Pediatr Surg Int (2006) 22: 462–464
DOI 10.1007/s00383-006-1636-5

CASE REPORT

E. Towu · M. Stanton

Gastrointestinal stromal tumour presenting with severe bleeding: a review of the molecular biology

Received: 10 June 2005 / Published online: 4 February 2006

Abstract Gastrointestinal stromal tumours (GIST) are rare in children. A 7-year-old boy presented acutely with a severe upper gastrointestinal bleed and was found following angiography to have such a tumour in the duodenum, which was resected at laparotomy. The presence of CD 117 positive immunostaining was a confirmatory diagnostic marker. The prognosis and underlying molecular biology of the tumour is discussed. Understanding of the molecular pathogenesis has given rise to promising new therapies.

Keywords GIST · Gastrointestinal bleed

Introduction

Gastrointestinal stromal tumours (GIST) are uncommon tumours that usually present in the fifth to seventh decade of life. There have been a few reports of these tumours affecting children, but usually above the age of 10. We describe our experience with such a tumour in a 7-year-old, who is the youngest case we are aware of. We hereby present a review of the current treatments and understanding of the underlying molecular biology, which has generated potentially useful therapeutic agents.

Case report

An otherwise healthy 7-year-old boy presented with a 4-day history of melaena, headache, malaise and pallor. On examination he was pale, with normal cardiovascular parameters, had no abdominal mass, and melaena was confirmed on rectal examination. His blood count demonstrated a haemoglobin of 4.8 g/dl. Following adequate transfusion, upper and lower gastrointestinal endoscopy were performed but failed to reveal a source of bleeding. A technetium-99 scan was negative for Meckel's diverticulum. An ultrasound suggested a 2-cm mass adjacent to the third part of the duodenum, slightly compressing the inferior vena cava, which was confirmed on CT scanning. He was then transferred to our unit following a further GI bleed. A labelled red cell scan was negative, but a selective coeliac and mesenteric angiogram demonstrated an abnormal leash of vessels arising from one of the early branches of the superior mesenteric artery, corresponding to the lesion seen on ultrasound and CT (Fig. 1).

At laparotomy, a duodenostomy was performed after kocherisation. A submucosal ulcerated mass was identified at the junction of the second and third parts of the duodenum. A segmental resection was performed, removing the tumour with 3 cm of duodenum, preserving the common bile duct and an accessory pancreatic duct.The child made a good recovery post-operatively.

The tumour was grey coloured. Microscopically it was composed of interwoven spindle cells with eosinophilic cytoplasm, elongated nuclei, and a low mitotic count (less than one per 10 HPF). There was strong positive immunostaining for CD 117, and negative staining for CD 34 and smooth muscle actin confirming a diagnosis of GIST.

Discussion

Gastrointestinal stromal tumours (GIST) are rare tumours, which were previously known as leiomyoma, leiomyoblastoma or epitheloid leiomyosarcoma. It is thought that there may be 150 cases per year of this tumour in the United States, although more recent estimates suggest that incidence may be as many as 5,000 new cases a year [1–3]. They usually present in the fifth

E. Towu (✉) · M. Stanton
Department of Paediatric Surgery, Lewisham University Hospital NHS Trust, Lewisham High Street, London, SE13 6LH, UK
E-mail: etowu@doctors.org.uk

E. Towu · M. Stanton
Southampton General Hospital, Southampton University NHS Trust, Tremona Road, Southampton, SO16 6YD, UK

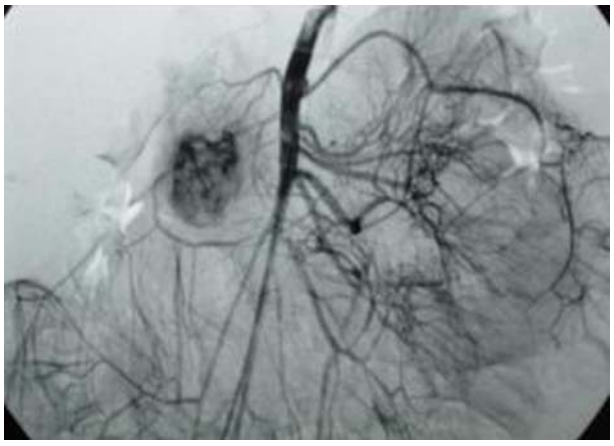

Fig. 1 Selective angiogram of superior mesenteric artery showing blood supply to tumour

to seventh decade of life, the majority of studies showing no gender predilection.

In a few case reports in children there has been some association with acquired immunodeficiency syndrome (AIDS). The remainder represents a combination of children whose tumours were benign or in a few cases malignant [4–6]. These tumours were reported to be in the stomach, duodenum, ileum and colon, most occurring above the age of 10 years.

Megan et al. reviewed the literature and were able to identify 24 children (newborn to 18 years of age) with tumors designated to be GISTs. They highlighted some important differences when children present with GIST, with 75% of the reported cases having been in girls, with the highest incidence occurring in the prepubertal years. The occurrence of metastases in adults is rare, the liver being the most common location for metastatic spread. Only two previous reported children before their report of three patients who had GIST in the stomach had been noted to have metastatic GIST. They observed that metastatic GIST in children show a more aggressive pattern of disease than had typically been noted [7].

Nilsson et al. [6] carried out a population based study in 1,460 patients who potentially had GIST diagnosed from 1983 to 2000 in western Sweden, with a population of 1.3–1.6 million, and identified 288 patients with primary GIST. Ninety percent of these patients were detected clinically due to symptoms (69%) or were incidental findings at surgery (21%); the remaining 10% of GISTs were found at autopsy, with tumour-related deaths occurring in 63% of patients of high risk and 83% of patients with overtly malignant GIST.

The annual incidence of GIST was 14.5 per million, with a prevalence of all GIST risk groups being 129 per million, and 31 per million for the high-risk group and the overtly malignant group [6].

GISTs occur anywhere in the intestine, with the most common site being the stomach (52%), followed by the small intestine (25%), large bowel (11%) and the oesophagus (5%), although they may be found in the mesentery, omentum or retroperitoneum. They usually present clinically as abdominal masses, with bleeding or as incidental findings. They may also cause anorexia, obstruction, perforation or fever [9, 10]. A combination of gastric leiomyosarcoma with a functioning extra-adrenal paraganglionoma and pulmonary chondroma is a recently described association named Carney's triad [11].

Macroscopically, gastrointestinal stromal tumours are usually grey-white in appearance. They arise in the muscularis propria, and can grow either exophytically out into the peritoneum, or endophytically into the lumen of the gut. The variety of microscopic appearances include: myoid, neuronal, ganglion plexus, autonomic nervous tumour (gastrointestinal autonomic tumour, GANT) or undifferentiated. They have been known to have a heterogeneous appearance, showing more than one type of pattern. The cells take up either a spindle shape or epitheloid (round cell) pattern [12]. Immunohistochemistry is usually positive for CD 117, which is often used as a diagnostic marker.

There have been recent developments in the understanding of these tumours. Mesenchymal tumours of the gastrointestinal tract had been thought to be of smooth muscle origin; hence they were referred to in the past as leiomyomas and leiomyosarcomas. However, they do not show complete smooth muscle differentiation, nor do they behave as smooth muscle tumours from other locations [12]. The term GIST was first applied to these tumours in 1983 [13]. The finding of positive CD 117 staining indicates the presence of the KIT protein, a tyrosine kinase receptor, encoded for by the c-*kit* proto-oncogene, which normally binds to its ligand, stem cell factor (SCF). It is thought that mutation of c-*kit* to produce a constitutively active KIT protein is a central event in the pathogenesis of GIST. Positive staining for the KIT has become one of the diagnostic features of GIST [3, 14, 15].

Positive CD117 staining is also seen in the interstitial cells of Cajal, and this has suggested to some that they both share the same primitive mesenchymal stem cell origin. Targeted inhibition of KIT has provided a promising new approach to the treatment of GIST.

Management depends on complete surgical resection, incomplete resection being associated with a median survival of less than 20 months. The wide margins of resection are not necessary as there is minimal local invasion, and similarly lymphadenectomy is not routinely necessary as local lymph nodes are not usually affected. Results from chemotherapy are disappointing [2, 16]. These tumours are difficult to treat with radiotherapy, given their location and the risk to adjacent organs. Improved understanding of the molecular biology underlying GIST has suggested promising new lines of adjuvant treatment. Imatinib mesylate (formerly STI-571) is a tyrosine kinase inhibitor that seems to be particularly effective against the KIT protein. Up to 50% of patients with advanced disease have been shown to respond to imatinib [5, 6, 18, 19].

Recurrence or metastasis after complete surgical resection may occur in more than two thirds of all GIST [16]. Recurrence is usually local or peritoneal, and often associated with liver metastases. Most recurrences occur within 2 years of the original tumour, although intervals of up to 10 years have been recorded [17]. Several predictors of malignancy have been identified. Large tumours are more likely to metastasise [12]; of tumours larger than 6 cm, 85% will metastasise, whilst 20% of those smaller than 6 cm will metastasise [14, 16]. Incomplete surgical resection is associated with a reduced survival [5, 6, 18, 19]. Microscopic appearance can also be a useful guide: metastasis is associated with observation of more than 1–5 mitoses per HPF, while observation of more than ten mitoses would be considered high grade. Tumours that have the c-*kit* exon 11 mutation are also at greater risk.

In conclusion, we have reported on one of the youngest patients with gastrointestinal stromal tumour. These are rare tumours, which until recently have been difficult to classify, stage or give a prognosis on. Treatment at present is based on satisfactory surgical removal, although molecular biology advances have suggested a new possible line of treatment.

References

1. Licht JD, Weissmann LB, Antman K (1988) Gastrointestinal sarcomas. Semin Oncol 15(2):181–188
2. Miettinen M, Sarlomo-Rikala M, Lasota J (1999) Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 30(10):1213–1220
3. Nishida T, Hirota S (2000) Biological and clinical review of stromal tumors in the gastrointestinal tract. Histol Histopathol 15(4):1293–1301
4. Chadwick EG, Connor EJ, Hanson IC, Joshi VV, Abu-Farsakh H, Yogev R et al (1990) Tumors of smooth-muscle origin in HIV-infected children. Jama 263(23):3182–3184
5. Durham MM, Gow KW, Shehata BM, Katzenstein HM, Lorenzo RL, Ricketts RR (2004) Gastrointestinal stromal tumors arising from the stomach: a report of three children. J Pediatr Surg 39(10):1495–1499
6. Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG (2005) Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. Cancer 103(4):821–829
7. Tervit GJ, Forster AL (1997) Leiomyoma of the small intestine in an 11-year-old boy. Eur J Pediatr Surg 7(1):44
8. Li P, Wei J, West AB, Perle M, Greco MA, Yang GC (2002) Epithelioid gastrointestinal stromal tumor of the stomach with liver metastases in a 12-year-old girl: aspiration cytology and molecular study. Pediatr Dev Pathol 5(4):386–394
9. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ (1999) Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. Am J Surg Pathol 23(1): 82–87
10. He LJ, Wang BS, Chen CC (1988) Smooth muscle tumours of the digestive tract: report of 160 cases. Br J Surg 75(2): 184–186
11. Carney JA, Sizemore GW, Sheps SG (1976) Adrenal medullary disease in multiple endocrine neoplasia, type 2: pheochromocytoma and its precursors. Am J Clin Pathol 66(2):279–290
12. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al (2002) Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 33(5):459–465
13. Franquemont DW (1995) Differentiation and risk assessment of gastrointestinal stromal tumors. Am J Clin Pathol 103(1):41–47
14. Mazur MT, Clark HB (1983) Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 7(6):507–519
15. Blume-Jensen P, Claesson-Welsh L, Siegbahn A, Zsebo KM, Westermark B, Heldin CH (1991) Activation of the human c-kit product by ligand-induced dimerization mediates circular actin reorganization and chemotaxis. Embo J 10(13):4121–4128
16. Heinrich MC, Blanke CD, Druker BJ, Corless CL (2002) Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. J Clin Oncol 20(6):1692–1703
17. Pidhorecky I, Cheney RT, Kraybill WG, Gibbs JF (2000) Gastrointestinal stromal tumors: current diagnosis, biologic behavior, and management. Ann Surg Oncol 7(9):705–712
18. Pierie JP, Choudry U, Muzikansky A, Yeap BY, Souba WW, Ott MJ (2001) The effect of surgery and grade on outcome of gastrointestinal stromal tumors. Arch Surg 36(4):383–389
19. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ et al (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347(7): 472–480