cells were negative for c-KIT. Postoperatively, the patient continued imatinib therapy and no recurrence or metastasis was found in the right kidney at the six-month follow-up.

DISCUSSION

Gastric stromal tumors are rare mesenchymal neoplasms of the stomach, accounting for approximately 3.6% of all gastric tumors (7). Previously, gastrointestinal mesenchymal tumors were categorized into two subgroups as benign and malignant smooth muscle tumors. Today, these tumors are classified as gastrointestinal stromal tumors. The ratio of male to female cases is 3:1 and the average age of patients presenting with the tumor is between 40-60 years. GISTs arise from any portion of the gastrointestinal tract, most commonly from the stomach (39%), small intestine (32%), and colorectal regions (15%). Multiplanar imaging methods, such as CT and magnetic resonance (MR) imaging, are very useful in differential

diagnosis. Surgical resection is the mainstay of treatment for patients with operable tumors and was the only effective intervention prior to the introduction of imatinib, since GISTs are highly resistant to chemotherapeutic agents. However, surgery is not curative in many cases. Imatinib is a potent and specific inhibitor of the KIT protein-tyrosine kinase, which is constitutively activated in more than 90% of GISTs as a result of gain-of-function mutations in the KIT protooncogene (8). The presence of KIT is readily detected through reactivity with the CD117 antigen on immunohistochemical assay, a marker that establishes the diagnosis in a gastrointestinal tract mesenchymal neoplasm with characteristic histologic features (9).

The repeated associations of specific tumors often serve as pointers to novel oncogene defects. The frequent co-expression of c-MET and c-KIT in solid tumors suggests the existence of common co-regulatory mechanisms (10).

The receptor tyrosine kinase family is rather large and any given agent would most likely only function as an antagonist against a subset of these critical receptors. Of greater concern would be potential activation of a subgroup of these receptors, which could predispose to secondary malignancies. Close observation of patients taking imatinib mesylate is required to allay this concern (10). Thus, there can be a development or progression of secondary malignancies in patients treated with imatinib mesylate. Furthermore, urologists should be aware of the emerging entity of GIST and the novel treatments being developed for its management and their impact on prognosis, because some patients with GIST may present with urologic involvement or develop other conditions requiring urologic management.

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