Gastrointestinal stromal tumors presenting as pelvic masses: Report of two cases

S. Erkanli[1], *M.D., Specialist*; **F. Kayaselcuk**[2], *M.D., Assoc. Prof.*; **N. Törer**[3], *M.D., Specialist*; **F. Bolat**[2], *M.D., Specialist*; **E. Tarim**[1], *M.D., Assist. Prof.*; **E. Simsek**[1], *M.D., Specialist*; **E. Kuscu**[1], *M.D., Assoc. Prof.*

[1]*Department of Obstetrics & Gynecology,* [2]*Department of Pathology,* [3]*Department of Surgery, Baskent University School of Medicine, Adana (Turkey)*

Summary

We present two cases of gastrointestinal stromal tumors (GISTs) that presented as pelvic masses. These tumors can present diagnostic problems and they may be difficult to discover preoperatively. GISTs are neoplasms that can be diagnosed utilizing immunohistochemistry, especially detecting CD117 (c-kit) reactivity along with associated histological features. GISTs, should be considered in the differential diagnosis of ovarian tumors especially when imaging studies and rectovaginal examination findings are inconclusive and vague. Histologic diagnosis of these tumors are important considering the efficacy of tyrosine kinase inhibitor therapy after surgery in such cases.

Key words: GIST; Pelvic mass; CD117; c-kit; Imatinib mesylate.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract [1]. CD117 (c-kit proto-oncogene protein) expression is the most prominent feature of GISTs [2]. They can present anywhere in the GI tract from the lower esophagus to the anus. Most occur in the stomach (60-70%) and small intestine (25-35%) where they are more aggressive [3]. GISTs primarily develop in the gastrointestinal (GI) tract, however they may also develop as primary tumors outside the GI tract such as in the omentum, retroperitoneum or the mesentery of the small bowel [4, 5]. These tumors, which are reported to be histologically similar to GISTs, are referred to as extra-gastrointestinal tumors (EGISTs) [4]. The most important differential diagnoses are true smooth muscle tumors, GI schwannoma and undifferentiated sarcomas. As the general radiographic findings of the tumor are very non-characteristic, GISTs can present diagnostic problems and they may be difficult to discover preoperatively.

There are only three reports of GISTs presenting as a pelvic mass in women in the literature and here we present the fourth report of two cases of GISTs that presented as pelvic masses.

Case Reports

Case 1

A 65-year-old patient presented with recent onset pelvic pain. A computed tomography scan reported a partially calcified, lobulated solid mass located at the uterine fundus appearing to be myoma uteri. At rectovaginal examination an irregular mass located anteriorly to the uterus was palpated. Tumor markers (CA125, CEA, CA19-9, CA15-3) were normal. Colonoscopy revealed no abnormalities. At laparotomy a 9 cm tumor mass originating in the small bowel but located in the pelvis was identified along with round shaped solid fragile metastatic implants on the left anterior peritoneum, bladder peritoneum and omentum. A suboptimal debulking procedure was performed the after a frozen section diagnosis of either GIST or malignant mesothelioma. In addition an ovarian wedge biopsy at the involved right side was performed. The ovaries and uterus looked completely normal. Serial sections of the mass showed neoplasm infiltrating surrounding tissues and formed by epithelioid cells with round vesiculated nuclei, prominent nucleoli, and large eosinophilic cytoplasm. In some areas circular muscle fibers and mature adipose tissue was surrounding the tumor. Bleeding areas, calcification and areas of necrosis were present across the tumor. The tumor showed high cellularity and mild atypia. There were 11 mitoses per 50 HPF. Tumor cells were diffusely positive for CD117, focally positive for S-100, and negative for calretinin and EMA (Figure 1). The Ki-67 index was 5%. The ovarian biopsy specimen was free of tumor. The findings were concordant with a histologic and immunohistochemical diagnosis of GIST arising from serosa of the small bowel. The patient was given adjuvant oral imatinib mesylate (STI-571 [Gleevec]; Novartis Pharmaceuticals Corp, East Hanover, NL) therapy, and is now free of disease after eight months.

Case 2

A 78-year-old patient presented with right lower quadrant pain of one week's duration. On rectovaginal examination an irregular solid mass starting from the anterior side of the uterus and going up to the umbilicus was palpated. Ultrasound revealed a suprapubic 12 cm partially calcified mass originating from the adnexa or colon. Tumor markers (CA125, CEA, CA19-9, CA15-3) were normal except for lactate dehydrogenase, which was elevated to 252 IU/l. Computed tomography

Revised manuscript accepted for publication July 22, 2005

Fig. 1

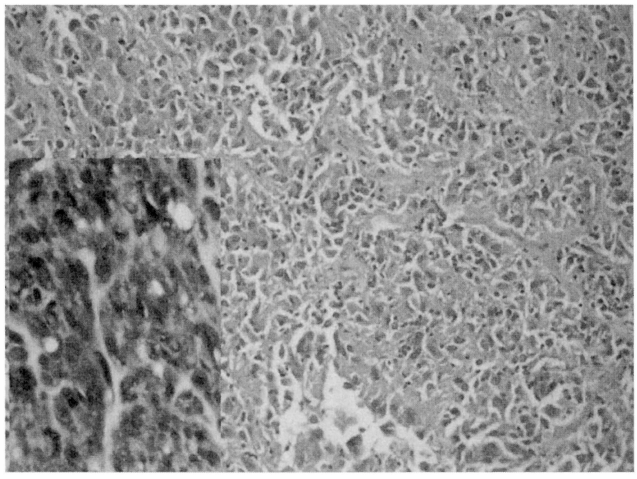

Fig.

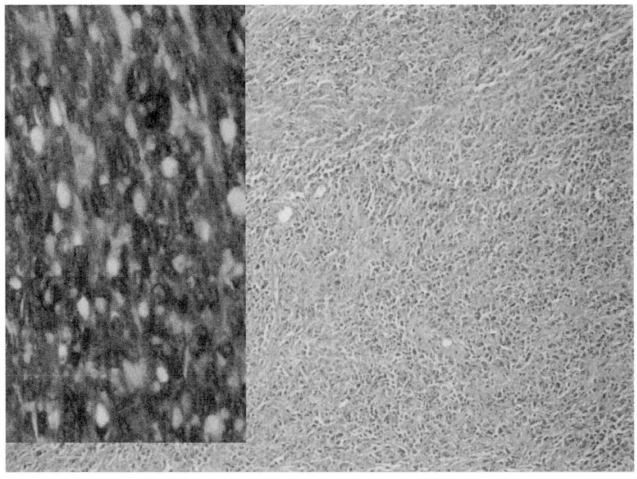

Figure 1. — Epitheloid GIST (H&E x 200); Inset: Immunohistochemistry - CD117.
Figure 2. — Spindle cell GIST (H&E x 200); Inset: Immunohistochemistry - CD117.

(CT) showed a pelvic mass and normal bowels. At laparotomy a 20 cm irregular solid mass that looked like a right ovarian tumor, extending high into the abdominal cavity and fixed to the small bowel, was observed. The mass was resected with a 10 cm segment of the small bowel followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. Frozen section diagnosis was low-grade malignant mesenchymal tumor. Serial sections showed a neoplasm formed by spindle cells with round hyperchromatic nuclei and prominent nucleoli forming bundles. Pleomorphism, necrosis and 26-27 mitoses per 50 HPF were present. Immunohistochemical studies were diffusely positive for CD117 (c-kit) and vimentin, focal and weak for S-100 and SMA (Figure 2). The small bowel also showed tumor of the same morphology, where tumor was present on the muscular and serosal layers. Final pathological diagnosis was GIST. The patient did not receive any adjuvant therapy and is alive and well after seven months.

Discussion

In the earlier literature GISTs were classified as smooth muscle tumors which were variants of benign and malignant leiomyomas such as epithelioid leiomyoma, leiomyomablastoma or leiomyosarcoma. However GISTs are now considered to be distinctive entities distinguished from leiomyoma variants and other mesenchymal tumors [6]. Hirota *et al.* [7] first described the c-kit gene mutation in GISTs. Several recent studies have also reported mutations or phosphorylation and activation of the c-kit gene [8]. GISTs are considered to originate from interstitial cells of Cajal, the gastrointestinal pacemaker cells, as these cells also express c-kit and CD34 [7]. Recently, Miettinen *et al.* [4] and then Reith *et al.* [5] reported tumors originating primarily from the omentum, mesentery and retroperitoneum, which were histologically and immunophenotypically similar to their gastrointestinal counterparts, and termed these tumors extra-gastrointestinal stromal tumors.

GISTs that have a low mitotic rate such as < 5/50 HPF usually have a benign behavior. However, some of these mitotically inactive tumors are definitely known to metastasize, which suggests that a low mitotic count is inadequate for ruling out malignant behavior. A combination of low mitotic count and tumor size smaller than 5 cm is considered more informative of good prognosis. Tumors larger than 5 cm or with a mitotic rate over 5 per 50 HPF are generally reported to be more aggressive [3]. Aneuploidy on DNA flow cytometry, presence of coagulative tumor cell necrosis, and a high Ki-67 index are among other proposed prognostic factors. Another important factor is the site of the tumor, as small intestinal GISTs of the same size and mitotic count seem to behave more aggressively than gastric ones.

CA125 was normal in both our patients, while in one patient lactate dehydrogenase (LDH) was found to be elevated preoperatively. To our knowledge serum tumor markers such as CA125 and LDH have not been specifically evaluated on GIST patients.

Histologically GISTs vary from cellular spindle cell tumors to epithelioid and pleomorphic ones. GISTs are by definition CD117 (c-kit) positive, whereas positivity for nestin and CD34 (60-70%) are also characteristic but less specific features. Smooth muscle actin (SMA) and heavy caldesmon are often expressed, however desmin and S-100 are usually negative, but can rarely be expressed in 5-10% of GISTs. Due to their mesenchymal character GISTs are typically strongly positive for vimentin [3]. Both our cases were strongly positive for CD117, whereas focally positive for S-100.

Complete surgical resection followed by observation had been the mainstay of treatment for GISTs. Adjuvant therapy with systemic or intraperitoneal chemotherapy, and radiotherapy had been used with little success. CD117 expression and c-kit mutations are important features of GISTs, not only for pathological diagnosis but also in defining a treatment alternative. Imatinib mesylate is an anti-tyrosine kinase drug that was originally developed for the treatment of chronic myeloid leukemia [9]. This drug also selectively inhibits the activity of the c-kit

among other tyrosine kinases such as abl, bcr-abl and PDGFR. Recently, the efficacy of this drug has been reported for the treatment of unresectable and metastatic GISTs [10]. Other reports have confirmed the safety and effectiveness of imatinib mesylate in advanced GISTs. Both of our cases were diffusely positive for CD117. We also used Imatinib mesylate for one of our GIST patients, while the other patient with a diagnosis of GIST refused any further therapy. Currently, there is intense scrutiny whether certain c-kit mutations play a role in predicting the response to this new therapy method.

Neither of the two presented patients had involvement of the ovaries or uteri with stromal tumor metastasis. With this at hand we believe there is no need for resection of the reproductive organs if they seem normal, when encountered with gastrointestinal stromal tumors at laparotomy performed with the expectation of a gynecologic neoplasm. We also believe that it is important to recognize GISTs in a situation where at times they are difficult to differentiate (as in our case 2) between an ovarian tumor metastasizing to the small bowel or the mesentery in contrast to a primary tumor arising from the small bowel or the mesentery and seemingly originating from the ovaries. Recognizing such a diagnostic possibility might give the advantage of resecting that segment of the small bowel without trying to dissect a tumor and inadvertently cutting it through its site of origin.

GISTs are neoplasms that can be diagnosed utilizing immunohistochemistry, especially detecting CD117 (c-kit) reactivity along with associated histological features. GISTs although rarely present in the pelvic region, should be considered in the differential diagnosis of ovarian tumors, especially when the imaging studies and pelvic examination findings are inconclusive and vague.

References

[1] Fletcher C.D., Berman J.J., Corless C. *et al.*: "Diagnosis of gastrointestinal stromal tumors: a consensus approach". *Hum. Pathol.*, 2002, *33,* 459.

[2] Miettinen M., Sobin L.H., Sarlomo-Rikala M.: "Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT)". *Mod. Pathol.*, 2000, *13,* 1134.

[3] Miettinen M., Lasota J.: "Gastrointestinal stromal tumors (GISTs): definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis". *Virchows Arch.*, 2003, *438,* 1.

[4] Miettinen M., Monihan J.M., Sarlomo-Rikala M., Kovatich A.J., Carr N.J., Emory T.S. *et al.*: "Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases". *Am. J. Surg. Pathol.*, 1999, *23,* 1109.

[5] Reith J.D., Goldblum J.R., Lyles R.H., Weiss S.W.: "Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome". *Mod. Pathol.*, 2000, *13,* 577.

[6] Miettinen M., Sarlomo-Rikala M., Sobin L.H. *et al.*: "Gastrointestinal stromal tumors and leiomyosarcomas in the colon: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases". *Am. J. Surg. Pathol.*, 2000, *24,* 1339.

[7] Hirota S., Isozaki K., Moriyama Y. *et al.*: "Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors". *Science,* 1998, *279,* 577.

[8] Rubin B.P., Singer S., Tsao C. *et al.*: "KIT activation is a ubiquitous feature of gastrointestinal stromal tumors". *Cancer Res.*, 2001, *61,* 8118.

[9] Druker B.J., Talpaz M., Resta D.J. *et al.*: "Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia". *N. Engl. J. Med.*, 2001, *344,* 1031.

[10] Dagher R., Cohen M., Williams G. *et al.*: "Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors". *Clin. Cancer Res.*, 2002, *8,* 3034.

Address reprint requests to:
S. ERKANLI, M.D.
Dept. Ob./Gyn. Baskent University
School of Medicine
Seyhan-Adana (Turkey)