Case Report

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Synchronous Acromegaly and Gastrointestinal Stromal Tumor: A Case Report

Eş Zamanlı Akromegali ve Gastrointestinal Stromal Tümör: Olgu Sunumu

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Abstract

Acromegaly is a rare endocrine disorder characterized by the manifestations of sustained hypersecretion of growth hormone and concomitant elevations in circulating concentrations of insulin-like growth factor-1. It has been reported that patients with acromegaly are at the increased risk of developing malignant tumors, particularly colorectal cancer. Gastrointestinal stromal tumors are mesenchymal tumors of the digestive tract. An association between gastrointestinal stromal tumors and insulin-like growth factor system has been reported. Here, we report a patient diagnosed with synchronous acromegaly and gastrointestinal stromal tumor. A 59-year-old man with iron deficiency anemia presented with enlarged hands, coarse facial feature and several skin tags. Thyroid function tests were within normal range. Growth hormone was 5.14 ng/mL, insulin-like growth factor-1 was 820 ng/mL, and no growth hormone suppression was observed on 75g oral glucose tolerance test. Pituitary magnetic resonance imaging revealed microadenoma, and the patient was diagnosed with acromegaly. Upper gastrointestinal tract endoscopy revealed an ulcerovegetan mass in the duodenum and the results of the histopathologcal analysis was consistent with gastrointestinal stromal tumor. The association of synchronous and asynchronous gastrointestinal stromal tumors with other malignancies have been reported. The most common accompanying neoplasms are colorectal and gastric adenocarcinomas, as well as pancreatic tumors. However, in the literature, the number of reported cases of synchronous acromegaly and gastrointestinal stromal tumor are limited, and there are no sufficient data on this association. *Turk Jem 2014; 2: 52-55*

Key words: Acromegaly, insulin-like growth factor-1, gastrointestinal stromal tumor

Özet

Akromegali, büyüme hormonu aşırı sekresyonu ve aynı zamanda sirkülasyondaki insülin benzeri büyüme faktörü-1 konsantrasyonunun artışı ile karakterize nadir bir endokrin hastalıktır. Akromegali hastalarında özellikle kolorektal kanser başta olmak üzere diğer kanserlerin gelişme riskinin arttığı bildirilmiştir. Gastrointestinal stromal tümör sindirim sisteminin mezanşimal tümörüdür. Gastrointestinal stromal tümör ile insülin benzeri büyüme faktörü sistemi arasında ilişki olduğu bildirilmektedir. Biz, eş zamanlı akromegali ve gastrointestinal stromal tümör saptadığımız vakayı bildirdik. Demir eksikliği anemisi bulunan 59 yaşındaki erkek hastanın ellerinde büyüme, kaba yüz görünümü ve birkaç adet cilt papillomu mevcuttu. Tiroid fonksiyon testleri normaldi. Büyüme hormonu 5,14 ng/mL, insulin-benzeri büyüme faktör-1 820 ng/mL ölçüldü ve 75 gr oral glukoz tolerans testinde büyüme hormonunda baskılanma olmadığı gözlendi. Hipofizin magnetik rezonans görüntülemesinde mikroadenom saptanan hastaya akromegali tanısı konuldu. Üst gastrointestinal sistem endoskopisinde duedonumda ülserovejetan kitle izlendi ve histopatolojisi gastrointestinal stromal tümor ile uyumlu idi. Gastrointestinal stromal tümörler ile diğer tümörlerin eş zamanlı ya da farklı zamanlarda görülen birliktelikleri bildirilmiştir. En sık eşlik eden tümörler kolorektal ve gastrik adenokarsinomlar ile pankreatik tümörlerdir. Ancak, literatürde eş zamanlı akromegali ve gastrointestinal stromal tümör görülen vaka sayısı oldukça azdır ve aralarındaki ilişkiye dair yeterli veri bulunmamaktadır. *Turk Jem 2014; 2: 52-55*

Key words: Akromegali, insülin benzeri büyüme faktörü-1, gastrointestinal stromal tümör

Introduction

Acromegaly is a disorder caused by excess secretion of growth hormone (GH), characterized by enlarged acral parts, coarse facial features, and visceromegaly. Patients with acromegaly may also be at an increased risk for malignancies in several systems such as the digestive tract, brain, kidney, breast and prostate (1). The GH/insulin-like growth factor-1 (IGF-1) axis plays a crucial role in tumorigenesis in acromegaly. In several studies, it has been reported that besides increased expression of IGF-1 and IGF receptor-1 (IGFR-1) in the tumor tissues, increased circulating IGF-1 levels are also involved in the development of these malignant tumors (2,3).

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Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal neoplasms affecting the gastrointestinal (GI) tract, and express constitutively activated forms of stem cell factor (KIT) or platelet-derived growth factor receptor-alpha (PDGFR-α) receptor tyrosine kinase, resulting in downstream signaling that involves the phosphatidylinositol-3-phosphate-kinase (PI3K) and the mitogen-activated protein kinase (MAPK) pathways (4,5). IGFR-1 is a transmembrane heterotetrameric protein, implicated in promoting oncogenic transformation, growth and survival of cancer cells (6). IGFR-1, under IGF-1 and IGF-2 stimulation, activates both PI3K and MAPK pathways.

In the literature, the synchronous occurrence of GISTs and other primary GI malignancies has been reported previously (7). Even so, the synchronous appearance of acromegaly and GISTs is very rarely encountered . Herein, we report a case of synchronous acromegaly and GIST.

Case Report

A 59-year-old man was admitted to the clinic after being diagnosed with iron deficiency anemia according to the results of the tests performed for the complaints of fatigue and shortness of breath. The patient had no history of weight loss, hematemesis, melena or hematochezia. In addition, the patient's family history revealed no carcinoma. On physical examination, blood pressure was 140/90 mmHg, and heart rate was 98/min and no arrhythmia was detected. The conjuctivas were pale, he had enlarged hands and coarse facial feature and, several discrete skin tags were noted. Other systemic examinations were within normal limits. The laboratory findings are presented in Table 1. Fecal occult blood test was negative. Thyroid function tests were within normal range, and GH and IGF-1 were 5.14 ng/mL and 820 ng/mL, respectively. 75g oral glucose tolerance test was performed, and GH values were unsuppressed (GH, 3.60 ng/mL at min 0; GH, 4.20 ng/mL at min 30; GH, 4.29 ng/mL at min 60; GH, 4.50 ng/mL at min 90; and, GH, 1.80 ng/mL at min 120). Pituitary magnetic resonance imaging (MRI) revealed a left pituitary microadenoma measuring 7 mm in diameter (Figure 1), and the case was diagnosed with acromegaly. Endoscopy of the upper GI tract revealed an ulcerovegetan mass in the duodenum. A biopsy was performed (Figure 2), and as a result of the histopathological investigation, a cellular spindle cell tumor with centrally placed nucleus, pale eosinophilic cytoplasms and forming ill-defined fascicles was observed (Figure 3). Immunohistochemical stains performed for differential diagnosis indicated the following results as positive ones: CD117 (c-kit) (Figure 4), CD34 (Figure 5) and vimentin (Figure 6), and negative ones: S100 and desmin. When the histopathological findings were assessed together with immunohistochemical results, the case was diagnosed with GIST. Colonoscopy was normal, and no metastasis was observed on abdominal computed tomography. The patient diagnosed with synchronous acromegaly and GIST was operated on due to GIST. After the GIST surgery, somatostatin analogue was administered to the patient in order to treat acromegaly because of patient's refusal of pituitary surgery.

Discussion

In this paper, we reported a case of synchronous acromegaly and GIST in which acromegaly was found incidentally while evaluating for iron deficiency anemia. In the literature, there are a limited number of reported cases of synchronous acromegaly and GIST (8-10). Additionally, no comprehensive study related to the co-occurrence of these two tumors is available. As opposed to this,

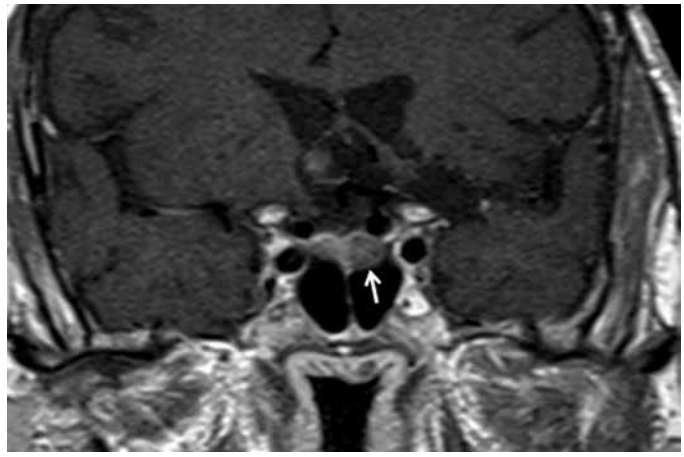

Figure 1. The left pituitary microadenoma in pituitary magnetic resonance imaging

Table 1. Laboratory findings of the case

Parameters	Values	Normal ranges
Hb (gr/dL)	8.6	12-18
Hct (%)	28.8	37-52
PLT (mm^3)	408000	130000-400000
WBC (mm^3)	6520	4500-10800
Iron (μg/dL)	38	65-175
Iron-binding capacity (μg/dL)	404	110-370
Ferritin (ng/mL)	3.4	22-322
ESR (mm/h)	42	0-25
Glucose (mg/dL)	94	70-105
Creatinine (mg/dL)	1.02	0.7-1.3
AST (U/L)	13	5-34
ALT (U/L)	11	0-55
GH (ng/mL)	5.14	0-1
IGF-1 (ng/mL)	820	81-225
Prolactin (ng/mL)	10.13	2.1-17.7
Cortisol (μg/dL)	12.58	4.3-22.4
TSH (μIU/mL)	0.68	0.35-5.5
fT4 (ng/dL)	1.09	0.74-1.79
Cortisol (μg/dL) (1 mg of dexamethasone suppression test)	1.12	

Hb: hemoglobin, Hct: hemotocrit, PLT: platelet, WBC: white blood cell, ESR: erythrocyte sedimentation rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GH: growth hormone, IGF-1: insulin-like growth factor-1, TSH: thyroid stimulating hormone, fT4: free tetraiodothyronine

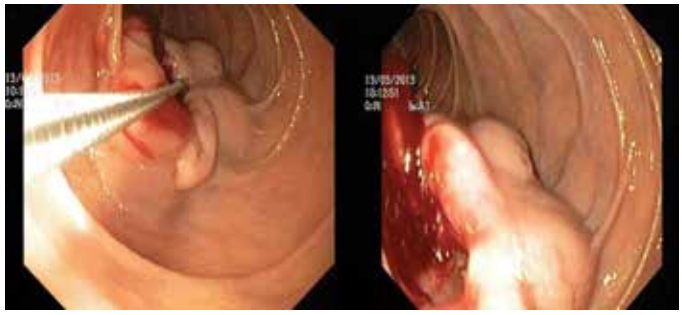

Figure 2. The ulcerovegetan mass in duedonum

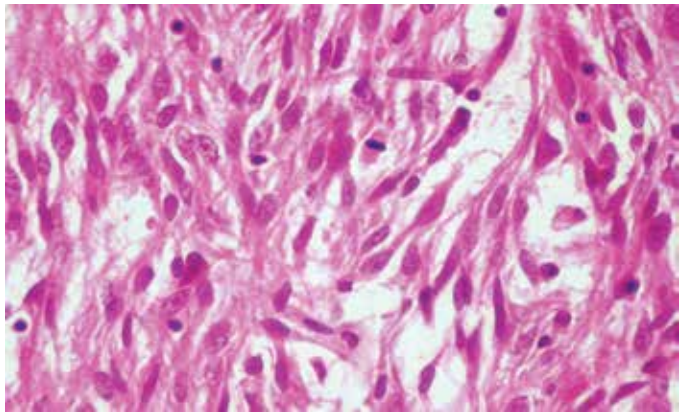

Figure 3. The stromal tumor with spindled-pattern of cells arranged in distinct ill-defined fascicles

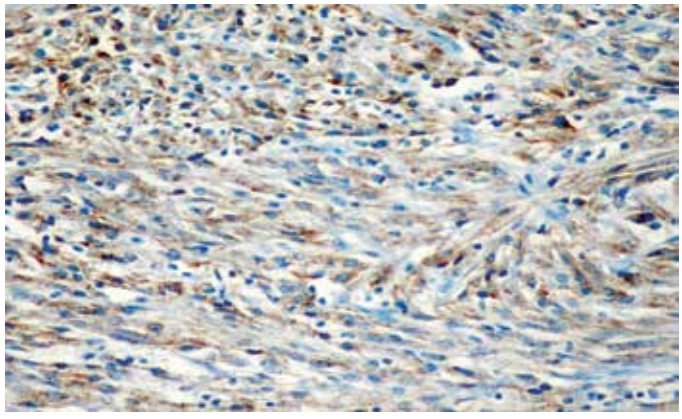

Figure 4. Immunstain for CD117 in a gastrointestinal stromal tumor

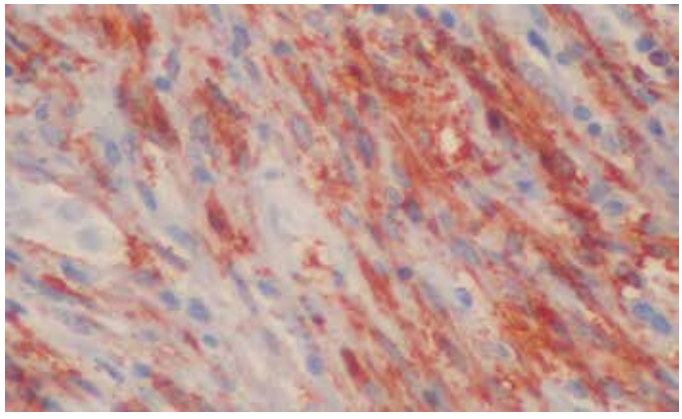

Figure 5. Immunstain for CD34 in a gastrointestinal stromal tumor

IGF system has been reported to play a role in the pathogenesis of GISTs. In a study performed recently, small bowel neoplasms were evaluated using videocapsule endoscopy in acromegaly patients, and the existence of GISTs was also observed in these patients (11). An increased risk for several cancers among acromegaly patients may be due to the elevated proliferative and anti-apoptotic activity associated with increased circulating levels of IGF-1. In a prospective study, it was suggested that normal population with high concentrations of IGF-1 are at an increased risk of colorectal cancer, and those with serum IGF-1 in the upper quintile of the normal range carry a 2.5-fold increased risk, compared to those in the lowest quintile (12). In some studies, high IGF binding protein-3 (IGFBP-3) levels were found to be associated with a lower risk of cancer (13). In acromegaly, GH excess increases serum IGF-1 and to a lesser extent, IGFBP-3 concentrations, and hence, the increase in GH concentrations leads to an elevation in IGF-1 to IGFBP-3 ratio. Thus, an elevated IGF-1 to IGFBP-3 ratio is expected to increase cancer risk in acromegaly. IGF-1 has proliferative and anti-apoptotic effects in various cell lines including colonic mucosa of acromegalic patients (14,15). IGFR-1 is also implicated in carcinogenesis and cancer proliferation, and associated with different degrees of malignancy (16).

It remains unknown whether the augmented systemic GH/IGF-1 axis in active acromegaly is involved in the expression of IGFR-1 and GH receptor (GHR) in the tumors. While few studies reported the expression levels of IGFR-1 and GHR in tumor tissues from acromegalic patients, several studies showed the increased expression of IGFR-1 and/or GHR in the tumors of non-acromegalic patients (3,17).

GISTs represent the most common intramural mesenchymal tumors of the GI tract. They arise from primitive cells with the same characteristics as interstitial cells of Cajal and occur predominantly in the stomach (70%) and small intestine (10%-20%). GISTs may be sporadic or inherited in an autosomal-dominant manner either alone or in association with other rare neoplasms (18). Additionally, GISTs may synchronously be associated with other tumors, and the most common accompanying neoplasms are colorectal and gastric adenocarcinomas, as well as pancreatic tumors.

The majority of GISTs are due to the hyperactivation of KIT and PDGFR-α downstream signaling that involves PI3K, MAPK and Janus Kinase (JAK) pathways (4,5). Recent evidence, however,

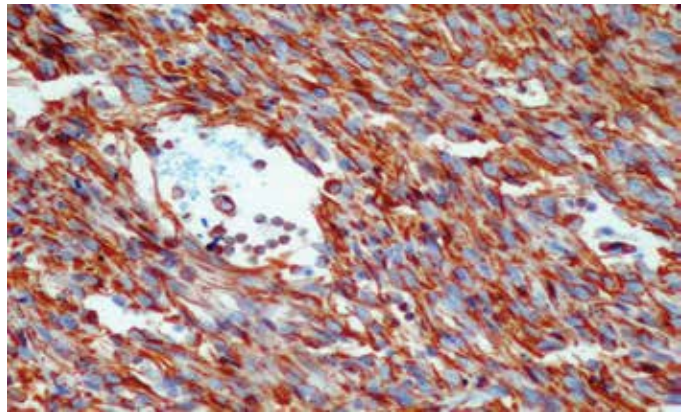

Figure 6. Immunstain for vimentin in a gastrointestinal stromal tumor

indicates that other signaling routes might also be involved in GIST pathogenesis. In a study by Braconi et al. performed on 94 patients, the involvement of IGF system in GISTs was indicated, and a strong expression of IGFR-1 was found in all cases. Strong IGF-1 expression was significantly correlated with higher mitotic index, larger, higher risk, metastatic and relapsed GISTs (19). Moreover, the involvement of IGF system in GISTs was indicated by the several cases of non-hyperinsulinemic hypoglycemia observed in GIST patients. In these patients, elevated plasmatic levels of pro-IGF-2 were detected, and pro-IGF-2 was hypothesized to be produced by GIST cells. Pro-IGF-2 was generated by abnormal processing of IGF-2 precursor in tumors (20,21).

Surgery remains the mainstay of therapy for patients with primary GIST with no evidence of metastasis and should be the initial therapy if the tumor is technically resectable and associated with acceptable risk for morbidity. All GISTs, in size of 2 cm or larger, should be resected. However, the management of incidentally encountered GISTs smaller than 2 cm remains controversial. For recurrent or metastatic GISTs, imatinib is the standard treatment (22,23). In patients with acromegaly, primary medical therapy may be considered particularly for those at high surgical risk, with tumors exhibiting extrasellar involvement (without chiasmal compression) and low likelihood of cure with surgery, and those expressing a preference for medical management (24). As consistent with the literature, our case was operated on for GIST, and somatostatin analogue was administered due to the patient's preference for medical treatment for acromegaly.

We diagnosed the patient with syncronous acromegaly and GIST, however, we could investigate no levels of IGF-1 receptor in GIST. Considering the interactions of IGF system in GISTs, we may speculate that the diagnosis of synchronous acromegaly may affect the prognosis. In order to detect such an effect, long-term follow-up is required, and further studies are needed to enlighten the association between acromegaly and GIST.

Conflicts of Interest

There are no conflicts of interest.

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