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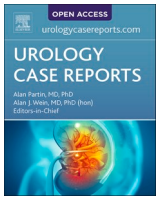

Oncology

Penile metastasis from a duodenal gastrointestinal stromal tumor: A rare case report

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ABSTRACT

Penile metastases are rare, and metastasis of a gastrointestinal stromal tumor (GIST) to the penis is exceedingly uncommon. An 81-year-old man with a history of duodenal GIST, initially treated with curative resection and tyrosine kinase inhibitor therapy for liver metastasis, presented with an enlarging penile mass. A biopsy confirmed penile metastasis from GIST. To relieve his symptoms, a total penectomy was performed. Molecular testing revealed a KIT exon 9 mutation and CDKN2A/B gene alterations, indicating aggressive tumor behavior and resistance to standard treatment. This case underscores the importance of recognizing atypical metastatic sites in GIST.

1. Introduction

Gastrointestinal stromal tumor (GIST) is rare neoplasm of mesenchymal origin, typically arising from the stomach or small intestine.[1] Duodenal GISTs account for less than 5 % of cases, and metastasis commonly involves the liver or peritoneum. Penile metastases are an extraordinary clinical finding, with less than 500 cases reported across all malignancies and only one involving GIST.[2,3] Here, we report the second known case of penile metastasis from GIST, originating from a duodenal primary tumor.

2. Case presentation

An 81-year-old man with a history of prostate cancer and lung adenocarcinoma, both in remission following radiotherapy, was diagnosed with duodenal GIST during evaluation for anemia. The tumor was surgically resected via subtotal gastrectomy with pancreas-preserving duodenectomy. Pathology confirmed a spindle-cell GIST with low mitotic activity (2/50 HPF) and KIT positivity, classified as low risk for recurrence per the Modified Fletcher criteria.

Three years postoperatively, hepatic metastases were detected, and the patient was started on imatinib (400mg daily). Despite treatment, the patient developed a progressively enlarging penile mass over the next year. MRI demonstrated a well-demarcated subcutaneous lesion on the ventral aspect of the penis (Fig. 1). Biopsy revealed spindle-shaped cells consistent with GIST, confirmed by positive KIT immunostaining. The patient underwent total penectomy for symptomatic relief. Pathological evaluation confirmed penile metastasis from GIST, with tumor infiltration beneath the penile skin and displacement of the corpora cavernosa (Fig. 2). Pathology of the resected penile tumor confirmed a spindle-cell GIST with high mitotic activity and KIT positivity, classified as high risk of Modified Fletcher criteria (Fig. 3). Molecular testing revealed a KIT exon 9 mutation in both the primary and penile metastatic sites. However, no alteration was found in platelet-derived growth factor receptor alpha (PDGFRA) genes. A comprehensive genomic profiling test in the metastatic site revealed Cyclin-dependent kinase inhibitor (CDKN) 2A/B gene alterations were found. Despite continued systemic therapy, the disease progressed rapidly, and the patient succumbed six months later.

3. Discussion

Penile metastasis is a very rare ty of type advanced malignancies and typically occurs due to direct extension or hematogenous spread from pelvic organs. Metastasis of GIST to the penis is extremely uncommon, with only one previously reported case involving a rectal primary

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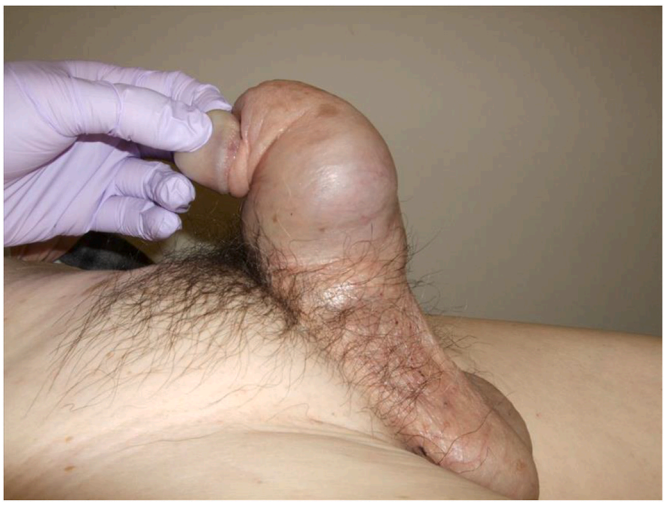

Fig. 1. Progressively enlarging penile mass.

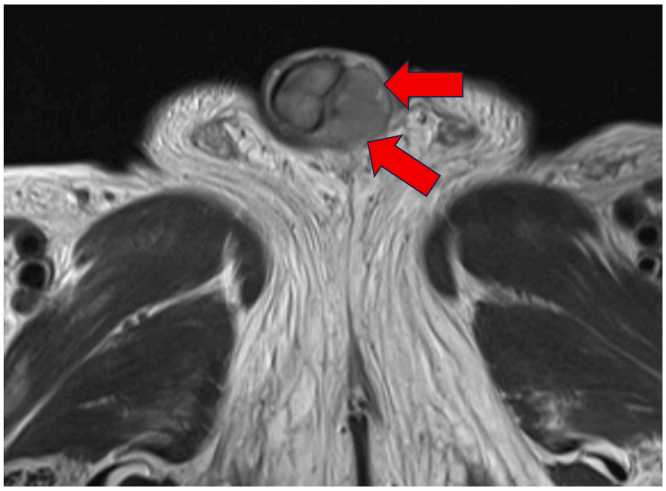

Fig. 2. T2 sequence of MRI of the pelvis demonstrates a well-demarcated subcutaneous lesion on the ventral aspect of the penis (arrow).

tumor.[3]

In this case, the patient was found to have a KIT gene mutation. Approximately 75–80 % of GISTs have mutations in the KIT gene, which leads to continuous activation of the receptor tyrosine kinase and promoting uncontrolled cell growth.[1,4] On the other hand, approximately 10–15 % of cases have PDGFR gene mutations, which are more commonly found in the stomach compared to KIT-mutated GISTs.[1,4] KIT exon 11 mutations are most common and rerated to good response to imatinib, exon 9 mutations are seen in 10–15 % of cases (4–6). They are more frequently found in GISTs arising from the small intestine and often linked to more aggressive disease and poorer response to standard-dose imatinib.[5–8] Higher doses of imatinib (800mg daily) have shown improved response rates and progression-free survival in metastatic cases.[7] Therefore, the standard dose for advanced GIST patients with KIT exon 9 mutations receiving first-line imatinib is 800 mg.[9] However, they benefit less from imatinib in both adjuvant and metastatic settings compared to exon 11 mutations.[7] This patient did not undergo PCR testing to determine the KIT mutation at the time of the initial diagnosis. If a PCR test had been performed in the early phase, a dose of 800 mg of imatinib might have been more effective for treating the cancer.

The patient also showed CDKN2A and CDKN2B deletions in the penile metastatic site, which are most commonly seen in patients with GIST.[10] CDKN2A and CDKN2B are tumor suppressor genes located on chromosome 9p21.[11] These genes encode tumor suppressor proteins that regulate the cell cycle, and their loss leads to uncontrolled cell growth and tumor formation.[12] A recent study in Japan showed that loss of CDKN2A/CDKN2B was only observed in KIT/PDGFRA-mutant GISTs.[10] In addition, more than 70 % of patients had both CDKN2A and CDKN2B deletions. CDKN2A/B deletions are more commonly seen in high risk GISTs compared with the other risk GISTs and also linked to aggressive tumor behavior and resistance to standard treatment.[13,14]

We observed a significant discrepancy in the histopathologic findings between the primary tumor and the clinical course. The primary tumor is classified as low risk based on tumor size and mitotic rate, which is expected to have a favorable clinical outcome. However, the tumor showed rapid progression and resistance to therapy. The combination of a KIT exon 9 mutation and CDKN2A/B deletions explains the aggressive progression observed in this case. This suggests that genetic mutations play a critical role in determining prognosis, beyond traditional risk factors.

Surgical intervention for metastatic GIST is typically performed either for symptom relief or when complete resection is feasible. In this case, a total penectomy was carried out to alleviate symptoms caused by

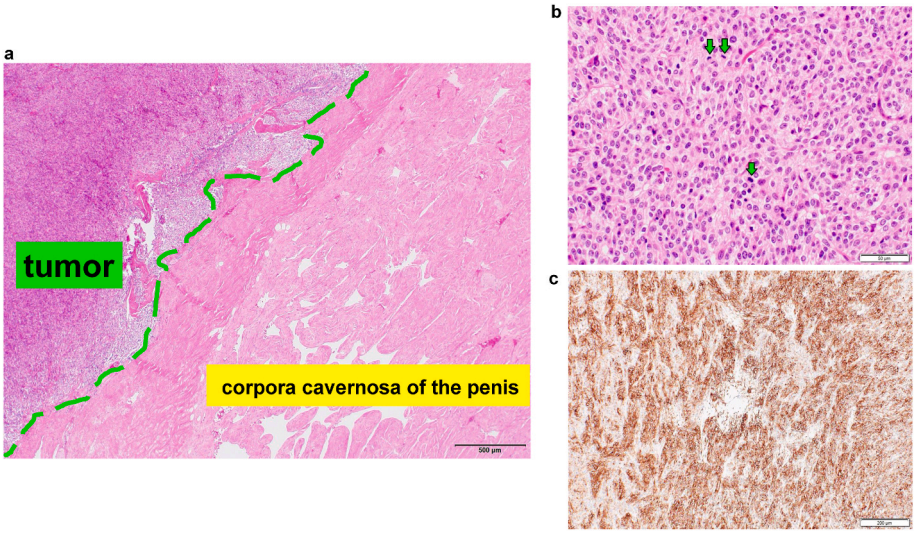

Fig. 3. The tumor is located beneath the penile skin and compresses the corpora cavernosa (a). Tumor cells are spindled (b) and diffusely positive for KIT (c).

penile metastasis. While the surgery improved the patient's quality of life, it did not affect disease progression, underscoring the importance of systemic therapy in advanced GIST cases. The exact mechanism of penile metastasis from GIST remains unclear. Interestingly, the first reported case of penile metastasis from GIST identified a KIT gene exon 11 mutation, which differs from the findings in our case.[3] Because penile metastasis is extremely rare, it is challenging to provide a definitive explanation for its mechanism.

This case highlights the importance of genomic profiling in GIST patients, especially those with atypical presentations or unexpected progression. Identifying genetic mutations might help guide personalized treatment strategies. Moreover, clinicians should note that even low-risk GISTs may behave aggressively when driven by certain genetic alterations.

CRediT authorship contribution statement

Fumiya Yoneyama: Data curation, Investigation, Resources, Validation, Writing – review & editing. **Teppei Okamoto:** Conceptualization, Data curation, Investigation, Resources, Validation, Writing – original draft, Writing – review & editing. **Tomoko Hamaya:** Writing – review & editing. **Hirotake Kodama:** Writing – review & editing. **Naoki Fujita:** Writing – review & editing. **Hayato Yamamoto:** Writing – review & editing. **Atushi Imai:** Writing – review & editing. **Shingo Hatakeyama:** Supervision, Writing – review & editing.

Statement of ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. No identifiable images or data are included in this report.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to edit English. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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