Retroperitoneal Extra-gastrointestinal Stromal Tumor Presenting With Lower Urinary Tract Symptoms

Yu-Chi Chen¹, Jen-Wei Tsai², Hsin-Pao Chen³, I-Chang Lin⁴, Victor C. Lin¹,⁵*

¹Division of Urology, Department of Surgery, E-Da Hospital, Kaohsiung, Taiwan
²Department of Pathology, E-Da Hospital, Kaohsiung, Taiwan
³Division of Colorectal Surgery, Department of Surgery, E-Da Hospital, Kaohsiung, Taiwan
⁴Department of Radiology, E-Da Hospital, Kaohsiung, Taiwan
⁵Department of Nursing, I-Shou University, Kaohsiung, Taiwan

Gastrointestinal stromal tumors are rare soft-tissue neoplasms, the incidence of which is 1–3% of all malignant gastrointestinal tumors. Tumor size is reported to be a major determinant of recurrence in patients with resectable gastrointestinal stromal tumors. Here, we describe our experience in managing a large extra-gastrointestinal stromal tumor arising from the retroperitoneum.

1. Introduction

The term gastrointestinal stromal tumor (GIST) was first introduced by Mazur and Clark¹ to describe gastrointestinal non-epithelial tumors lacking microscopic evidence of smooth muscles or characteristics of neural immunoreactivity. They are thought to originate from the interstitial cells of Cajal, and are relatively rare soft-tissue neoplasms with an estimated incidence of 14.5 per 1,000,000 patients affected.² They are most commonly found in the stomach (50–60%), small intestines (20–30%), colon and rectum (10%), and esophagus (5%).³

As vascular tumors, GISTs primarily present with gastrointestinal bleeding (50%), palpable mass (35%, sometimes with obstructive features), pain (20%) and, rarely, as an incidental finding. These lesions often present with only nonspecific symptoms such as bloating and early satiety unless they ulcerate, bleed, or grow large enough to cause pain or obstruction.⁴

In contrast to GIST, extra-gastrointestinal stromal tumor (EGIST) represents an unusual location of GIST without clinical evidence of a gastrointestinal primary, and is exceedingly rare. Although the majority of GISTs are located in the GI tract, some GISTs occur in the omentum, mesentery and retroperitoneum.⁴ However, EGIST of the prostate and urinary bladder, associated with urinary tract symptoms, have been reported.⁵,⁶ Here, we report the case of a 47-year-old man diagnosed with primary retroperitoneal EGIST and describe our experience in the management of the large EGIST.

2. Case Report

A 47-year-old male consulted at the Urology Outpatient Clinic for complaints of progressive dysuria and constipation for 7 months. There was no gross hematuria or bloody stool. The patient denied having any other medical history except for right herniorrhaphy for right inguinal hernia in September 2006. Physical examination revealed a large, fixed and firm non-tender mass protruding from the lower abdomen. There were also varicoceles noted over bilateral spermatic cords symmetrically. Magnetic resonance imaging demonstrated a pelvic mass about 20 x 10 x 10 cm in size, causing left-sided displacement of the rectum and urinary bladder (Figure 1). Colonoscopy and cystoscopy revealed external compression of the mass without evidence of invasion.

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The hypervascular pelvic tumor adhered tightly to the urinary bladder. Hence, exploratory laparotomy for en bloc resection of the tumor, urinary bladder and prostate was performed. A 4-cm long laceration injury of the low rectum was noted perioperatively and was repaired with 3-0 silk interrupted sutures. Loop sigmoid colostomy over the left lower quadrant of the abdominal area and ileal conduit over the right lower quadrant were then performed.

Postoperatively, the patient was transferred to the intensive care unit for 2 days of close monitoring. Partial parenteral nutrition was started on the 4th postoperative day for ileus, which subsided on the 9th day. He was discharged on the 13th day. Chest X-ray, abdominal sonography and abdominal computed axial tomography were performed every 6 months thereafter. In addition, physical examination was done every 2 months. He was disease-free with no evidence of local recurrence or distant metastases at the 30-month follow-up.

Grossly, the soft tissue tumor measured 16×10×9 cm, was encapsulated, and was elastic-to-firm with multilobular and flesh-colored cut surface. Hemorrhage and necrosis were not obvious. There was no evidence of involvement of the gastrointestinal tract, omentum, mesentery, prostate, seminal vesicle or urinary bladder. Microscopically, the tumor was composed of nests and sheets of epithelioid cells bearing pale-to-eosinophilic cytoplasm and round-to-ovoid nuclei with indistinct cell borders. There was some degree of nuclear atypia with increased mitotic activity. Vascular spreading was focally seen but tumor necrosis was not obvious (Figure 2).

Immunohistochemical studies showed that the tumor cells were negative for cytokeratin, CD117, S100, desmin and smooth muscle actin (Figure 2). The tumor cells only expressed vimentin, CD34 and CD99. According to the results of immunohistochemical and histologic examinations, carcinoma, neurogenic tumor and smooth muscle neoplasm were excluded. However, the possibility of EGIST was considered due to the epithelioid morphology, which is a frequent histologic finding of CD117(−) GISTs.

Subsequent KIT and platelet-derived growth factor receptor-α (PDGFRA) mutational analysis by polymerase chain reaction failed to reveal any detectable mutation in both genes. According to the literature, about 10% of GISTs have wild-type KIT and PDGFRA genes, and probably a different pathogenetic pathway leading to tumor formation. Our case may belong to this subgroup after excluding other soft tissue tumor entities. Thus, primary retroperitoneal EGIST was still considered.

3. Discussion

EGISTs are a group of GISTs that are located at unusual sites without clinical evidence of a gastrointestinal primary. The clinical, pathological and prognostic features of GISTs are widely known, while there is a paucity of data on EGISTs. Most EGISTs arise from the omentum and mesentery, and have immunopathologic comparability with GISTs in the digestive tract. In a series by Agaimy and Wunsch,7 14 of 200 cases with typical morphologic and immunohistochemical features of GIST were initially described as EGIST. However, after detailed review of the so-called EGISTs, associated gastrointestinal mucosa was found to be present. EGIST also arises in the retroperitoneum, although the incidence is exceedingly rare.8 Other unusual origins, such as the prostate and urinary bladder, have likewise been reported. Clinicians should therefore be aware of this possibility when a retroperitoneal mass is encountered.
GISTs show lineage differentiation similar to the interstitial cells of Cajal and frequently express CD117 (KIT protein) diffusely and strongly. Microscopically, tumor cells in GISTs are usually spindle- or epithelioid-shaped. However, there are morphologic mimics simulating carcinoma, smooth muscle neoplasm, neurogenic tumor, and plasmacytoma. Under such circumstances, a careful histologic examination with immunohistochemical study using a panel of markers, or even gene mutational analysis, is indicated.

In immunohistochemical studies, GISTs are more often positive for CD117, CD34 and smooth muscle actin than for cytokeratin, desmin and S100. A small portion of GISTs lacks CD117 expression. Most of them have mutant PDGFRA gene and epithelioid features. Most GISTs also have gain-of-function mutation of CD117 (80–85%), although some demonstrate mutation of the PDGFRA gene (5–10%). About 10% have wild-type KIT and PDGFRA genes. In GISTs lacking KIT and PDGFRA mutations, there are probably other mechanisms that lead to tumor formation.

The histologic features and immunophenotype of EGISTs are similar to those of GISTs, showing mainly spindle or epithelioid cytomorphology, as well as CD117 (100%) and CD34 (50%) reactivity. There are limited data on the cytogenetic and mutational status of EGISTs. Instead, it is presumed that they possess similar findings as GISTs.

EGISTs and GISTs are often asymptomatic until they reach a large size and cause mass effect, bleeding or rupture. Some patients with EGISTs have been diagnosed by transrectal ultrasound-guided prostate biopsy due to abnormal findings on digital rectal examination. Neoadjuvant therapy with imatinib mesylate followed by prostatectomy have been performed; results indicate partial response and disease stability longer than 12 months, with updated data showing a disease-free survival of 65% at 21 months. However, the possibility of tumor spread or rupture, abscess formation, or fecal fistula should be a preoperative concern before surgical biopsy. In addition, biopsy may incompletely sample the lesion and a false diagnosis is possible in some cases. Therefore, this should not be performed if the tumor is potentially resectable.

Except for those that are unresectable or metastatic, surgery remains the standard treatment for EGIST. Complete en bloc removal of EGIST and the surrounding organs that are involved is required. The recurrence rate after surgery in reported series ranges from 17% to 24%. Historically, surgery is considered to be the only effective therapy because GISTs are known to be resistant to conventional cytotoxic chemotherapeutic regimens. Recently, promising results from several studies have led to the introduction of targeted therapy—imatinib (a c-kit tyrosine kinase inhibitor)—for treating GISTs, after it was proven to

Figure 2  (A) The tumor grew in a lobular pattern and formed sheets and nests with epithelioid features (hematoxylin & eosin, 40×). (B) Increased mitotic activity with nuclear atypia was noted (hematoxylin & eosin, 400×). (C) Immunohistochemical stain of tumor cells was negative for CD117 (400×).
be safe and efficacious. Targeted therapy is indicated and effective for positive KIT and unresectable or metastatic GISTs as adjuvant or neoadjuvant therapy. However, in cases of negative immunohistochemical staining for c-kit and tumor-free surgical margins, additional treatment with imatinib or chemotherapy is not indicated.

In the past, numerous retrospective analyses have tried to identify prognostic factors. Only tumor size and the presence of mitotic figures have been accepted as the most useful predictive factors of poor outcome with good reproducibility and statistical consistency. In a retrospective study of 100 patients with resectable GISTs, multivariate analysis demonstrated that tumor size > 10 cm was associated with higher recurrence rates ($p = 0.032$) and was the only independent prognostic factor of poor survival ($p = 0.020$).

A follow-up protocol is recommended, which should include abdominal sonography and abdominal computed axial tomography every 6 months in the first year and annually thereafter, or whenever recurrence is suspected. Due to the large size of the EGIST, our patient needed close follow-up.

References