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Case study

Gastrointestinal stromal tumor of the prostate: a case report and literature review

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Summary We report a case of gastrointestinal stromal tumor (GIST) of the prostate in a 75-year-old man with dysuria and urinary retention. Digital rectal examination revealed a markedly enlarged prostate. The serum level of prostate-specific antigen was 0.2 ng/dL. Imaging studies showed an expanded prostate, measuring 6.7 × 5.6 × 5.5 cm, with heterogeneity in contrast enhancement. No metastatic disease was found. The pathologic diagnosis of prostatic GIST was made based on characteristic morphological features, immunoprofiles, and molecular analysis. The possibility of secondary involvement by a rectal GIST was excluded by radiological and intraoperative findings. To our knowledge, this is the second case of a primary GIST of the prostate reported in the literature.

1. Introduction

Gastrointestinal stromal tumor (GIST) is the designation for a specific group of mesenchymal neoplasms that express the KIT protein (CD117). As literally implied, GISTs almost exclusively occur in the gastrointestinal tract and comprise most gastrointestinal mesenchymal tumors. In exceptional cases, GISTs may occur as primary tumors outside the gastrointestinal tract [1-4]. It has been proposed that GISTs originate from interstitial cells of Cajal, known as pacemaker cells in the gut, or from stem cells differentiating toward a pacemaker cell phenotype [5-7]. Recently, interstitial cells of Cajal, as well as a case of primary prostatic sarcoma with characteristics of GIST, were described in the prostate [8,9]. We report another case of a primary prostatic GIST presenting with acute urinary retention in a 75-year-old man.

2. Case report

A 75-year-old man had hypertension under medical control for more than 10 years. Otherwise, there was no personal or family history of major medical problems. In recent months, he had been experiencing hesitancy and pain upon initiating the urinary stream, frequency, nocturia, occasional hematuria, and episodes of acute urinary retention. No bowel habit change or bloody stool passage

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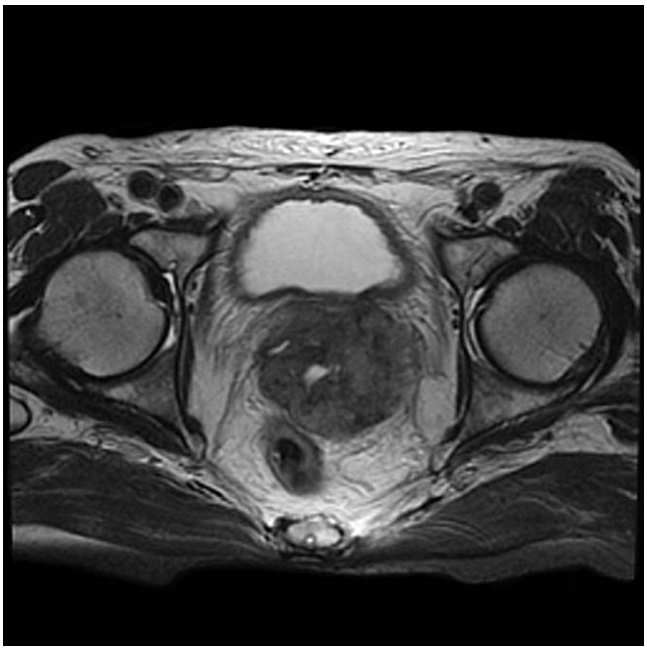

Fig. 1 Magnetic resonance imaging showing an enlarged prostate with symmetrical expansion and compression of the rectum and urinary bladder. The tumor was largely confined to the prostate without evidence of direct involvement of adjacent organs.

was noted. During a digital rectal examination, the prostate was markedly enlarged with a smooth, bulging surface and usual consistency on palpation. The serum level of prostate-specific antigen was 0.2 ng/dL. The initial diagnosis was benign prostatic hyperplasia, and transurethral resection of the prostate (TURP) was performed. Under spinal anesthesia, the resectoscope was smoothly inserted. It was noted that the urethral lumen was almost totally obstructed by an intrusion of an enlarged prostate. The TURP specimen weighed 36 g. The histologic diagnosis was an unclassified sarcoma. Painful and difficult urination recurred within 1 month after TURP. Pelvic computed tomography and magnetic resonance imaging revealed an expanded prostate, measuring 6.7 × 5.6 × 5.5 cm, with heterogeneity after contrast enhancement (Fig. 1). The rectoprostatic angle was obliterated. The rectal wall was intact without evidence of tumor involvement. Colonoscopy showed no abnormalities except a small elevation covered by intact rectal mucosa at the level of the prostate. Additional imaging studies including a chest roentgenogram and whole-body bone scan showed no metastatic disease. The patient underwent a laparoscopic radical prostatectomy. The prostate was easily separated from the adjacent structures. The specimen, weighing 14.5 g, was excised in pieces because of its necrotic nature. Microscopically, both the transurethral and radical excision specimens of the prostate had been almost entirely replaced by a cellular tumor composed of short fascicles of spindle cells with variable amounts of collagenized stroma [Fig. 2(A)]. The tumor cells had oval to elongated nuclei with mild to moderate pleomorphism, a finely granular chromatin pattern, one or more small nucleoli, and frequent mitoses [Fig. 2(B)]. The mitotic count was 15 per 50 high-power fields. Perivascular collars of tumor cells surrounded by large areas of tumor necrosis were frequently seen [Fig. 2(C)]. A few tumor cells possessed an epithelioid pattern with polygonal-shaped, round-nucleated cells arranged in a sheetlike arrangement. Tumor cells showed strong immunoreactivity for vimentin, CD34, and CD117 (KIT) [Fig. 2(D)] and were negative for pan-cytokeratin (AE1/AE3), smooth muscle actin, S-100 protein, prostate-specific antigen, progesterone receptor, and estrogen receptor. The tumor possessed a pushing border with a focally infiltrating growth pattern into the surrounding soft tissue. The seminal vesicles were free of tumor involvement. The tumor DNA, extracted from a paraffin block, was subjected to polymerase chain reaction amplification and sequence analysis for exons 9, 11, 13, and 17 of the *c-kit* gene and for exon 14 of the *PDGFR* gene. The results showed an in-frame deletion involving codons 557 and 558 (TGG AAG) in exon 11 (Fig. 3), which confirmed the diagnosis of GIST. The patient has been observed for 6 months and is in good condition except for experiencing mild urinary incontinence.

3. Discussion

Sarcomas of the prostate account for 0.1% to 0.2% of all malignant prostatic tumors. Leiomyosarcomas and rhabdomyosarcomas are the most common sarcomas involving the prostate in adults and children, respectively. Other primary sarcomas of the prostate are exceedingly rare. Those reported include prostatic stromal sarcoma (PSS), malignant fibrous histiocytoma, angiosarcoma, osteosarcoma, chondrosarcoma, malignant peripheral nerve sheath tumor, and synovial sarcoma [10]. Each of these tumor types, except the PSS, shows similar morphologic features and immunophenotypes to its counterpart found elsewhere in the body.

Van der Aa et al [9] reported the first case of GIST originating from the prostate. The patient was a 49-year-old man who presented with acute urinary retention, body weight loss, and an abnormal result on the digital rectal examination. Imaging studies showed a large tumor confined to the prostate with multiple liver metastases. Pathologic features including immunohistochemistry and molecular analysis results were consistent with a GIST. The patient was treated with imatinib mesylate resulting in reduction of the tumor volume. In the current report, we present another case of GIST of the prostate with characteristics of its gastrointestinal archetype in morphological features, immunophenotypes, and the presence of a KIT-activating mutation.

GIST comprises most gastrointestinal mesenchymal tumors and almost exclusively occurs in the gastrointestinal tract. Most GISTs are composed of highly cellular fascicles of spindled tumor cells with prominent perinuclear vacuo-

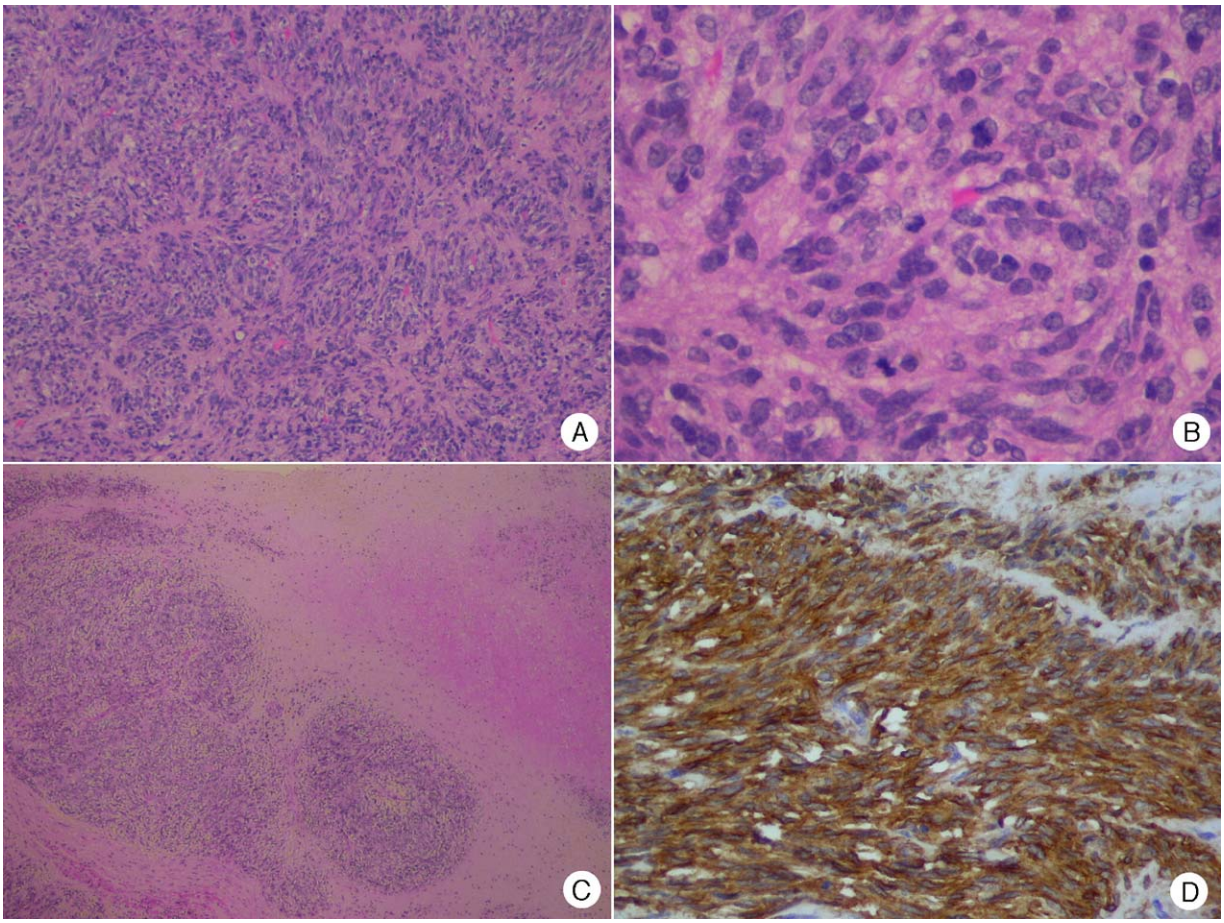

Fig. 2 The prostate having almost totally been replaced by a cellular tumor composed of spindle and a few epithelioid cells with a vague arrangement in short fascicles (A), moderate cytological pleomorphism with a high mitotic rate (B), large areas of necrosis (C), and a diffuse and strong immunoreactivity for CD117 (D).

lization and may resemble smooth muscle tumors. Nuclear palisading with stromal myxoid change is a common feature that may mislead into the diagnosis of nerve sheath tumors. Some GISTs are composed of epithelioid, or rarely, pleomorphic tumor cells instead of spindled ones. Most GISTs show immunoreactivity for CD117, approximately 70% to 80% and 30% to 40% of cases are positive for CD34 and smooth muscle actin, respectively, and very few are reactive for desmin and S-100 protein [6,7]. It has been reported that exceptional cases of GIST arising from the rectum or sigmoid colon present clinically as prostatic masses [11]. All of these cases were in an advanced stage, and involvement of the rectum or sigmoid colon is the rule. In our case, because the imaging studies and intraoperative findings argued against the possibility of rectal involvement, it stands to reason that the prostate was the tumor origin. Tumors that are histologically similar to GISTs do exceptionally occur as primary tumors outside the gastrointestinal tract, such as in the omentum, mesentery, and retroperitoneum, or present as a mass in the uterus, gallbladder, and pancreas [1-4].

The differential diagnosis of spindle cell tumors in the prostate should include most of the above-mentioned entities as well as prostatic carcinosarcoma. Making a distinction between GISTs and other primary prostatic sarcomas is important because the use of imatinib adjuvant therapy may considerably influence patients' outcomes. Immunohistochemical studies are helpful in making the differentiation. Strong and diffuse expression of CD117 is very limited in soft tissue sarcomas other than GISTs [12]. However, uncertainty does exist. Typically, PSS is histologically similar to phyllodes tumor of the breast with a biphasic pattern of neoplastic stromal component and nonneoplastic epithelial component showing a cloverleaf architecture. Some PSSs are purely composed of round and plump to spindled stromal cells arranged in sheets or short fascicles [10,14], and these cases may be confused with GISTs. Both GIST and PSS show immunoreactivity for vimentin and CD34 and, occasionally, for actin. Additional immunoreactivity for progesterone receptor is not always observed in all cases of PSS [13-15]. To our knowledge, only one reported case of PSS to date has mentioned its

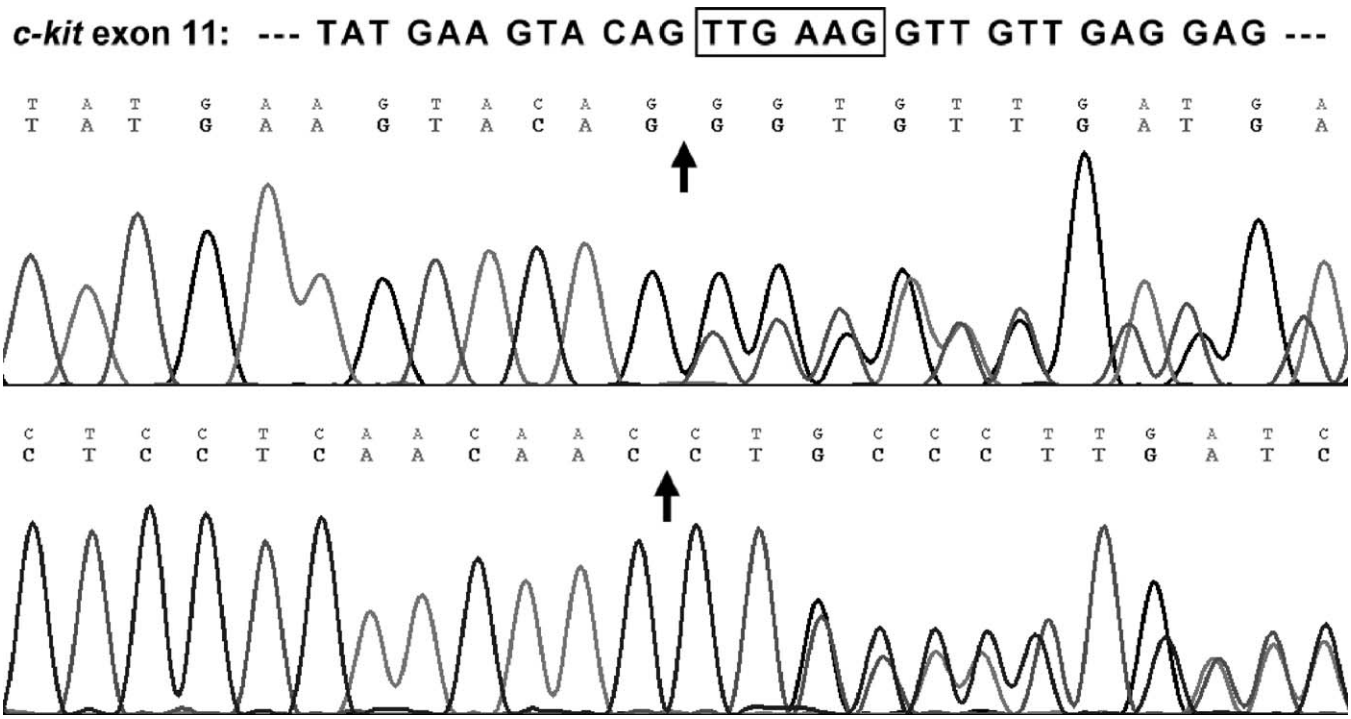

Fig. 3 Molecular analysis of the *c-kit* gene revealing an in-frame deletion of codons 557 and 558 in exon 11 (arrows). Top, forward strand; bottom, reverse strand.

negative immunoreactivity for CD117 [15]. Considering the similarity of morphologic features and immunoprofiles between PSS and GIST, it may be difficult to differentiate between the two in a small specimen, or in cases with an atypical presentation, and it is of interest whether these entities represent independent or related events. More case studies are needed to clarify the situation.

Since the application of imatinib as an effective targeted molecular agent for the treatment of solid neoplasms, the histogenesis, biological nature, diagnostic criteria, and genetic changes of GIST have attracted interest [6,7]. Based on the morphological and immunophenotypic similarities, it has long been believed that GIST originates from interstitial cells of Cajal within the gastrointestinal tract [5]. However, in contrast to interstitial cells of Cajal normally expressing CD117, the CD117 expression by GIST is due to a different mechanism—a gain-of-function mutation in the *c-kit* proto-oncogene. In 50% to 60% of cases of GIST, the KIT-activating mutations occur in the *c-kit* juxtamembrane domain (exon 11) and frequently cluster in a "hot spot" located in the proximal part of exon 11 between codons 550 and 561. Most of them present in-frame deletions [7]. *c-kit* mutations in extracellular (exon 9) and tyrosine kinase (exons 13 and 17) domains have been found in cases that lack exon 11 mutations. Some authors have suggested the origin of GISTs from intestinal mesenchymal precursor cells with differentiation toward Cajal cells and that their development depends on cellular signaling regulated by the KIT protein [6,7]. The latter hypothesis is supported by observations of avian and mouse intestinal mesenchymal precursor cells that differentiate into both Cajal cells and smooth muscle cells [7]. This could explain why GISTs show marked variability in their morphological, ultrastructural, and immunohistochemical features that reflect the line of differentiation as tumors showing differentiation toward either smooth muscle cells or neural elements, tumors showing dual differentiation toward smooth muscle and neural elements, or tumors lacking differentiation toward either cell type [6]. This could also explain why GISTs can arise outside the gastrointestinal tract.

In summary, we report a rare case of GIST arising from the prostate. The identification of GISTs has become very important because the introduction of specific, targeted therapy with a KIT tyrosine kinase inhibitor offers a promising outcome for metastatic GISTs. Clinicians should be aware of this rare entity and adopt appropriate strategies of treatment that can achieve the best outcome for patients.

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