

## Primary extragastrointestinal stromal tumor arising in the vaginal wall: Significant clinicopathological characteristics of a rare aggressive soft tissue neoplasm

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### Abstract

Gastrointestinal (GI) stromal tumor is the most common mesenchymal neoplasm of the GI tract but also occurs with a lower frequency in extragastrointestinal regions and is called extragastrointestinal stromal tumor (EGIST). We report an unusual case of EGIST presenting as a vaginal mass. A 41-year-old woman presented with a gradually enlarging vaginal mass for the last 2 years. Physical examination revealed an elliptical, non-tender mass about 7.5 cm × 7 cm in size in the posterior vaginal wall and was resected completely. Under histological examination, the tumor showed a spindle cell type with coagulation necrosis, hemorrhage and high mitotic count. Immunohistochemical analysis revealed tumor cells were positive for DOG1, CD117, CD34 and p53 protein. Ki-67 labeling was 8%. Genetic analysis showed a deletion of exon 11 of the *c-kit* gene at codons 557-558. EGISTs should be kept in mind in the differential diagnosis in patients presenting with solid mass of the vaginal wall.

**Key words:** Platelet derived growth factor receptor alpha; Extragastrointestinal stromal tumors; Vagina; *c-kit*; Mutation

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**Core tip:** Gastrointestinal (GI) stromal tumor is the most common mesenchymal neoplasm of the GI tract but also occurs with a lower frequency in extragastrointestinal

regions and is called extragastrointestinal stromal tumor (EGIST). We report an unusual case of EGIST presenting as a vaginal mass and describe its clinicopathological, immunohistochemical and genetic features. Our data shows that this case was a primary malignant EGIST in the vaginal wall but few cases of primary vaginal EGIST have been reported to date. EGISTs should be kept in mind in the differential diagnosis of patients presenting with a solid mass of the vaginal wall.

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## INTRODUCTION

Gastrointestinal (GI) stromal tumors (GISTs) are the most common mesenchymal neoplasms of the GI tract. They affect all segments of the digestive tract, usually originate in the wall of the stomach or small intestine and develop from the interstitial cells of Cajal<sup>[1]</sup>. The pathogenesis of GISTs is related to *c-kit* gene mutation, which results in activation of a *c-kit* receptor tyrosine kinase (KIT, also called CD117 or stem cell factor receptor), then cell proliferation induction and apoptosis inhibition. Most GISTs harbor gene mutations in either the *c-kit* or platelet-derived growth factor receptor alpha (*PDGFRA*) gene. Rarely, GISTs arise primarily in the omentum, mesentery, retroperitoneum or undefined abdominal sites, which are referred to as "extragastrointestinal stromal tumors" (EGISTs)<sup>[2]</sup>. To the best of our knowledge, few cases of primary EGIST have been reported arising in the vaginal wall. In this study, we present a rare case of vaginal EGIST and a brief literature review.

## CASE REPORT

A 41-year-old woman complained of a painless mass in the perineal region which had gradually increased in size, initially from about 3 cm × 3 cm to 7.5 cm × 7 cm over a period of 2 years. The patient had no significant past medical or surgical history.

The gynecological examination revealed that the vagina was unobstructed and found a mass measuring about 7.5 cm × 7 cm in size with poor mobility and tenderness in the posterior vaginal wall. Its interior pole was closed to the vaginal opening with no discomfort symptoms such as bearing down. The ultrasonograph diagnosed cervix leiomyoma. The magnetic resonance imaging (MRI) revealed an elliptical mass in the cervix and posterior vaginal wall with a clear margin measuring about 9 cm × 7 cm × 6 cm in size, with equal T1 and T2 signals and a few punctate long T2 signal. The MRI also

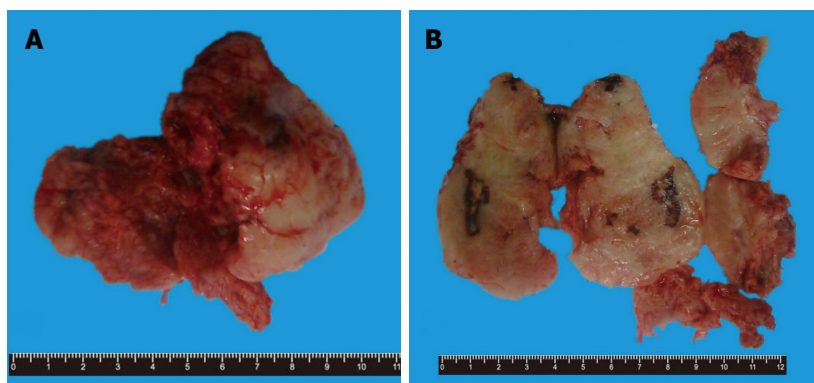
diagnosed leiomyoma. Other laboratory examinations were normal. The mass was completely removed along with part of the vaginal wall using vaginal resection and during the operation gynecologists found the margin of the mass was from the vaginal opening to the fornix vaginae, which was close to the rectum but the mass did not invade the bowel wall.

Grossly, the mass was elliptical, gray-white and grey-red, about 8 cm × 7.5 cm × 5 cm in size. The specimen was a well circumscribed mass and was surrounded by a fibrous capsule with pushing borders. Its section was also gray-white and grey-red in color with medium texture, containing multiple hemorrhages and necrosis (Figure 1).

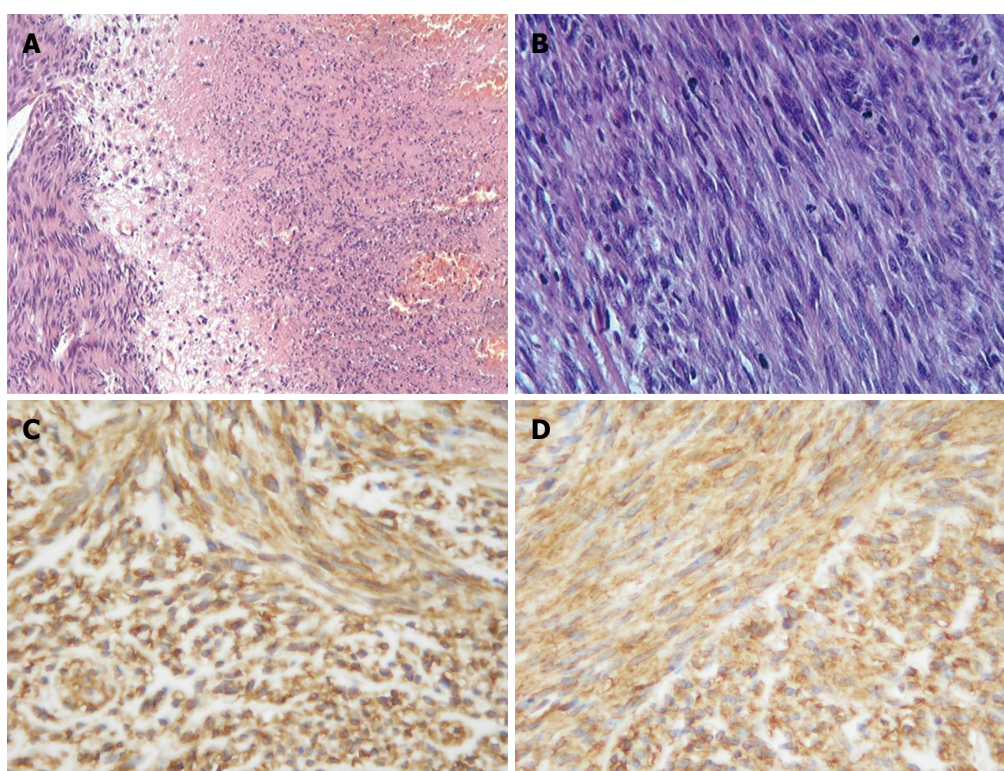
The fresh specimen was fixed in 10% formalin buffer solution and embedded in paraffin. Sections (3-4 μm) were cut from the block and stained with hematoxylin and eosin. Microscopic examination showed that the mass was mainly composed of spindle cells which were arranged in fasciculation or paliform, like leiomyoma or neurilemmoma. The cytoplasm of the tumor cells was eosinophilic and some had clear cytoplasm or paranuclear vacuoles. The nucleus of tumor cells was oval or rod shape with some vesicular chromatin and small prominent nucleoli. There were multiple large or small areas of coagulation necrosis and hemorrhage, accompanied by variable amounts of myxoid stroma (Figure 2A and B). Average mitotic figures were about 25 mitoses per 50 HPFs.

Immunohistochemical study was performed and the following antigens were used. CD117 (*c-kit* oncogene production, No.A4502, polyclonal, 1:70), CD34 (QBEND10, No.M7165, monoclonal, 1:150), S-100 protein (No.Z0311, polyclonal, 1:300), smooth muscle antibody (SMA, No.M0851, monoclonal, 1:200), desmin (No.M0760, monoclonal, 1:150), p53 protein (DO-7, No.M7001, monoclonal, 1:300) and Ki-67 (No.M7248, monoclonal, 1:100) were purchased from Dako Corp. Discovered on GIST 1 (DOG1) (DOG1, clone SP31, Cat.#RM-9132, monoclonal, ready to use) was applied by LabVision Corp. The slides were inserted in 10 mmol/L citrate buffer solution, pH 6.0 and heated in a microwave oven at a high setting for 5 min for epitope retrieval. The slides were incubated with 3,3'-diaminobenzidine tetrahydrochloride, following the use of the EnVision staining technique, and counterstained with hematoxylin. The tumor cells showed diffusely strong positivity for DOG1, CD117 (Figure 2C and D) and CD34 at both the cytoplasmic and membranous components and p53 protein at the nucleus, while tumor cells were completely negative for SMA, desmin and S-100 protein. Ki-67 labeling was about 8%.

Direct sequencing of polymerase chain reaction (PCR) productions was applied to detect the gene mutations of the *c-kit* gene (exons 9, 11, 13, 17) and the *PDGFRA* gene (exons 12, 18). Sections (10 μm) were cut and DNA was extracted from paraffin embedded tissue, according to the protocol of the Dneasy Tissue Kit (Cat.69504, Qiagen, Hilden, Germany). The product was



**Figure 1** Gross findings of the specimen. A: Elliptical gray-white and grey-red soft tissue mass with fibrous capsule; B: Medium texture with multiple hemorrhage and necrosis on the cut surface.



**Figure 2** Histological findings of the tumor. A: The tumor was composed of cellular spindle cells with a large area of necrosis. Hematoxylin and eosin ( $\times 200$ ); B: Active mitosis of tumor cells. Hematoxylin and eosin ( $\times 400$ ). Immunohistochemical findings of the tumors; C: Diffusely and strongly DOG1 positive in the tumor cells ( $\times 400$ ); D: Diffusely and strongly CD117 (*c-kit* pro-oncogene product) positive in the tumor cells ( $\times 400$ ).

stored at  $-20^{\circ}\text{C}$ . Based on the *c-kit* gene and *PDGFRA* gene, 6 pairs of primers were designed and are shown in Table 1<sup>[3]</sup>. The PCR reaction conditions, recommended by Perkin Elmer, were the standard ones. The annealing temperature was set at  $55^{\circ}\text{C}$ . PCR productions were fractionated on 50 g/L polyacrylamide gelatins and then stained with ethidium bromide. The ABI Prism 310 DNA sequencer (Applied Biosystems) was used to perform the direct sequencing by use of the same primers mentioned above. The Big Dye Terminator cycle sequencing ready reaction kit (Applied Biosystems Inc., Foster City, Calif.) was used for the sequencing reactions, according to the manufacturer's instructions.

PCR amplification and DNA sequencing revealed exon 11 mutation of *c-kit* gene. Sequence analysis showed the deletion of 6 bp at codons 557-558 (Figure 3). Other mutations were not found.

The maximal diameter of this mass was 8 cm and average mitotic figures were about 25 mitoses per 50 HPFs. There was multiple coagulation necrosis and hemorrhage. According to the results of immunohistochemistry and genetic mutation in exon 11 of *c-kit* gene, the histopathological diagnosis of this case was primary malignant EGIST in the vaginal wall. The patient was well after surgery and discharged with imatinib (STI-571) treatment. After 5 mo of follow-up,



imatinib (STI-571). DOG1, known also as TMEM16A and ANO1, is currently considered the most specific and sensitive marker of GIST<sup>[13]</sup>. Also, its expression does not depend on the gene mutation state of *c-kit* or *PDGFRA* gene and it is a very valuable marker, especially in CD117-negative cases<sup>[14]</sup>. In molecular genetics, 86% of GISTs present with mutations in the *c-kit* gene and 15% in *PDGFRA* gene<sup>[1]</sup>. In our case, immunohistochemical analysis showed diffusely strong positivity for DOG1, CD117, CD34 and p53 protein, while it was completely negative for SMA, desmin and S-100 protein. Mutational analysis revealed exon 11 mutation of *c-kit* gene that was deletion mutation at codons 557-558. He *et al*<sup>[15]</sup> reported that *c-kit* mutations were identified in 76.1% of CD117 positive GISTs and most were mutations of exon 11 (67.1%). Hou *et al*<sup>[16]</sup> discovered that many mutational sites of exon 11 were not fixed and had a central tendency. Point mutations and frame deletions were most frequently concentrated at codons 550-560 but duplications were most observed at codons 570-585. Terada<sup>[3]</sup> reported that primary EGIST of the omentum showed a deletion mutation of exon 11 of the *c-kit* gene at codons 552-558. Zheng *et al*<sup>[17]</sup> analyzed gene mutations from 25 cases of EGIST and found that the pattern of *c-kit* and *PDGFRA* mutation in EGISTs was essentially similar to that in GISTs, that is, *c-kit* mutations were detected in 44% of EGISTs and all were exon 11 mutations. The *c-kit* gene mutation state and type was not only correlated to malignant degree and prognosis of GIST, but also a predictive factor of imatinib (STI-571) therapeutic reaction, which has important significance in the clinical diagnosis of GIST. Exon 11 gene mutation occurred especially in malignant GISTs and might be a clinical useful adjunct marker in the evaluation of GISTs<sup>[16]</sup>. In our case, exon 11 mutation also occurred and presented with deletion mutations at codons 557-558, identical to those reported in the literature.

The diagnosis of primary EGIST should be based on morphology, immunophenotype and molecular genetic features, and at the same time differentiated from other mesenchymal tumors of GI tract. The present data on EGIST is insufficient to make a final conclusion regarding pathogenesis, biological behavior, treatment, prognosis and recurrence. Thus, follow-up for a long period of time is required.

## COMMENTS

### Case characteristics

A rare extragastrointestinal stromal tumor (EGIST) arising in the vaginal wall.

### Clinical diagnosis

Leiomyoma.

### Differential diagnosis

Leiomyoma, malignant peripheral nerve sheath tumor and stromal sarcoma.

### Pathological diagnosis

EGIST.

### Treatment

Excision and administration of imatinib.

### Related reports

In early reports, extragastrointestinal stromal tumor presented as a recurrent vulvar mass.

### Term explanation

EGIST is a subtype of GIST and occurs in extragastrointestinal regions.

### Experiences and lessons

EGIST mostly has the same biological behavior as GIST.

### Peer-review

This case (GIST in the vaginal wall) is an extremely rare case and well organized. The presentation of the case is clear and the discussion conducted well with updated references.

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