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CASE REPORT

Gastrointestinal stromal tumor presenting as a hormonally inactive adrenal mass

Márta Sereg · István Buzogány · Gábor Gonda · Zoltán Sápi · Éva Csöregh · Zsuzsa Jakab · Károly Rácz · Miklós Tóth

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Abstract Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Rarely, tumors with the same histological and immunohistochemical features arise in organs having no connection to the tubular gastrointestinal tract designated as extragastrointestinal stromal tumors (EGISTs). In this article, we report the first case of an EGIST presenting as a hormonally inactive adrenal mass. A 68-year-old woman with a 3-month history of right abdominal pain was clinically diagnosed as having a hormonally inactive right adrenal tumor sizing 15 cm in diameter. This mass and the tightly fixed right adrenal gland were resected *en bloc*. Histologically, the tumor was composed primarily of monomorphic spindle cells. Mitotic figure was 2–3 per 50 high power fields. Immunohistochemical analysis revealed strong positivity for CD117 (c-KIT) and smooth muscle actin (α-SMA), but negativity for beta-catenin, CD34, pankeratin, S-100, desmin, and H-caldesmon. Genetic analysis showed no mutations in *KIT* gene exons 9, 11, 13, and 17, and in exon 18 of the platelet-derived growth factor-2 receptor gene (*PDGFR*). The patient proved to be tumor free at the 18-month follow-up. This case under study demonstrates that EGIST should be included in the differential diagnosis of hormonally inactive adrenal tumors. CD117 (c-KIT) immunohistochemistry should be applied in the pathological workup of soft tissue adrenal tumors. This case is an additional example suggesting that the prognosis of even a very large EGIST is not definitely grave.

Keywords Adrenal tumor · Extragastrointestinal stromal tumor · KIT · CD117

M. Sereg · É. Csöregh · Z. Jakab · K. Rácz · M. Tóth (✉)
2nd Department of Medicine, Semmelweis University, Szentkirályi u. 46, Budapest 1088, Hungary
e-mail: totmik@bel2.sote.hu

Z. Sápi
1st Department of Pathology, Semmelweis University, Budapest, Hungary

I. Buzogány
Department of Urology, Péterfy Sándor Street Hospital, Budapest, Hungary

G. Gonda
Department of Pathology, Péterfy Sándor Street Hospital, Budapest, Hungary

Introduction

Hormonally inactive adrenal tumors are usually found incidentally, and most of them have either adrenocortical or adrenomedullary origin. However, the differential diagnosis of adrenal tumors includes a wide variety of other primary adrenal, periadrenal, and secondary tumors, and even pseudoadrenal and infectious masses [1, 2]. Apart from myelolipomas, mesenchymal adrenal tumors (including liposarcomas, angiosarcomas, desmoid, myelofibroblastic tumors, etc.) are very rare neoplasia consisting far less than 1% of all adrenal tumors in surgical [3] and even pathological series [4, 5].

In this study, we describe a case with a hormonally inactive large tumorous mass in the right suprarenal region which proved to be an extragastrointestinal stromal cell tumor (EGIST) by immunochemical analysis. We shall discuss the pathogenesis of EGISTs and different options for the drug treatment of these tumors. To our best knowledge, this is the first case which was detected as one of EGIST and operated as an adrenal tumor.

Case report

A 68-year-old-woman with a history of reflux esophagitis, postmenopausal osteoporosis, and benign nodular goitre was referred to our hospital because of a 3-month history of right abdominal dullness and pain radiating in the back. Ultrasonography revealed an inhomogeneous, well-margined, hypoechoic, and solid but partly cystic tumor with a size of 151 × 126 mm in the right suprarenal region. Computed tomography showed a round lesion with cystic components measuring 15 cm in diameter between the liver and the right kidney (Fig. 1). The right kidney was compressed and dislocated into caudal direction. Scintigraphic studies were not performed during clinical evaluation.

Hormonal evaluation including measurements of midnight and morning serum cortisol concentrations, morning serum dehydroepiandrosterone sulfate, aldosterone, 17-hydroxyprogesterone, testosterone and chromogranin A, plasma adrenocorticotropic hormone, and plasma renin activity failed to show any significant abnormality (Table 1). Morning plasma cortisol demonstrated a normal suppression after administration of 1-mg dexamethasone at midnight. 24-h urinary excretions of vanilmandelic acid, homovanillic acid, metanephrine, and normetanephrine were all within normal limits. Based on these hormone findings, the tumor was considered as a hormonally inactive adrenal tumor. Serum tumor markers including CA125, CA19-9, CA72-4, carcinoembryonic antigen, and alpha-fetoprotein were within reference ranges (data not shown).

In November, 2008, a 15-cm retroperitoneal tumor fixed to the right adrenal but without having any connection to the gastrointestinal tract was removed during laparotomy. The tumor showed no signs of invasiveness or seedling, and it seemed to be completely excised. Light microscopy confirmed the tight direct connection of the tumor with the histologically normal adrenal gland (Fig. 2). Histologically, the tumor was composed primarily of monomorphic spindle cells, in some areas embedded in an abundant loose myxoid stroma (Fig. 3). Mitotic figure was 2–3 per 50 high power fields. The pathological differential diagnoses considered in this case included various fibroblastic lesions and fibromatoses, schwannoma, amelanotic melanoma, leiomyosarcoma, and pheochromocytoma. Immunohistochemical analysis revealed strong positivity for CD117 (c-KIT)

Table 1 Laboratory data of the patient with incidentally discovered adrenal mass

	Hormonal findings	Reference range
Serum cortisol, 0800 h (μg/dl)	17.90	8.00–25.00
Serum cortisol after LDDST (μg/dl)	0.60	<3.6
Plasma adrenocorticotropic hormone (pg/ml)	30.00	7.20–63.30
Serum chromogranin A (ng/ml)	129.20	19.40–98.10
Plasma renin activity (ng/ml/h)	4.10	0.20–2.80
Serum aldosterone (ng/dl)	5.00	4.00–10.00
Serum 17-hydroxyprogesterone (ng/dl)	62.00	40.00–250.00
Serum DHEAS (μg/dl)	32.00	30.00–230.00
Serum testosterone (ng/dl)	5.00	4.00–60.00
Urinary vanilmandelic acid (mg/24 h)	2.50	1.80–6.70
Homovanillic acid (mg/24 h)	3.40	0.00–6.20
Urinary metanephrine (μg/24 h)	51.50	74.00–297.00
Urinary normetanephrine (μg/24 h)	218.50	105.00–354.00

DHEAS dehydroepiandrosterone sulfate, *LDDST* low dose dexamethasone test

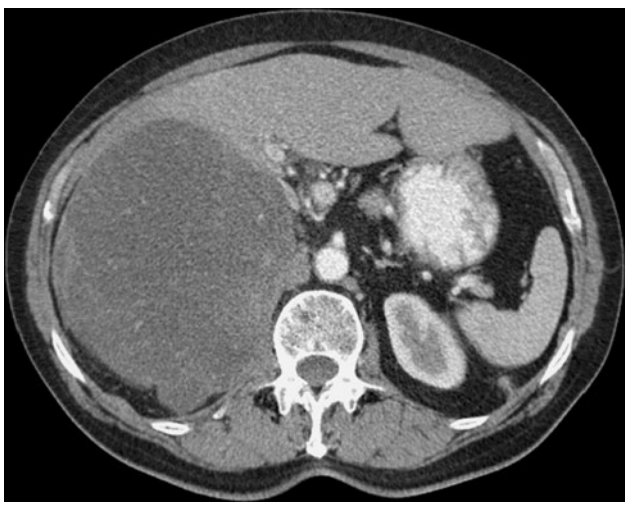

Fig. 1 Computed tomographic scan of the abdomen showing a voluminous right retroperitoneal mass

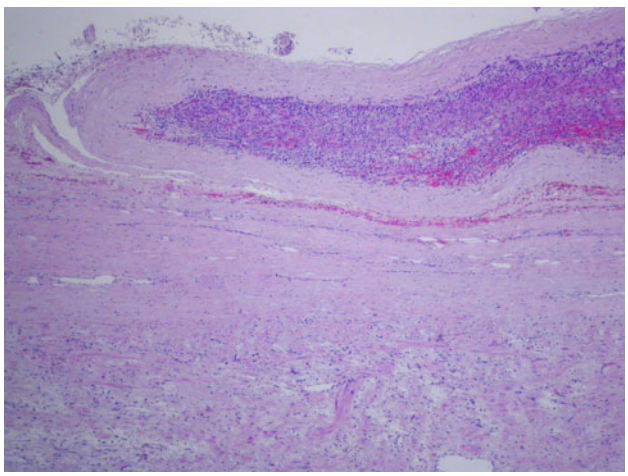

Fig. 2 Microscopic photograph showing spindle-cell tumor (*lower part*) tightly connected to the adrenal gland (*upper part*) (×25, H&E)

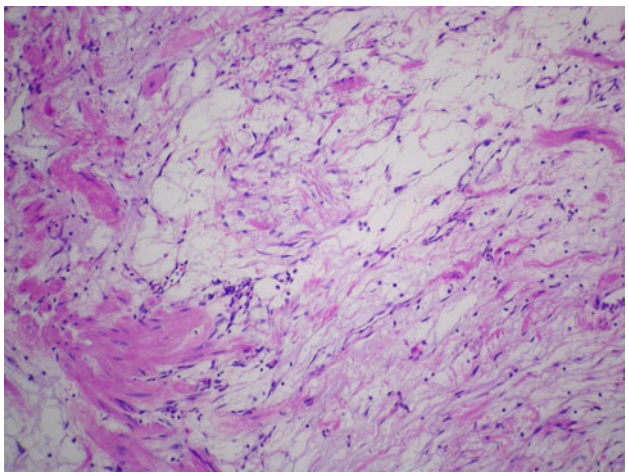

Fig. 3 Microscopic photograph showing interlacing bundles of spindle cells in a loose myxoid stroma (×40, H&E)

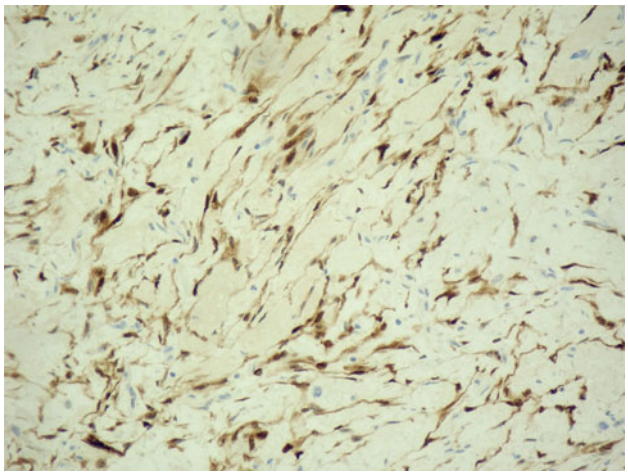

Fig. 4 Strong CD117 positivity in the spindle tumor cells (×60)

(Fig. 4) and smooth muscle actin (α-SMA), but negativity for beta-catenin, CD34, pan-keratin, S-100, desmin, and H-caldesmon. After a detailed review of intraoperative findings, gross appearance, light microscopic, and immunohistochemical results, a diagnosis of EGIST was established. Because of its large size, the tumor was considered as a high-risk neoplasm.

The *KIT* mutation status of the patient was analyzed by direct sequencing of the c-KIT gene. DNA was extracted from formalin-fixed, paraffin-embedded tissue sections according to the standard salting-out method. The primer sequences and the polymerase chain reaction conditions have been previously described by Penzel et al. [6]. The specific primer sequences used in PCR for c-KIT gene are shown in Table 2. Polymerase chain reaction products were directly sequenced on an ABI Prism 310 Genetic Analyzer (Applied Biosystems, Foster City, CA) using the BigDye Terminator v.3.1 kit (Applied Biosystems) according to the manufacturer's instructions. Sequence analysis showed no mutations in *KIT* gene exons 9, 11, 13, and 17, and in exon 18 of the platelet-derived growth factor-2 receptor gene (*PDGFR).*

Abdominal and chest CT scan performed 3, 9, and 12 months after surgical intervention did not show any signs of residual mass or metastases. At the 18-month follow-up, the patient was without any complaint, and abdominal ultrasonography was also negative.

Discussion

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract [7, 8], which develop most frequently within the stomach (about 60%) and the small intestines (about 30%). Rarely (in about 5% of all CD117-positive neoplasms [9]), tumors with the same histological and immunohistochemical features arise in organs such as the liver [10], gall bladder [11, 12], pancreas [13–15], omentum [16], rectovaginal septum [17], urinary bladder wall [18], and even in the retroperitoneum [9, 19, 20]. These mesenchymal tumors sharing immunohistochemical features of GISTs but having no connection to the tubular gastrointestinal tract are designated as extragastrointestinal stromal tumors (EGISTs) [20]. EGISTs arising in the rectovaginal septum, prostate, and scrotal mass are extremely rare. Our patient presented

Table 2 The specific oligonucleotide primer sequences used for the amplification of exons of the c-KIT gene

Exons	Primers	Seq 5′–3′	T_A (°C)	PCR product (bp)
9	KIT9-F	GCCACATCCCAAGTGTTTTATG	60	310
	KIT9-R	GAGCCTAAACATCCCCTTAAATTG		
11	KIT11-F	CCAGAGTGCTCTAATGACTG	60	223
	KIT11-R	AGCCCCTGTTTCATACTGAC		
13	KIT13-F	CTTGACATCAGTTTGCCAGTTGT	60	203
	KIT13-R	GACAGACAATAAAAGGCAGCTTG		
17	KIT17-F	TGGTTTTCTTTTCTCCTCCAA	60	184
	KIT17-R	GCAGGACTGTCAAGCAGAGA		

F forward, *R* reverse

with a huge retroperitoneal EGIST found in the right suprarenal region. Because of their rarity, the clinicopathologic and immunohistochemical features, prognostic parameters of EGISTs are far less elucidated, as compared to those of GISTs.

GISTs are believed to be derived from interstitial cells of Cajal (ICC) (pacemaker cells) which are present in the muscular layer of the gastrointestinal walls [21]. ICCs express CD117 (c-kit, a transmembrane tyrosine kinase receptor) and CD34 (a highly glycosylated cell surface antigen) [21]. Immunohistochemical demonstration of CD117 and/or CD34 is a hallmark of the pathological diagnosis of GIST [21–23]. In this case under study, immunohistochemical analysis revealed staining for CD117 and SMA, while beta-catenin, CD34, desmin, S-100 protein, and H-caldesmon staining were absent.

While the origin of GISTs seems to be unambiguously clarified, the histopathogenesis of EGISTs is partially controversial [9]. It has been suggested that EGISTs may develop from the pluripotent mesenchymal stem cells, while others proposed that they may be the consequence of an extensive outgrowth of GISTs loosing their contact with the gut wall [9]. Soft tissue tumors thought to be of adrenal origin may develop both outside and inside of the adrenal capsule; adrenal leiomyosarcomas have been proposed to originate from smooth muscle cells associated with the central adrenal vein or its tributaries. The EGIST tumor of our patient had a distinctively tight connection with the fibrous capsule of the adrenal gland, which may suggest but certainly does not prove its adrenal origin. More importantly, tumoral invasion or intra-adrenal seedling was not observed during the detailed pathological examination.

Since pre- and post-operative imaging did not show any sign of residual mass or metastatic disease until the 18th postoperative month, medical oncotherapy was not started. In this context, we have to emphasize that it is presently unknown whether the generally accepted prognostic indicators of GISTs [7] can be applied to EGISTs. The prognostic system of GISTs currently used is based on tumor size and mitotic activity [7]. While GISTs larger than 10 cm in site are proposed to be classified as high-risk tumors (independently of mitotic activity) [7], some authors believe that this may not be applicable for EGISTs (Yamamoto's prognostic criteria for EGISTs [24]). Some case reports [17, 25] and a recent review of five cases of pancreatic EGISTs [15] suggest that despite the usually large size of these tumors, the prognosis of EGISTs is frequently excellent.

The treatment of choice of resectable GISTs is surgically removed. While traditional chemotherapeutic agents are ineffective in the treatment of GISTs [26], recently a very effective drug therapy has been developed and proved to be beneficial in over 80% of patients with GIST. The tyrosine kinase inhibitor imatinib mesylate is the standard first-line treatment in patients with metastatic or unresectable tumors. The c-KIT mutation status may play a role in planning drug treatment since patients with c-KIT exon 11 mutations are sensitive to standard dose imatinib (400 mg/day), while patients with exon 9 mutations are suggested to be treated with the initial daily dose of 800 mg [27]. Patients who develop resistance to imatinib may be successfully treated with sunitinib, a new member of tyrosine kinase inhibitors [26]. Most recent reports indicate that imatinib may be useful even in an adjuvant setting, as its use after resection of the primary GIST increased the recurrence-free survival of seemingly tumor-free patients compared with placebo [28].

In summary, the case under this study demonstrates that EGISTs should be included in the differential diagnosis of hormonally inactive adrenal masses and that CD 117 [c-KIT] immunohistochemistry is essential for precise and specific diagnosis of GIST among adrenal tumors. The recognition of GISTs in patients with metastatic or unresectable tumors may give the opportunity for the administration of highly effective targeted drug therapy with tyrosine kinase inhibitors.

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