CASE REPORT

Giant seminal vesicle cyst: an unusual site for a malignant extragastrointestinal stromal tumour

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SUMMARY

Mesenchymal tumours with clinicopathological and molecular profiles similar to gastrointestinal stromal tumours (GISTs) are, on occasion, found in extragastrointestinal locations. Extra GIST (EGIST) is a singular occurrence in the genitourinary tract. A 30-year-old man, catheterised following urinary retention, was found to have a complex pelvic retrovesical cyst on imaging. At operation, origin from the right seminal vesicle was evident with histopathology confirming a GIST. The patient received adjuvant therapy with tyrosine kinase inhibitor and is currently disease free at 2 years. This is only the second report of an EGIST at this anatomic locale. The current literature presents significant uncertainty in defining the true origin of EGISTs, particularly those in the pelvis. We propose the designation origin indeterminate stromal tumour (OIST), to facilitate disambiguation and advance accurate profiling of EGIST; a subject in evolution.

BACKGROUND

Mesenchymal tumours with clinicopathological and molecular profiles similar to gastrointestinal stromal tumours (GIST) are, on occasion, found in extragastrointestinal locations, engendering the subset, extra GIST (EGIST).¹ These unusual tumours comprise <1% of all GISTs with a defined origin.² The majority of EGISTs in larger series are intra-abdominal, reportedly arising from the mesentery or the omentum, while retroperitoneal GISTs are less common. The majority of retroperitoneal GISTs have been reported to be of rectovaginal or vaginal origin, while fewer cases attribute origin to the genitourinary system—bladder, prostate, seminal vesicles and urethra. To the best of our knowledge, this is the second report of EGIST arising from a seminal vesicle.

The predominantly cystic feature in the imaging of this case led to a variety of differentials before pathological confirmation. A review of the literature suggests that reports of EGISTs (particularly those in the pelvis), often cannot confirm site of origin; thereby overstating the incidence of this rare entity. There is a niche within stromal tumour nomenclature for a novel entry—origin indeterminate stromal tumour (OIST).

CASE PRESENTATION

A 30-year-old man had an episode of acute urinary retention following a 3-month history of lower urinary tract symptoms and low-grade fever. Initial evaluation elsewhere revealed a pelvic mass that was palpable per rectum. Diagnosis of

prostatic malignancy or abscess was considered. The patient underwent ultrasound-guided transrectal core biopsy after placement of a suprapubic catheter. A blood-stained aspirate was obtained: fluid cultures were negative, smear was negative for malignant cells and the biopsy was indeterminate. The patient was referred to us for further evaluation.

INVESTIGATIONS

MRI confirmed the presence of a 11×10×10 cm, well-defined, predominantly cystic lesion with an irregular, nodular soft tissue rim and septations, centred on the right seminal vesicle, with mass effect on the prostate and left seminal vesicle (figure 1). Solid papillary projections were also noted. Fat planes were preserved between the lesion, the posterior bladder wall and the anterior rectal wall.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of seminal vesicle mass lesions includes: benign (papillary adenoma, cystadenoma, congenital cyst, hydatid cyst) and malignant (adenocarcinoma, sarcoma, cystosarcoma phyllodes) seminal vesicle lesions, Müllerian duct cyst, prostatic utricle cyst, ejaculatory duct cyst and primary pelvic retroperitoneal GIST.³

TREATMENT

The patient underwent laparotomy and excision of the retrovesical lesion. Intraoperatively, the surgical plane anterior to the rectum was well defined. The cyst was inadvertently entered and turbid fluid drained from a loculated cystic mass that had replaced the right seminal vesicle (figure 2). Gross section of the cyst wall revealed a firm, grey-white, fibrotic cut surface. Light microscopy showed sheets and short fascicles of spindle-shaped cells with moderately pleomorphic, oval to elongated, vesicular nuclei with visible nucleoli and moderate amounts of eosinophilic cytoplasm (figure 3A, B). Mitotic activity of 2–3 per 10 high power fields (HPF) was noted. Tumour cells were positive for CD117 (figure 3C), h-caldesmon and DOG-1 (discovered on GIST-1) while negative for smooth muscle actin (figure 3D), desmin and ALK1 (anaplastic lymphoma kinase). Microscopic resection margin had focal positivity for tumour cells. In consideration of this finding, the patient was started on adjuvant treatment with imatinib mesylate, a tyrosine kinase inhibitor (TKI).

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Figure 1 T2-weighted MRI of the pelvis. Sagittal (A), axial (B) and coronal (C) views. Retrovesical cyst with solid components and papillary projections from the wall compressing the bladder (suprapubic catheter in situ).

OUTCOME AND FOLLOW-UP

The patient made a full and rapid recovery after surgery. Upper gastrointestinal scopy did not reveal tumours in the stomach nor in the duodenum. Repeat MRI of the abdomen and pelvis at 1 year after operation was negative for local recurrence or metastatic disease (figure 4). The patient is currently disease free at 2 years.

DISCUSSION

GISTs are the most common non-epithelial mesenchymal tumours of the gastrointestinal tract. They constitute <1% of primary gastrointestinal malignancy with an overall incidence of 10–20 per million.² The term GIST was coined in 1983 by Mazur and Clark, following a seminal study of muscular and neural immunohistochemical markers in soft tissue tumours formerly classified as epithelioid leiomyosarcoma or leiomyoma.⁴

All stromal tumours including EGISTs exhibit typical immunophenotype and histopathology. The immunohistochemical hallmark of GISTs is the expression of a transmembrane tyrosine kinase receptor, KIT (CD117), of the interstitial cells of Cajal (ICC). Found in the myenteric plexus (Auerbach) within the muscularis of the gut, the ICC act as gastrointestinal pacemakers. Mutations of the KIT gene are near ubiquitous in benign and malignant GISTs. They lead to constitutional activation of tyrosine kinase, causing cellular proliferation and resistance to apoptosis.

Approximately 75% of adult GISTs have gain of function KIT mutations and overexpress KIT receptor tyrosine kinase. Platelet-derived growth factor α (PDGFRA) mutations have been found in 10% of KIT mutation-negative (KIT wild-type) tumours.⁵ Immunohistochemically, KIT-negative tumours may have either KIT mutations with failure of KIT overexpression

or exclusively PDGFRA mutation. Specific mutations have a bearing on the efficacy of TKI therapy; the commonest KIT mutation (exon 11) is classically responsive to the first-line TKI imatinib, while the commonest PDGFRA mutation (D842V) confers resistance.^{6–7} Absence of both KIT and PDGFRA mutations features in up to 10% of adult GISTs and are more likely to be resistant to imatinib.⁸ Yamamoto *et al* studied patterns of KIT and PDGFRA in EGISTs and found them similar to those in conventional GISTs. Anoctamin-1, a chloride channel protein also known as DOG-1, is positive in about 97% of GISTs including those that are KIT negative. The combination of KIT and DOG-1 overlaps to cover nearly 100% of these tumours.⁹ Among other markers, CD34 is expressed in 70%, smooth muscle actin in 30–40% and desmin is usually absent.

The presence of KIT receptor expression in EGISTs has been broadly attributed to three hypotheses. It has been proposed that they may arise from ICC in smooth muscle outside the gastrointestinal tract, from multipotent mesenchymal stem cells or, alternatively, from a conventional GIST that grows extramurally until it loses attachment to the intestinal wall and then parasitises adjacent organs.^{2–10} The majority of GISTs have a remarkably uniform population of cells in two distinct morphologies: spindle cell type (70%) and epithelioid type (20%); the remainder consisting of a mixture of these types.¹¹

Behaviour of stromal tumours varies with location. Small intestinal GISTs have a worse prognosis than tumours of the oesophagus and stomach. EGISTs have been found to have aggressive behaviour similar to GISTs of the hindgut. Criteria for assessment of biological potential of GISTs have been studied extensively and risk stratification systems have been applied.^{11–12} However, similar work with EGISTs is still

Figure 2 Intraoperative photograph. (A) Retrovesical cyst replacing the right seminal vesicle. (B) Fleshy papillary projections on the inner cyst wall.

Figure 3 Histopathology and immunohistochemical studies. (A) Fascicles of spindle-shaped cells (H&E $\times 10$). (B) Spindle cells (H&E $\times 20$). (C) Tumour with CD117 positivity. (D) Tumour negative for smooth muscle actin.

evolving. The National Institutes of Health consensus classification system risk-stratifies GISTs into groups based on tumour size and mitotic index. The Miettinen-Lasota/Armed Forces Institute of Pathology risk stratification system for GIST

incorporates location as an independent prognostic factor. Other factors with weaker statistical association are: mucosal invasion, tumour necrosis and high cellularity.¹¹ With regard specifically to EGISTs, Reith *et al*¹ have correlated three factors to adverse prognosis: high cellularity, necrosis and mitosis $>2/50$ HPF. Recently, Yamamoto *et al*¹³ proposed that the combination of the mitotic rate $>5/50$ HPF and MIB-1 labelling index $>10\%$, are associated with aggressive behaviour in EGIST. Neither author found correlation between tumour size and prognosis.

Management of EGISTs parallels that of conventional GISTs. Surgical resection is the mainstay of management of localised, technically resectable disease. The objective of surgery is to achieve a grossly complete resection with negative microscopic margins while minimising morbidity. Lymph nodal metastasis being infrequent, lymphadenectomy is seldom required. Preservation of the pseudocapsule and avoidance of tumour spillage are important oncological principles. Targeted therapy may be offered for locally advanced unresectable disease, or for patients in whom surgical morbidity may be limited by reducing tumour bulk preoperatively. Primary unresectable tumours, and recurrent and metastatic disease are best treated with TKIs—imatinib, sunitinib and, recently, rigorafenib. Surgery in this group is indicated for limited progression of disease unresponsive to TKI and disease rendered resectable by targeted therapy.¹⁴ The rationale for TKI therapy is based on the pivotal identification of gain of function mutations in the KIT gene. The KIT receptor tyrosine kinase proved an ideal target for TKI therapy, being both a phenotypic marker as well as the keystone of GIST pathophysiology.

There is significant ambiguity in the reporting of EGISTs. Much of this is due to the inability to objectively exclude gastrointestinal origin. The veracity of diagnoses has been called into

Figure 4 MRI of the pelvis on follow-up. Coronal view: (A) prostate appears normal (arrow). Sagittal view: (B) right seminal vesicle is absent in section just to the right of midline.

question particularly in pelvic tumours where the label EGIST must be applied with caution.^{10–15} Within the confines of the pelvis, stromal tumours often present as large masses in apposition with the rectum, vagina, bladder and prostate. Rectovaginal GISTs could take origin from the rectum, vagina or rectovaginal septum. In our case, we could not identify normal seminal vesicle tissue on histopathology. Although imaging and operative findings corroborated origin from the right seminal vesicle, we admit that some uncertainty exists as to exactly where this tumour arose from. This issue has also surfaced previously in a report of EGIST of presumed prostatic origin.¹⁶ Various case reports and series appear to identify the source of pelvic GISTs somewhat arbitrarily.^{10–15} This is a cause for concern, as inaccurate designation will obfuscate site-wise prognostication as more of these tumours are reported.^{5–11} When gastrointestinal origin can neither be proven nor excluded, it may be prudent to classify these as origin indeterminate stromal tumours; OIST as it were.

The genitourinary tract is a rare primary site for an EGIST; location in a seminal vesicle is exceptional.^{17–19} Acute urinary retention as reported in this case is a fairly common presenting symptom of cystic seminal vesicle lesions and serves as an indicator of the site of pathology when a pelvic mass is present in a man.²⁰ The mode of presentation and radiological findings in this case were typical of a seminal vesicle cyst. The differential diagnosis was broad, and final histopathological diagnosis was a surprise. Pelvic EGIST appears on imaging as a large, solid, heterogeneous density hypervascular enhancing mass that may contain areas of necrosis, haemorrhage or cystic degeneration. Areas of low signal intensity representing fibrosis may be seen on T2-weighted MRI.²¹

Learning points

- ▶ Acute urinary retention in a young man is a common presentation of seminal vesicle lesions.
- ▶ When imaging of a pelvic mass is suspicious for stromal tumour, true extragastrointestinal stromal tumour (EGIST) is worth excluding with the aid of immunohistochemical markers and molecular genetics.
- ▶ Management of an EGIST differs significantly from that of other tumours in that surgery followed by targeted therapy has proven efficacy whereas radiotherapy is not recommended and conventional chemotherapy is ineffective.
- ▶ Management of EGISTs parallels that of conventional gastrointestinal stromal tumours. Surgical resection is the mainstay of management of localised, technically resectable disease. Primary unresectable tumours, and recurrent and metastatic disease are best treated with tyrosine kinase inhibitors.
- ▶ The incidence of pelvic EGIST in the literature is overestimated. Many cases do not have conclusive proof that refutes gastrointestinal origin. Diligence must be exercised in appropriately classifying these rare and intriguing tumours.

Contributors APG, AD and RJB participated in the care of the patient. RJB performed the literature review and drafted the manuscript. RM obtained the pathological data. APG and AD assisted in revising the manuscript. All the authors read and approved the final manuscript.

Competing interests None declared.

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