CASE REPORT

Gastrointestinal stromal tumour metastatic to the epididymis

Ali Ahmad,¹ Norman Peter Libbey,² Ponnandai Somasundar,¹ Steven C Katz¹¹Department of Surgery, Roger Williams Medical Center, Providence, Rhode Island, USA²Department of Pathology, Roger Williams Medical Center, Providence, Rhode Island, USA

Correspondence to

Dr Ponnandai Somasundar, psomasun@chartercare.org

Accepted 2 September 2015

SUMMARY

Gastrointestinal stromal tumours (GIST) are mesenchymal neoplasms with a propensity to metastasise to the liver and peritoneal cavity. Since the advent of tyrosine kinase inhibitors, outcomes for patients with metastatic GIST have improved dramatically. Secondary to the longevity in survival, patients may develop metastatic disease in very unusual locations, which poses significant diagnostic dilemmas and management challenges. We report a case of a patient with GIST who presented with an epididymal metastasis manifesting as a scrotal mass. Resistance to targeted medical therapies continues to pose a challenge, and our case highlights the importance of a multidisciplinary approach in such patients, including long-term follow-up.

BACKGROUND

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal (GI) tract. The most common site of origin is the stomach, however, these tumours can arise anywhere along the GI tract.¹ The clinical behaviour of GIST is highly variable, ranging from slow-growing indolent tumours to aggressive malignancies with early dissemination. Features that appear to be most predictive of outcome are tumour size, primary site and the mitotic rate.² Rectal GISTs constitute about 5% of all GISTs and tend to have more aggressive biological behaviour.³ The diagnosis is confirmed with immunohistochemistry to demonstrate KIT and DOG-1 expression, which helps differentiate these tumours from other mesenchymal neoplasms such as leiomyomas and leiomyosarcomas.² Mutations in KIT or other tyrosine kinase proteins drive GIST proliferation and growth.^{2 3}

The most common metastatic sites of GIST are the liver and peritoneal surface, with involvement of both in many cases.⁴ Lymph node involvement is rare. Although surgery remains the mainstay of treatment of non-metastatic GIST, tyrosine kinase inhibitors (TKI) have significantly improved survival outcomes in patients with disseminated GIST.⁵ Surgical resection of GIST metastases is appropriate in select cases, based on site of disease and responsiveness to TKI.^{4 6} The longevity in survival in these patients has translated into development of metastases in uncommon locations. We report a case of a rectal GIST with metastatic involvement of the epididymis. The rarity of such an atypical metastasis poses a challenge in diagnosis and treatment of such lesions.

CASE PRESENTATION

A 50-year-old man with an unremarkable medical history, underwent an abdominoperineal resection for a rectal GIST, at an outside institution. His pathology from the initial surgery revealed a high-grade GIST with 22 mitotic figures per 50 high power fields. He received adjuvant imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA) at 400 mg/day for 1 year, followed by radiographic surveillance. Four years later, he presented with peritoneal metastases and imatinib therapy was reinitiated at an escalated dose of 800 mg/day. While imatinib initially induced a partial response, focal disease progression involving the right colon and the pelvis suggested development of TKI-resistant tumour clones. The disease burden at that time included two lesions: one involving the ileum and caecum, and measuring 6 cm, and the other along the right pelvic side wall, measuring approximately 4 cm in greatest dimension. Given the low volume of disease and apparent resistance to TKI therapy, surgical resection was performed on the patient, rendering him disease free. Mutation analysis of the specimen revealed secondary KIT mutations involving exons 11 and 17. Because of the acquired resistance to imatinib, second-line TKI therapy with sunitinib malate (Sutent; Pfizer Incorporated, New York, New York, USA), was started. Sunitinib conferred a 2-year progression-free survival benefit. However, after 2 years, the patient's disease progressed and he presented with new peritoneal surface and liver metastases. During that presentation, the patient reported scrotal fullness and a scrotal mass was found on physical examination. Evaluation of this anomalous scrotal mass included an ultrasound of the scrotum, which revealed a bilobar dense hypervascular mass measuring 3.7×2.0×2.0 cm (figure 1A), likely originating from the epididymis

Figure 1 (A) Ultrasound of the scrotum showing a hypodense tumour (yellow asterisk) abutting the right testis (double yellow asterisk). (B) Ultrasound revealing the same tumour (yellow asterisk) with cephalad extension along the right testis (double yellow asterisk) abutting the epididymis.

CrossMark

To cite: Ahmad A, Libbey NP, Somasundar P, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211555

and distorting the right testis (figure 1B). This mass, along with multiple satellite nodules along the spermatic cord, were also seen on CT scan (figure 2A, B). Apart from that, five liver metastases were also demonstrated on CT and three of those lesions showed progression on serial imaging.

Following multidisciplinary case review, targeted surgical resection was offered to the patient in light of the fact that the tumour had acquired a novel mutation conferring resistance to second-line TKI therapy. The patient underwent laparotomy for resection of resistant lesions and scrotal exploration for diagnostic purposes. A left partial hepatectomy with microwave ablation of two other intrahepatic tumours was performed in conjunction with a radical right orchiectomy. Stable or responsive disease in the posterior right lobe of the liver was left in place and a large left pelvic mass encasing the left ureter and iliac vessels was deemed unresectable. Multiple small tumour nodules were noted along the peritoneal lining and the omentum. The patient recovered well and third-line TKI therapy, regorafenib (Stivarga; Bayer Healthcare Pharmaceutical, Montville, New Jersey, USA), was initiated.

INVESTIGATIONS

Pathologic findings

Gross examination of the right orchiectomy specimen revealed a 3.0×2.2×1.8 cm pale tan, firm, fibrotic nodule involving the rete testis and the tail of the epididymis. The mass abutted the testicle without gross involvement. Multiple additional smaller nodules were visualised throughout the length of the spermatic cord.

Figure 2 (A) CT scan (coronal section) demonstrating a tumour metastasis (yellow asterisk) along the spermatic cord in the right inguinal canal. (B) CT scan (axial cross-section) demonstrating tumour (yellow asterisk) within the right hemiscrotum.

Figure 3 (A) Metastatic involvement of the right epididymis. Spindle-shaped tumour cells (right of image) can be seen involving the epididymal lining (left of image) (H&E staining, low magnification). (B) High magnification image of tumour demonstrating spindle cell neoplasm with moderate nuclear pleomorphism and abundant mitosis (arrow) (H&E staining).

Histological examination revealed a spindle cell neoplasm (figure 3A, B) with moderate nuclear pleomorphism and abundant mitosis (15 per 50 high power fields). Immunohistochemical studies (table 1) performed on the specimen demonstrated strong positivity for vimentin, CD34, CD117 (figure 4A) and DOG-1 (figure 4B), but were negative for desmin, S-100, pancytokeratin and SMA. Staining for Ki-67 (proliferation index) was strongly positive in 20–30% of tumour cells, consistent with a diagnosis of a metastatic high-grade GIST.

Table 1 Immunohistochemical stain results

Antibody	Results
Vimentin (V9)	Positive in tumour cells
CD34 (QBEnd/10)	Positive in tumour cells
CD117 (C-Kit) (YR145)	Positive in tumour cells
DOG-1 (SP31)	Positive in tumour cells
Factor XIIIa (EP3372)	Positive in tumour cells
Ki-67 (30–9)	Positive in 20–30% of tumour cells
Desmin (DE-R-11)	Negative in tumour cells
Pan cytokeratin (AE1/AE3/PCK26)	Negative in tumour cells
S100 (polyclonal)	Negative in tumour cells
SMA	Negative in tumour cells

Figure 4 (A) Strong uniform staining of the tumour cells for CD117. (B) Similar strong staining for DOG-1 (Immunohistochemistry staining).

OUTCOME AND FOLLOW-UP

While on regorafenib, the patient has had stable disease for 10 months since the last surgery.

DISCUSSION

GISTs are the most common mesenchymal tumours of the GI tract, and originate from the interstitial cells of Cajal.⁵ Approximately 5% of GISTs arise from the rectum and up to 85% are characterised by a mutation in the gene for a tyrosine kinase growth factor receptor (KIT) with over expression of CD117 antigen.⁶ The most common mutation involves exon 11, but mutations in exons 9 and 13 of the KIT gene have also been reported.⁷ About 10% of the mutations involve the platelet derived growth factor α (PDGFA) receptor and the remainder are considered wild type without known mutations.^{6,7}

Recognition of the KIT gene mutation has led to the development of TKI such as imatinib mesylate. The efficacy of imatinib in the treatment of GISTs has resulted in significantly improved survival rates.⁴ Because of the longer survival, the incidence of metastases in uncommon locations has increased.

Another phenomenon that has been recently recognised is the formation of mutated clones depicting resistance to treatment.⁸ Secondary mutations usually occur in KIT kinase domains in patients during or after imatinib treatment and lead to secondary drug resistance.^{8–10} In GIST without KIT mutations, PDGFRA mutations occur with a frequency of approximately 30–40% leading to primary imatinib resistance. Furthermore, various tumour sites are associated with distinct chromosomal imbalances; gastric GISTs predominantly show losses of 14q,

whereas intestinal GIST more frequently exhibit losses of 15q chromosome.^{8,9} Selective surgical planning in combination with targeted therapies has shown promise in such patients.

TKI therapy remains the primary treatment for metastatic GISTs, with surgical resection in patients with low volume disease or focal resistance.⁴ GISTs metastasise via haematogenous and intra-coelomic routes.⁶ Hence the most common sites of metastasis are the liver and peritoneal lining.^{5,6} Our patient demonstrated multifocal-resistant disease in the liver, peritoneal cavity and, surprisingly, in the scrotum, a very rare location for metastasis.

Secondary involvement of the genitourinary tract by GISTs has been previously described by Froehner *et al*,¹¹ who reported a case of a large mesenteric GIST extending through the inguinal canal and presenting as a scrotal mass. There have been two other published case reports of GISTs with metastatic involvement of the tunica vaginalis presenting as inguinoscrotal masses.^{12,13} In our case, there was bulky involvement of the epididymis. It can be speculated that this aberrant site of metastasis in our patient was likely a result of direct tumour seeding from the peritoneal cavity through a patent processus vaginalis. While we cannot exclude haematogenous spread, direct intraperitoneal dissemination is supported by the presence of multiple tumour nodules along the length of the spermatic cord. To the best of our knowledge, there have been no documented cases of epididymal involvement by metastatic GIST.

In summary, we have reported a rare presentation of a metastatic GIST involving the epididymis. With advancements in modern targeted therapies and subsequently improved outcomes in patients with GISTs, our case highlights the importance of a broad multidisciplinary approach in the management of such patients. Peritoneal metastases from GISTs may extend into the inguinal canal and scrotum. As such, patients with GIST referable to these anatomic sites require dedicated imaging studies to exclude unusual patterns of spread. Long-term follow-up is mandated as recurrent disease can occur in unusual locations.

Learning points

- ▶ Recognition of the epididymis and the inguinal canal as a site of metastasis from gastrointestinal stromal tumours (GIST).
- ▶ Role of imaging and relevant clinical history in surgical planning.
- ▶ Importance of pathological confirmation and differentiating from primary testicular tumours.
- ▶ Role of selective surgical approach for GIST metastases resistant to medical treatment.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006;23:70–83.
- 2 Fletcher CD, Berman JJ, Corless C, *et al*. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002;33:459–65.
- 3 Dematteo RP, Gold JS, Saran L, *et al*. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). *Cancer* 2008;112:608–15.
- 4 DeMatteo RP, Maki RG, Singer S, *et al*. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg* 2007;245:347–52.

- 5 Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006;130:1466–78.
- 6 Demetri G. Chapter 87. In: DeVita L, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's cancer: principles and practice of oncology*. 9th edn. 2011. Philadelphia, PA: Lippincott, Williams, & Wilkins ISBN: 978-1-4511-0545-2.
- 7 Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. *Histopathology* 2008;53: 245–66.
- 8 Antonescu CR, Besmer P, Guo T, *et al*. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res* 2005;11:4182–90.
- 9 Maleddu A, Pantaleo MA, Nannini M, *et al*. Mechanisms of secondary resistance to tyrosine kinase inhibitors in gastrointestinal stromal tumours (review). *Oncol Rep* 2009;21:1359–66.
- 10 Chen LL, Trent JC, Wu EF, *et al*. A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. *Cancer Res* 2004;64:5913–19.
- 11 Froehner M, Ockert D, Aust DE, *et al*. Gastrointestinal stromal tumor presenting as a scrotal mass. *Int J Urol* 2004;11:445–7.
- 12 Dorić M, Radović S, Babić M, *et al*. Testicular metastasis of gastrointestinal stromal tumor of the jejunum. *Bosn J Basic Med Sci* 2007;7:176–9.
- 13 Perrone N, Serafini G, Vitali A, *et al*. Gastrointestinal stromal tumor metastatic to the scrotum. *J Ultrasound Med* 2008;27:961–4.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow