Gastrointestinal Stromal Tumor: A Rare Abdominal Tumor

Citation
Shaheen, Shagufta, and Achuta K. Guddati. 2013. Gastrointestinal stromal tumor: a rare abdominal tumor. Case Reports in Oncology 6(1): 148-153.

Published Version
doi:10.1159/000350061

Permanent link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:11181010

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

Share Your Story
The Harvard community has made this article openly available. Please share how this access benefits you. Submit a story.

Accessibility
Gastrointestinal Stromal Tumor: A Rare Abdominal Tumor

Shagufta Shaheen Achuta K. Guddati

Department of Internal Medicine, Massachusetts General Hospital, Harvard Medical School, Harvard University, Boston, Mass., USA

Key Words
Gastrointestinal stromal tumor · Abdominal tumor · CD117 · Rare tumor · Size · Gastric tumor

Abstract
Gastrointestinal stromal tumors (GISTs) are rare abdominal tumors which arise from the interstitial cells of Cajal in the gastrointestinal tract. Gastric GISTs are the most commonly seen GIST tumors and may grow to a very large size. They are often associated with abdominal pain, anorexia and weight loss. Most of them can be detected by CT. These tumors have been found to harbor mutations in CD117 which causes constitutional activation of the tyrosine kinase signaling pathway and is considered to be pathognomonic. Tyrosine kinase inhibitors such as imatinib have revolutionized the treatment of these tumors, which are otherwise resistant to conventional chemotherapy and radiotherapy. Although surgical resection is the mainstay of treatment, tyrosine kinase inhibitors have been useful in prolonging the recurrence-free survival of these patients. Resistance to imatinib has been reported in GISTs with specific mutations. We present a case of gastric GIST which grew to a very large size and was associated with abdominal pain and weight loss. It was successfully resected and the patient was commenced on imatinib therapy.

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that may arise from any part of the gastrointestinal tract. GISTs have been shown to originate from the interstitial cells of Cajal, which are located in the submucosal and myenteric plexus of the gastrointestinal tract [1–3]. GISTs are rare tumors and comprise less than 1% of all gastrointestinal tumors, and it is estimated that up to 6,000 new cases are diagnosed in the US every year [4, 5]. This likely represents an underestimation as many smaller-sized GISTs may go undetected [6, 7]. They are rarely detected in children and present with metastasis in adults over the
age of 50 years [8]. An equal distribution in gender has been observed though there have been reports of a male preponderance [9]. GISTs present as round masses with clearly defined borders arising from the submucosal layer. Based on their histology, they are divided into eight subtypes, but all of them stain for the stem cell factor receptor (CD117/KIT) [10]. GISTs which do not express KIT may express alpha-type platelet-derived growth factor receptor (PDGFRA), protein kinase C theta (PKC-θ) and discovered on GIST-1 (DOG-1) [11–13]. Malignancies such as melanoma, mastocytoma, Ewing’s sarcoma, lung small cell carcinoma, etc. may also express KIT, and their presence in the gastrointestinal tract likely represents metastases and they need to be distinguished from GISTS [14–16]. An autosomal dominant pattern of inheritance has been described in familial GIST [17–19]. Mutations involving succinate dehydrogenase subunits B, C and D have been observed in the familial form of GIST [20]. GISTs have been observed in the small intestine of patients with neurofibromatosis type-1 [21, 22]. A separate inherited syndrome consisting of paragangliomas and GISTs has also been described [23].

Gastric GISTs are known to reach sizes exceeding 40 cm and have a better prognosis than intestinal GISTs of similar size and mitotic rate [10]. Extraintestinal GISTs (EGISTs) have been reported in the gall bladder, urinary bladder and rectovaginal septum [24–26]. EGISTs are considered to be metastases but paradoxically exhibit a better overall prognosis [27]. CT scans and endoscopic ultrasound are commonly used diagnostic modalities.

Case Summary

The patient is a 41-year-old male with a past medical history significant for type 1 diabetes, gastroesophageal reflux disease and hypertension. He presented in our gastroenterology clinic with abdominal discomfort, distention and unintentional weight loss of 24 pounds over the past 2 months. The patient underwent a CT scan of the abdomen which revealed a 20-cm epigastric mass with several areas of necrosis suggestive of hemangioma of the liver. The patient was scheduled to be seen in the general surgery clinic, but his symptoms worsened and he presented to our hospital with a fever of 102 F and worsening abdominal pain. A repeat CT scan of the abdomen revealed a large heterogeneous mass measuring 31 × 10 × 26 cm, predominantly solid and containing small cystic areas in the right abdomen and pelvis. The patient was admitted to the medical service where he became hypotensive and anemic with a significant hematocrit drop. The patient was hemodynamically stabilized and underwent an arterial embolization of the gastroduodenal artery to control the hemorrhage. Thereafter, the patient underwent resection of the tumor en bloc with the stomach, gastrectomy, Billroth II reconstruction and wedge biopsy of segment six of the liver. The patient tolerated the procedure well, with no significant post-operative complications. On gross examination, the tumor measured 34 cm in its greatest dimension, with notable hemorrhage and necrosis (fig. 1). Microscopic examination and immunohistochemical staining confirmed the tumor to be a GIST with tumor cells staining positive for CD117 (fig. 2a, b). Segment 6 of the liver was reported as metastatic GIST. The patient was started on chemotherapy with imatinib.

Discussion

The most common site of occurrence for GISTs is the stomach (60%) followed by the small intestine (30%) [28]. It is difficult to distinguish extraintestinal GISTs from metastases.
The mainstay of management of GISTs is surgical resection when possible. Regional lymphadenectomy is not advocated as GISTs have not been observed to metastasize to lymph nodes [29, 30]. However, there is a very high risk of recurrence if there is intra-peritoneal rupture or spillage during surgery [31]. The 5-year overall survival in patients with complete resection has been estimated to be superior compared to that of patients with incomplete resection (42 vs. 95%) [32]. Tyrosine kinase inhibitors such as imatinib have been successfully used to treat GISTs [33]. KIT mutations cause constitutive activation of tyrosine kinase and the most common mutations are duplications in the 3’ region of exon 11 of the KIT gene. Mutations involving codons 557–558 and point deletions carry a worse prognosis [34]. Imatinib resistance has been noted in patients with PDGFRA mutations in the absence of KIT mutations [35]. Chromosomal losses at 1p, 14q (gastric GISTs), 15q (intestinal GISTs) and 22q have been observed, and the type of mutations have been noted to correlate with the response to imatinib [36, 37]. Mitotic rate, tumor size and location have been utilized for predicting the risk of progression in completely resected primary GISTs [38, 39].

Considering that GISTs may reach large sizes and therefore making surgical resection risky, neoadjuvant therapy with tyrosine kinase inhibitors has been utilized to reduce their size. This strategy has been used to reduce surgical morbidity and improve the operability of these tumors [40, 41]. However, the mutational status (KIT vs. PDGFRA) of the tumor largely determines the effect of preoperative tyrosine kinase inhibitor therapy and monitoring of response by PET scan is advised. A duration of 4–6 months of neoadjuvant therapy with continuous monitoring has been recommended [42, 43]. Up to 66% of patients with high-risk GISTs who have undergone resection experience recurrence [44]. The American College of Surgeons Oncology Group (ACOSOG) Z9000 clinical trial showed that patients with PDGFRA mutations had the best outcomes with 90% recurrence-free survival at 3 years. The ACOSOG Z9001 trial involved adjuvant therapy with 400 mg of imatinib and resulted in 98% recurrence-free survival [45]. The dosing and the type of tyrosine kinase inhibitors that are optimal for the patient’s treatment depend on the type of mutation [46–48]. Abdominal CT, MRI and PET scans have been used for follow-up and for monitoring the progression of the disease [49]. The follow-up frequency has ranged from months to years and depends on the risk profile of the initial disease [50].

Acknowledgement

The study has not been presented in any form in any meeting or forum and is not under consideration in any other journal. The authors declare that there was no funding for this study.

Disclosure Statement

The authors declare no conflict of interest.

References

1. Mazur MT, Clark HB: Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 1983;7:507–519.
Walker P, Dvorak AM: Gastrointestinal autonomic nerve (GAN) tumor. Ultrastructural evidence for a newly recognized entity. Arch Pathol Lab Med 1986;110:309–316.

Robinson TL, Siracar K, Hewlett BR, Chorneyko K, Riddell RH, Huizinga JD: Gastrointestinal stromal tumors may originate from a subset of CD34-positive interstitial cells of Cajal. Am J Pathol 2000;156:1157–1163.

Judson I, Demetri G: Advances in the treatment of gastrointestinal stromal tumours. Ann Oncol 2007;18(suppl 10):x20–x24.

Corless CL, Heimrich MC: Molecular pathobiology of gastrointestinal stromal sarcomas. Annu Rev Pathol 2008;3:557–586.

Kawanowa K, Sakuma Y, Saburui S, et al: High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 2006;37:1527–1535.

Agaimy A, Wunsch PH, Hofstaecker F, et al: Minute gastric schwannomas of the stomach (GIST tumourlets) are frequent and may show c-KIT mutations. Hum Pathol 2007;38:113–120.

Nowain A, Bhakta H, Pais S, Kanel G, Verma S: Gastrointestinal stromal tumours: clinical profile, pathogenesis, treatment strategies and prognosis. J Gastroenterol Hepatol 2005;20:818–824.

Miettinen M, Sarlomo-Rikala M, Lasota J: Stromal tumours of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol 2005;29:1373–1381.

Sevinc A, Camci C, Yilmaz M, Buyukhatipoglu H: The diagnosis of C-kit negative GIST by PDGFRα staining: clinical, pathological, and nuclear medicine perspective. Onkologie 2007;30:645–648.

Motegei A, Sakurai S, Nakayama H, Sano T, Oyama T, Nakajima T: PKC theta, a novel immunohistochemical marker for gastrointestinal stromal tumours (GIST), especially useful for identifying KIT-negative tumors. Pathol Int 2005;55:106–112.

West RB, Corless CL, Chen X, et al: The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumours irrespective of KIT or PDGFRα mutation status. Am J Pathol 2004;165:107–113.

Montone KT, van Belle P, Elenitsas R, et al: Clinical, pathological, molecular and therapeutic findings in a large kindred with gastrointestinal stromal tumours. Int J Cancer 2008;122:711–718.

Miettinen M, Sobin LH, Sarlomo-Rikala M: Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with reference to CD117 (KIT). Mod Pathol 2000;13:1134–1142.

Nishida T, Hirota S, Taniguchi M, et al: Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet 1998;19:323–324.

Chompret A, Kannengiesser C, Barrois M, et al: PDGFRα germline mutation in a family with multiple cases of gastrointestinal stromal tumour. Gastroenterology 2004;126:318–321.

Kleinbaum EP, Lazar AJ, Tamborini E, et al: Clinical, histopathologic, molecular and therapeutic findings in a large kindred with gastrointestinal stromal tumor. Int J Cancer 2008;122:711–718.

Matyakhina L, Bei TA, McWhinney SR, et al: Genetics of carney triad: recurrent losses at chromosome 1 but lack of germline mutations in genes associated with paragangliomas and gastrointestinal stromal tumours. J Clin Endocrinol Metab 2007;92:2938–2943.

Takazawa Y, Sakurai S, Sakuma Y, et al: Gastrointestinal stromal tumours of neurofibromatosis type I (von Recklinghausen’s disease). Am J Surg Pathol 2005;29:755–763.

Miettinen M, Fetsch JF, Sobin LH, Lasota J: Gastrointestinal stromal tumours in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol 2006;30:90–96.

Carney JA, Stratakis CA: Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 2002;108:132–139.

Peereboom ID, Irvin TT, Sarsfield PT, Harington JM: GIST (gastro-intestinal stromal tumour) of the gallbladder: a case report. Acta Chir Belg 2004;104:107–109.

Melini A, Chelly I, Azzouz H, et al: Extragastrintestinal stromal tumor of the urinary wall bladder: case report and review of the literature. Pathologica 2008;100:173–175.

Zhang W, Peng Z, Xu L: Extragastrintestinal stromal tumor arising in the rectovaginal septum: report of an unusual case with literature review. Gynecol Oncol 2009;113:399–401.

Reith JD, Goldblum JR, Lyles RH, Weiss SW: Extragastrintestinal (soft tissue) stromal tumours: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol 2000;13:577–585.

Edge SB: American Joint Committee on Cancer: AJCC Cancer Staging Manual. New York, Springer, 2010, xiv, p 648.

Pierie JP, Choudry U, Muzikansky A, Yeap BY, Souba WW, Ott MJ: The effect of surgery and grade on outcome of gastrointestinal stromal tumors. Arch Surg 2001;136:383–389.

Gold JS, Gonen M, Gutierrez A, et al: Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10:1045–1052.
31 Ratkowski P, Nowecki Z, Michej W, et al: Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Ann Surg Oncol 2007;14:2018–2027.

32 Novitsky YW, Kercher KW, Sing RF, Heniford BT: Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. Ann Surg 2006;243:738–745, discussion 737–745.

33 Lopes LF, Bacchi CE: Imatinib treatment for gastrointestinal stromal tumor (GIST). J Cell Mol Med 2010;14:42–50.

34 Martin J, Poveda A, Llombart-Bosch A, et al: Deletions affecting codons 557–558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). J Clin Oncol 2005;23:6190–6198.

35 Corless CL, Schroeder A, Griffith D, et al: PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357–5364.

36 Gunawan B, von Heydenbreck A, Sander B, et al: An oncogenetic tree model in gastrointestinal stromal tumours (GISTs) identifies different pathways of cytogenetic evolution with prognostic implications. J Pathol 2007;211:463–470.

37 Heinrich MC, Owzar K, Corless CL, et al: Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26:5360–5367.

38 Fletcher CD, Berman JJ, Corless C, et al: Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33:459–465.

39 Miettinen M, Lasota J: Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70–83.

40 Fiore M, Palassini E, Fumagalli E, et al: Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). Eur J Surg Oncol 2009;35:739–745.

41 Catania V, Consoli A, Cavallaro A, Liardo RL, Malaguerna M: The neo-adjuvant treatment in gastrointestinal stromal tumor. Eur Rev Med Pharmacol Sci 2010;14:727–730.

42 Hohenberger P, Wardelmann E: Surgical considerations for gastrointestinal stromal tumor (in German). Chirurg 2006;77:33–40.

43 Eisenberg BL, Smith KD: Adjuvant and neoadjuvant therapy for primary GIST. Cancer Chemother Pharmacol 2011;67(suppl 1):S3–S8.

44 Nilsson B, Bumming P, Meis-Kindblom JM, et al: Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the pre-imatinib mesylate era – a population-based study in western Sweden. Cancer 2005;103:821–829.

45 Corless CL, Ballman KV, Antonescu C, et al: Relation of tumor pathologic and molecular features to outcome after surgical resection of localized primary gastrointestinal stromal tumor (GIST): results of the intergroup phase III trial ACOSOG Z9001. J Clin Oncol 2010;28(suppl):abstr. 10006.

46 Debiec-Rychter M, Sciot R, Cesne AL, et al: KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006;42:1093–1103.

47 Kontogianni-Katsarou K, Dimitriadis E, Lariou C, Kairisou E, Pandis N, Kondi-Paphiti A: KIT exon 11 codon 557/558 deletion/insertion mutations define a subset of gastrointestinal stromal tumors with malignant potential. World J Gastroenterol 2008;14:1891–1897.

48 Patel S, Zalberg JR: Optimizing the dose of imatinib for treatment of gastrointestinal stromal tumors: lessons from the phase 3 trials. Eur J Cancer 2008;44:501–509.

49 Reichardt P, Blay JY, Mehren M: Towards global consensus in the treatment of gastrointestinal stromal tumor. Expert Rev Anticancer Ther 2010;10:221–232.

50 Gaschi PG, Blay JY: Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(suppl 5):v98–v102.
Shaheen et al.: Gastrointestinal Stromal Tumor: A Rare Abdominal Tumor

**Fig. 1.** Excised tumor with a part of the stomach. The gastric mucosa can be seen in the lower part of the specimen.

**Fig. 2.** a Hematoxylin and eosin staining of the tumor shows a mildly eosinophilic cytoplasm. b CD117 staining with a membranous distribution is shown.