Gastrointestinal stromal tumor presenting with lower urinary tract symptoms – A series of five cases with unusual clinical presentation

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INTRODUCTION
Spindle cell lesions of the prostate are very uncommon and the majority involve the prostate secondarily from adjacent organs. Gastrointestinal stromal tumors (GISTs) are specific C-kit (CD 117) expressing mesenchymal tumors occurring in the gastrointestinal tract, commonly in the stomach and intestine; however, it is seldom seen involving the prostate. Although primary prostatic GISTs have been described, majority of them are secondary involvement from rectal GIST. The patient usually presents with urinary tract symptoms or prostate enlargement simulating a prostatic neoplasm. GIST as a differential diagnosis for prostatic mass is never thought of. We present a series of five cases of GIST arising from/involving the prostate mimicking a primary prostatic malignancy and the challenges associated with them for diagnosis and treatment.

CASE SUMMARIES
We retrieved and identified five cases of primary prostatic GIST from the records. The age of the patients was 58, 84, 69, 55, and 65 years with a mean age of 66.2 years. All the five patients had symptoms of LUTS which included dysuria and frequent micturition (n = 5) and obstructive symptoms (n = 3). The serum prostatic specific antigen (PSA) levels were within normal limits in all cases with a range of 10.4103/iju_267_21

Access this article online
Quick Response Code:
Website: www.indianjurol.com
DOI: 10.4103/iju._267_21

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For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com
Received: 19.06.2021, Revised: 30.08.2021
Accepted: 14.09.2021, Published: 01.10.2021
Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.
Case 1 showed radiological recurrence in the sigmoid mesentery and the patient had been then switched to sunitinib chemotherapy. The patient showed complete radiological regression on sunitinib therapy on subsequent follow-up imaging and is alive with no recurrence/relapse for 4 years (48 months). Case 2 underwent transurethral resection of prostate chips which was reported as a smooth muscle tumor of uncertain malignant potential in view of focal H-caldesmon and CD34 positivity. However, the tumor progressed in size over the next 3 months and underwent CP which was confirmed to be a GIST using a broad panel of immunohistochemistry. The patient was then started on imatinib mesylate therapy; however, further follow-up was not available. Case 3 and Case 5 were referred cases for pathology diagnosis and were reported as GIST on prostate biopsy specimens with the help of ancillary immunohistochemical findings. Case 4 underwent a 12-core biopsy which was initially reported as low-grade leiomyosarcoma. (Figure 2 a-e) However, after the multidisciplinary meeting, a differential diagnosis of GIST was thought of which was then confirmed with the help of immunohistochemistry. The patient received neoadjuvant chemotherapy with imatinib mesylate and had complete metabolic resolution of the disease with marked regression in the size of the mass followed by cystoprostatectomy. Sequencing studies revealed exon 11 mutation in the tumor. (Figure 2f) Total follow-up duration following diagnosis is 47 months and disease-free survival following stopping of imatinib mesylate is 3 months [Table 2].

**DISCUSSION**

Till date, only 13 cases of primary prostatic GIST and <30 cases of EGIST involving the prostate have been reported in the literature, with a mean age of 59.5 years similar to our patients. The mean age of the patients in this review was 60 years with a wide age range of 31–92 years. Serum PSA levels ranged from 0.2 to 2.45 ng/mL. The mean range of serum PSA in our series was 0.046–1.889 ng/mL. The tumor size varies and ranges from 1.5 cm to as large as 15 cm. The largest tumor had a size of 12 cm in our series.

The histomorphologic features of EGIST are similar to conventional GIST and are composed of cellular spindle cells with perinuclear vacuolations, arranged in long intersecting fascicles mimicking a smooth muscle tumor. Nuclear palisading in a myxoid stroma may be a reminiscent of nerve sheath origin. Mitosis is variable. The risk stratification of GIST is based on tumor size and mitotic activity. On risk stratification of GIST, 3 out of 5 cases in our series were categorized as GIST of high malignant potential or aggressive tumor based on either their large size (case 2 and case 4) and/or high mitotic activity (>5/50 hpf) and necrosis (case 1). The

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**Table 1: Clinical profile of the patients**

| Age (years) | PSA (ng/mL) | Tumor site | Tumor size (cm) | Radiology | Surgery | Risk potential | Recurrence | Metastases |
|-------------|-------------|------------|----------------|-----------|---------|----------------|------------|------------|
| 58          | 0.8         | Prostatic mass attached to rectum | 6.5          | A large mass 6.5 cm involving the prostate with diffuse wall thickening of the rectosigmoid colon | CP + resection of anterior rectal wall | High risk | Occurred after 1 year on imatinib sigmoid mesentery deposit | None       |
| 84          | 0.046       | Prostate mass | 12            | A heterogeneously enhancing mass completely replacing the prostate and measured 12 cm in the largest dimension | CP | High risk | Occurred after initial TURP | None       |
| 69          | 0.7         | Prostate mass | -             | NA | TURP | Low risk | Not known | Not known |
| 55          | 1.889       | Prostatic mass infiltrating rectum | 11           | A hypermetabolic mass in the pelvis posterior to the urinary bladder and anterior to the rectum with epicenter in the prostate and infiltration in the anterior rectal wall | CP+AR | High risk | Not known | None       |
| 65          | 1.1         | Prostate mass | -             | NA | TURP | Low risk | Not known | Not known |

CP = Cystoprostatectomy, AR = Anterior resection, PSA = Prostate specific antigen, TURP = Transurethral resection of the prostate, NA = Not applicable
mitotic activity was <5/50 hpf in case 3; however, the tumor size information was not available for risk stratification. Most EGISTs of prostate are of large size involving the pelvis and rectum, and hence, it is difficult to accurately suggest their organ of origin.\textsuperscript{[3,6]}

The immunoprofile of EGIST is similar to intestinal GIST with 90%–100% of the tumor showing strong and diffuse immunoreactivity to CD117/c-kit and DOG-1. SMA and CD34 positivity is reported in 30%–40% of cases. C-kit can be negative in approximately 20%–30% of the cases.\textsuperscript{[5,8]}

With the discovery of KIT gain-of-function mutation in GIST, targeted therapies were studied upon and imatinib was used for the treatment of GIST in the year 2000.\textsuperscript{[10]} Platelet-derived growth factor receptor alpha (PDGFRA-A) and BRAF are other mutations associated with GIST.\textsuperscript{[2]} One of our patients (case 4) underwent sequencing for KIT mutation and showed exon 11 mutation. Molecular studies were not performed in rest of the patients due to financial constraints and referral nature of the sample.

There is no consensus regarding the treatment of EGIST, and the patients are treated as per the risk stratification.\textsuperscript{[11]} The choice of surgery depends on the tumor size, location, and extent of infiltration. Complete resection in EGIST of prostate/involving prostate would entail a radical prostatectomy. RP for low- and medium-risk resectable tumors and RP + adjuvant/neoadjuvant chemotherapy for medium- and high-risk tumors are the recommended lines of management.\textsuperscript{[11,12]} Imatinib and sunitinib are the tyrosine kinase inhibitors recommended for treatment, especially for EGIST showing expression of CD117.\textsuperscript{[11,12]}

Rectal GIST due to its anatomical location can sometimes present with symptoms simulating as prostate primary and histologically may resemble a prostatic stromal tumor. Hence, identifying these tumors is important due to their treatment implications. Due to a handful of cases of EGIST

### Table 2: Microscopy and immunohistochemical features

| Features                  | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---------------------------|--------|--------|--------|--------|--------|
| Cellularity               | Yes    | Yes    | Yes    | Yes    | Yes    |
| Nuclear pleomorphism      | Present| Present| Absent | Present| Absent |
| Mitosis/50 hpf            | >5     | >5     | <5     | >5     | <5     |
| Necrosis                  | Present| Absent | Absent | Absent | Absent |
| Initial immunoprofile     | C-kit  | Focal H-caldesmon | C-kit | SMA, h-caldesmon | C-kit |
| Diagnosis                 | GIST   | STUMP  | GIST   | Leiomysarcoma | GIST   |
| Additional immunohistochemistry | C-kit, DOG1 and CD34 | C-kit | C-kit | - |
| Revised diagnosis         | -      | GIST   | -      | GIST   | -      |

STUMP = Smooth muscle tumor of uncertain malignant potential, GIST = Gastrointestinal stromal tumor, DOG-1 = Discovered on GIST-1, SMA = Smooth muscle antigen, hpf = High-power field

Figure 2: Hematoxylin and eosin stained sections (a-c) show a cellular spindle cell tumor with moderate nuclear pleomorphism and eosinophilic cytoplasm. Immunohistochemistry showed strong and diffuse positivity for C-kit (d) and DOG-1 (e). KIT sequencing revealed 1 bp heterozygous substitution in exon 11: c.1749G>T (f)
reported till now, long-term prognosis following therapy is still not fully established.

**CONCLUSION**

EGIST may present with LUTS arising from or in relation to prostate. The accurate diagnosis depends on the imaging studies, pathological examination, and immunohistochemical results and has clinical implications with targeted TKI-based therapy.

**Acknowledgement**

The authors would like to thank Dr. Mandar Anolkar and Dr. Omshree Shetty, Scientific Officer in Department of Molecular Pathology and Translational Medicine, Tata Memorial Centre for providing support with the molecular testing and corresponding image.

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**How to cite this article:** Yadav SC, Menon S, Bakshi G, Katdare A, Ramadwar M, Desai SB. Gastrointestinal stromal tumor presenting with lower urinary tract symptoms – A series of five cases with unusual clinical presentation. Indian J Urol 2021;37:357-60.