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CASE REPORT

Primary Prostatic Extra-Gastrointestinal Stromal Tumor Treated with Imatinib Mesylate as Neoadjuvant and Adjuvant Therapy: A Case Report and Literature Review

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Abstract: The current study presents a case of primary prostatic extra-gastrointestinal stromal tumor (EGIST) in a 43-year-old man who suffered acute urinary retention. The serum level of prostate-specific antigen was normal. Imaging examinations demonstrated a diffusely enlarged prostate compressing the rectum without evidence of metastasis. After excluding the possibility of secondary involvement by a rectal GIST, the pathologic diagnosis of primary prostatic EGIST was established based on microscopic study, immunohistochemistry, and molecular analysis. This patient is the first case with primary EGISTs of prostate received imatinib mesylate as neoadjuvant and adjuvant therapy reported in the literature to date. We hope this case could provide the experience of diagnosis and treatment of primary prostatic EGISTs.

Keywords: extra-gastrointestinal stromal tumor, EGIST, prostate, imatinib mesylate

Introduction

Gastrointestinal stromal tumors (GISTs) are common mesenchymal neoplasms predominantly originating from the gastrointestinal tract. The significant immunohistochemical feature of GISTs, positive for CD117, CD34 and DOG-1, is crucial for differentiating GISTs from other mesenchymal tumors.[1,2] With similar pathological and molecular biological characteristics of GISTs, extra-gastrointestinal stromal tumors (EGISTs) occur primarily outside the gastrointestinal tract such as the omentum, mesentery and retroperitoneum.[3] Primary prostatic EGISTs are extremely rare and only a few cases were previously reported in literature.

In this study, we firstly reported a patient with primary EGISTs of prostate treated with imatinib mesylate as neoadjuvant and adjuvant therapy, followed with the literatures of primary prostatic EGISTs.

Case Report

A 43-year-old male patient with a history of acute urinary retention 2 months before referred to our center. The patient presented with no frequency, urgency or gross hematuria. His medical history was uneventful besides hypertension under medical control. The total prostate-specific antigen (tPSA) level was within normal range (2.70 ng/mL). Ultrasonography and magnetic resonance imaging (MRI) examination demonstrated

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a diffusely enlarged prostate compressing the wall of bladder, with the length of 13.2 cm. The capsule of prostate was intact. Based on these findings, further transrectal ultrasound (TRUS) guided prostatic biopsy was performed. The immunohistochemical staining established the diagnosis of EGIST with strongly positive for CD117 (c-kit), CD34 and DOG-1. A gene mutation analysis of the c-kit (exon 9, 11, 13 and 17) and the platelet-derived growth factor receptor-α (PDGFRA) with exon 12 and 18 was also conducted. The mutation of c-kit exon 11 in genetic analysis confirmed the diagnosis and indicated the sensitivity to molecular-targeted therapy. Therefore, the patient started taking imatinib mesylate (400 mg per day), a tyrosine kinase inhibitor of c-kit, as neoadjuvant therapy. After 23 days, he was admitted to our department for radical surgery. Digital rectal examination (DRE) revealed a markedly enlarged prostate with a smooth and bulging surface without tenderness or nodules on palpation. The tPSA level was 1.973 ng/mL. Ultrasound showed a grossly expanded prostate of volume about 533 mL and multiple heterogeneous foci. MRI showed 1) an enlarged prostate with abnormal morphology, 2) a large prostate compressing against bilateral seminal vesicles, the anterior wall of rectum and other adjacent pelvic structures, 3) several foci with abnormal signal mixed in the prostate (Figure 1). In addition, obvious lymph node enlargement was presented, including bilateral inguinal and pelvic area. Other metastases were not found on the chest X-ray or ultrasonography. At last, the patient underwent robot-assisted laparoscopic prostatectomy. During the surgery, a massively enlarged prostate (about 13×10×16 cm) pressing rectum was found. The tumor adhered to rectum anterior wall so tightly that it could not be easily separated. Therefore, partial rectal resection and ileostomy were performed. The microscopic examination showed that neoplasm was composed of spindle cells and epithelioid cells (Figure 2A–C). The mitotic rate was <5/50 high-power fields (HPFs) and foci of coagulative tumor necrosis were observed. The bilateral seminal vesicles and rectum were not involved which excluded the possibility of secondary involvement by a rectal GIST. However, the surgical margin of urethra was positive. The immunohistochemistry analysis showed strong positivity for CD117, CD34 and DOG-1 (Figure 2D–F), but negative for S-100, desmin, smooth muscle actin (SMA) and cytokeratin (CK). Furthermore, the Ki-67 index was approximately 1%.

Based on these findings, consistent with the previous biopsy, the diagnosis of primary prostatic EGIST was finally established. Imatinib mesylate as an adjuvant molecular targeted therapy was suggested after surgery. The postoperative course remained uneventful. The patient was still in good physical condition and no recurrence or distant metastasis was observed at 6-month follow-up.

Discussion

Most of GISTs arise from the gastrointestinal tract, among which stomach accounts for approximately 70%.[4] EGISTs are relatively rare, only constituting <10% of GISTs mainly located in the mesentery, omentum and retroperitoneum.[5–7]

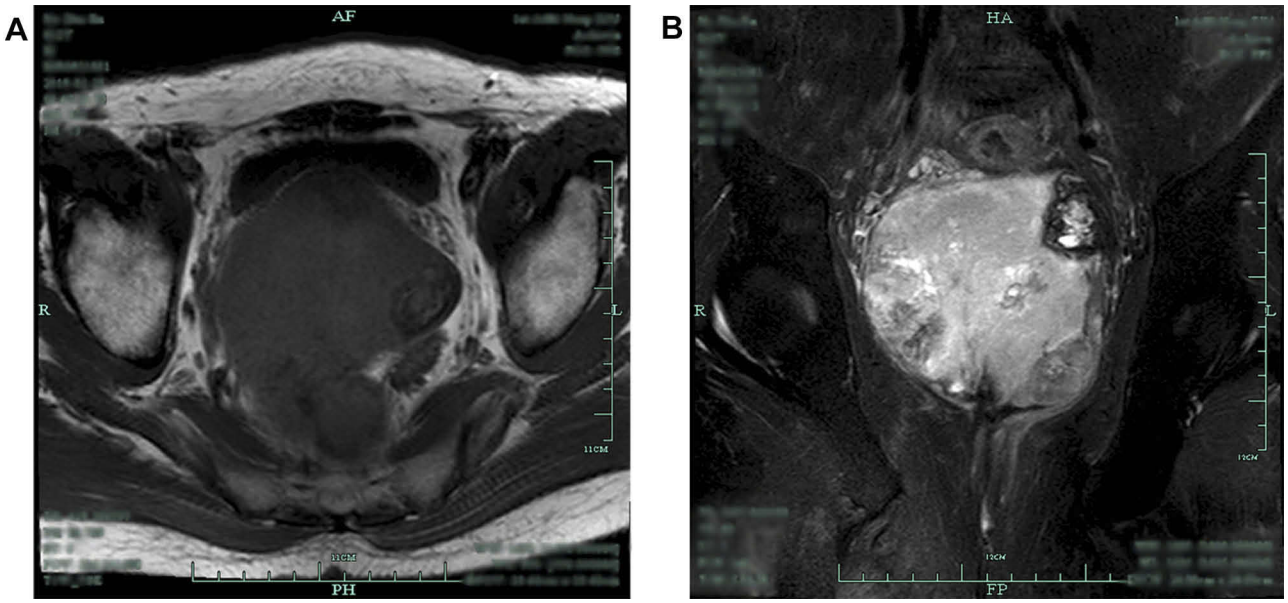


Figure 1 Magnetic resonance imaging (MRI): showed an enlarged prostate with abnormal morphology, a large prostate compressing against bilateral seminal vesicles, the anterior wall of rectum and other adjacent pelvic structures, several foci with abnormal signal mixed in the prostate. (**A**) T1WI and (**B**) T2WI.

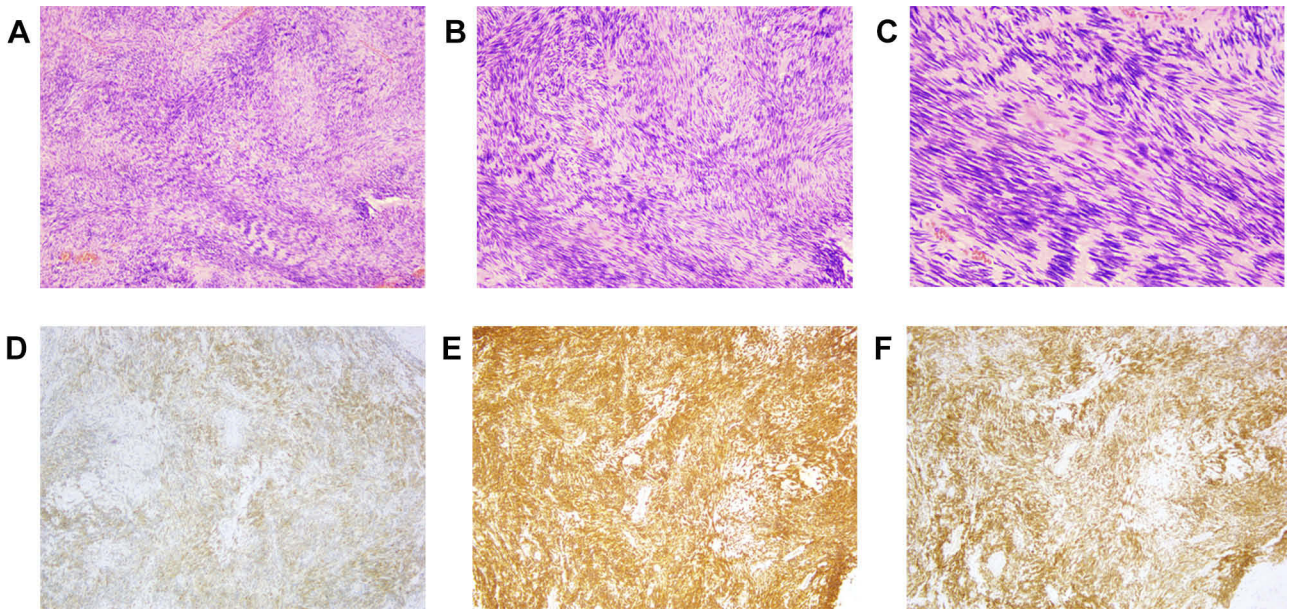


Figure 2 Histopathology and immunohistochemistry of the tumor. (**A–C**) H & E staining showed disordered diffusion of tumor cells, mainly composed of spindle and epithelioid cells. (**C**) The karyokinetic phase of the tumor cell was observed (<5/10 HPFs). Immunohistochemical examination showed diffusely positive for CD117 (**D**), CD34 (**E**) and DOG-1 (**F**). (Magnification: **A, D, E, F**, ×50; **B**, ×100; **C**, ×200).

The primary prostatic EGISTs are extremely rare. The first case was reported by Van Der Aa et al in 2005.[8] As far as we know, only 13 cases have been reported in English on PubMed. Herein, this present case should be the 14th literally reported primary prostatic EGISTs. The major clinical manifestation reported in literature includes frequency, urgency, dysuria, acute urinary retention, vague perineum pain and constipation.[9–13] However, some cases were occasionally found by routine general physical examination without any symptoms.[14] The early diagnosis of prostatic EGISTs is difficult because of its rarity and lack of typical symptoms. MRI and CT are crucial imaging methods for the diagnosis of primary prostatic EGISTs. The features of tumor and adjacent tissues are simultaneously showed by MRI and CT, making it useful to identify other original sites, especially to determine whether the EGIST is associated with the rectum. Madden et al reported that GISTs arising from the rectum with clinical manifestation as prostatic masses could easily be misdiagnosed.[15] In some cases, ^{18}F-FDG PET/CT was performed to find other primary sites.[11,14] Ultrasonography and MRI showed an enlarged prostate compressing backward the rectum without any other suspicious lesions in our case. Similar to GISTs, the diagnosis of EGISTs mainly depends on the feature of microscopic study and immunohistochemistry. Microscopically, neoplasm cell morphologies are mainly comprised of spindle cells, epithelioid cells and polymorphic cells. The immunohistochemical staining demonstrated that the positive ratio for CD117, CD34 and DOG-1 of EGISTs were about >81%, 50% and 92%, respectively.[12,16,17] Moreover, gene mutation screening of c-kit and PDGFRA facilitates to confirm the diagnosis.[18] Based on the positivity of CD117, CD34 and DOG-1 in immunohistochemistry and the mutation of c-kit exon 11, the diagnosis of EGISTs in our case was established.

Surgical resection remains the primary treatment for non-metastatic EGISTs. Completely removal of the tumor together with invaded surrounding organs as possible is required. Considering EGISTs are not sensitive to conventional chemotherapy and radiotherapy, imatinib mesylate is proposed as adjuvant therapy for advanced, unresectable and metastatic cases. As a tyrosine kinase inhibitor of c-kit and PDGFRA, imatinib mesylate has been proven to be an effective therapy for GISTs and EGISTs.[19–21] Tumor size and mitotic activity have been reported as significant prognostic factors, which should be considered for precise risk stratification and classification.[22,23] With the maximum tumor size of 6 cm and mitotic rates of <5/50 HPFs, the present case belonged to the intermediate-risk group. Therefore, the patient received neoadjuvant therapy of imatinib mesylate for about 1 month, followed by radical prostatectomy. Because of the positive urethral margin, the patient was administrated to adjuvant imatinib mesylate therapy and no recurrence or metastasis was found in the 6-month follow-up period. It is the first

literature case report of pre- and post-surgery treatment in primary prostatic EGISTs ever since imatinib mesylate has been proven effective to GISTs. According to the 6 months follow-up evidence, imatinib mesylate showed a significantly beneficial outcome as an adjuvant pre- and post-surgery therapy for advanced cases. However, more clinical evidence was warranted to prove the therapeutic value of imatinib mesylate in primary prostatic EGISTs.

Conclusion

In summary, we reported an extremely rare case of primary EGISTs originated from the prostate. EGISTs should be considered in cases with enlarged prostate but slightly elevated or normal PSA level, even in a young man. The diagnosis mainly depends on the positivity of CD117, CD34 and DOG-1 in immunohistochemistry findings. Radical surgery is the predominant treatment of non-metastatic prostatic EGISTs. And, the role of both neoadjuvant and adjuvant with imatinib mesylate in certain selected cases needs to be incorporated.

Ethics Approval and Consent for Publication

Written informed consent for publication of the clinical details was obtained from the patient, and this study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University.

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Disclosure

The authors report no conflicts of interest in this work.

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