Clinical Case Report

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Gastrointestinal stromal tumor presenting as a rectovaginal septal mass

A case report and review of literature

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Abstract

Introduction: Gastrointestinal stromal tumors (GISTs) arising from the gynecological tract are extremely rare. A case of GIST with an unusual presentation as a vaginal mass is presented with comprehensive literature review, aiming to gain a better understanding of the diagnostic and treatment strategy of the disease.

Patient concerns: A 78-year-old woman presented with persistent vaginal bleeding and difficulty in micturition. Although the tumor mass was diagnosed, the results of preoperative evaluations are uncertain.

Diagnosis: Preoperative evaluation included the computed tomography examination (a 6.3×5.3 cm cervical mass lesion with rectal and vaginal invasion), colonoscopy (an external compression with an intact mucosa), tumor markers, and biopsy (spindle cell tumor). Postoperative histopathology confirmed the diagnosis of GIST.

Interventions: Posterior exenteration with complete resection was performed. The patient received postoperative adjuvant imatinib therapy.

Outcomes: The patient has survived without the disease for more than 3 years.

Conclusion: It is still a challenge to diagnose GISTs in women with rectovaginal mass preoperatively. Efforts should be made, including a high suspicion and an assistance of immunohistochemistry. A precise diagnosis may offer a better surgical and treatment plan, especially on the preservation of reproductive organs and accessibility of targeted therapy.

Abbreviations: CT =computed tomography, EGST = extragastrointestinal stromal tumor, GIST = gastrointestinal stromal tumor, HPFs = high power fields, NIH = National Institutes of Health, SMA = smooth muscle actin.

Keywords: gastrointestinal stromal tumor, mesenchymal tumor, rectovaginal space, spindle cell tumors

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W-LL and P-HW contributed equally to this article.

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1. Introduction

Gastrointestinal stromal tumors (GISTs) are the commonest mesenchymal tumors in gastrointestinal tract,[1] with the most common sites at the stomach (70%), small intestine (20–30%) and others (<10%), including esophagus, colon, rectum, and extragastrointestinal sites.[2,3] GISTs outside the gastrointestinal tract are referred to as extragastrointestinal stromal tumors (EGISTs), comprising only 5% to 7% of GISTs.[3] GISTs or EGISTs rarely occur in the gynecological tract, and sometimes are difficult to distinguish since their origins are unclear. We herein report a case of GIST, which is manifested as a vaginal mass, and patient has written informed consent for publication of the case. To further understand the disease, a systematic literature review was conducted to identify the similar cases and summarize the clinical findings and treatment plan.

2. Clinical case

A 78-year-old woman, gravida 7, para 3, without significant past medical history was referred to our hospital with persistent vaginal bleeding and difficulty of micturition for ten days. Hemoglobin level was 11.0 g/dl on the day of admission. Pelvic-rectal examination revealed a hard, unmovable mass lesion protruding from the right lateral and posterior vaginal wall. The inferior border of the tumor extended to 2 cm above the anus verge. A computerized tomography was performed and demonstrated a heterogeneous soft tissue mass (6.3 cm × 5.3 cm) with

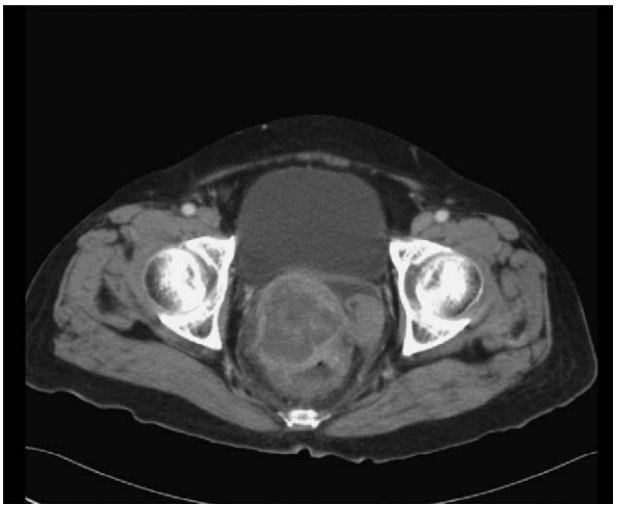

Figure 1. Contrast-enhanced computed tomography revealed a heterogeneous soft tissue mass (6.3 × 5.3 cm) at rectovaginal space abutting to uterine cervix and rectum.

suspicious rectal and vaginal wall invasion, resulting in hydrocolpos, without pelvic or inguinal lymph node involvement (Fig. 1). Serum tumor markers (CA-125 = 16.1 U/ml, CEA = 2.9 ng/ml, SCC = 0.7 ng/ml) were within normal limits. Cervical biopsy through colposcopy was done and showed atypical spindle cells. Immunohistochemical staining of p40, actin, and S100 were negative. Due to inadequate specimen and suspected cervical cancer, a loop electrosurgical excision procedure was performed, and neither spindle cell neoplasm nor evidence of malignancy was identified under pathologic examination. Upon equivocal diagnosis of spindle cell tumor with obstructive micturition, exploratory laparotomy was performed, and the tumor was completely resected. Grossly, the specimen contained an 8.5 × 6 × 3 cm gray-tan necrotic soft tissue with direct invasion to the rectal mucosal (Fig. 2). Microscopically, the tumor consisted of fascicular, spindle-shaped cells. The mitotic count was 7 mitoses per 50 high-power fields (HPFs). Immunohistochemical analysis was strongly and diffusely positive for CD117, DOG1, and h-Caldesmon, but negative for S-100 and smooth muscle actin (SMA) (Fig. 3). The diagnosis was GIST with high risk of malignancy, most likely arising from rectum. The specimens from uterine, bilateral fallopian tubes, and ovaries were unremarkable. The postoperative course was uneventful, and the patient was referred to Department of Medical Oncology for imatinib treatment. To date, the patient has survived without the disease for more than 3 years.

3. Literature search and results

To further understand the disease and treatment strategy, a detailed systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was

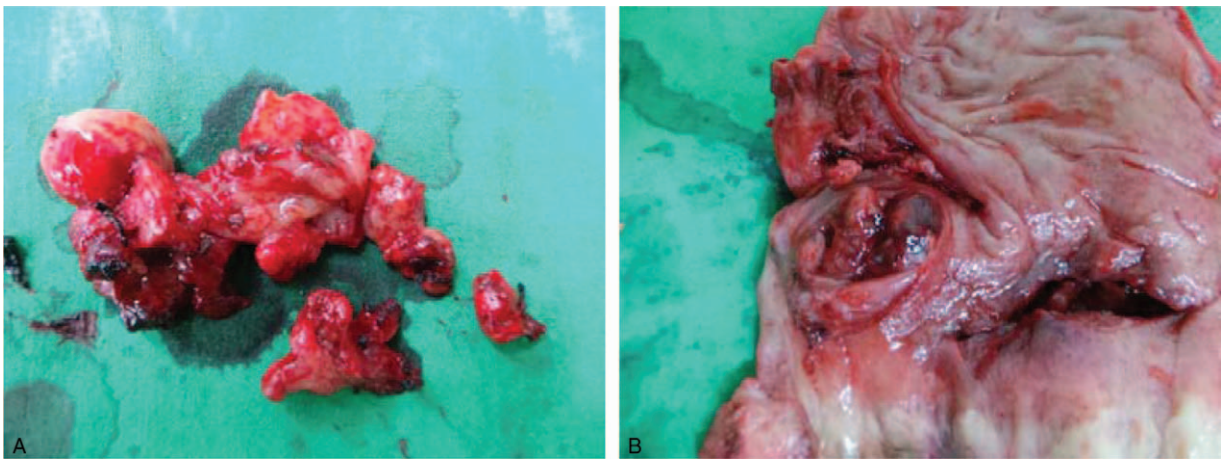

Figure 2. (A) Gross appearance of resected right posterior vaginal wall tumor with necrotic gray-tan soft tissue. (B) Submucosal tumor with 3 × 2 cm mucosal perforation at anterior rectum wall.

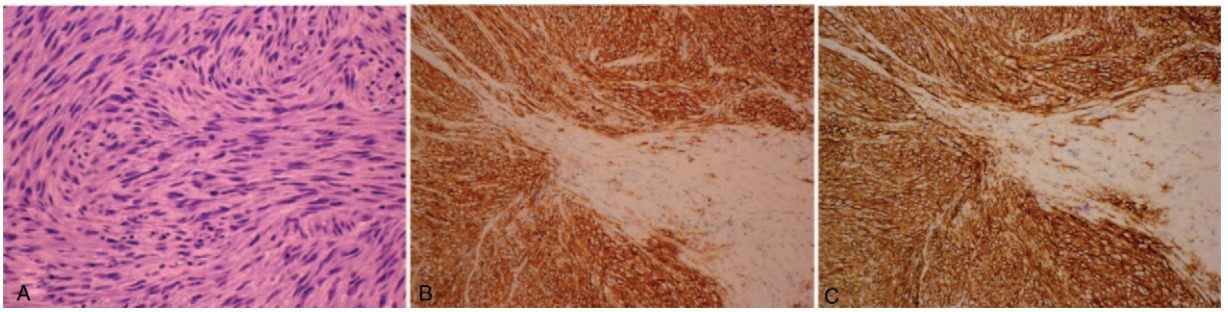

Figure 3. (A) Photomicrograph of resected tumor of rectum revealed spindle-shaped cells with fascicular pattern. (B) Neoplastic cells displayed strongly and diffusely positive for CD117 and (C) DOG1.

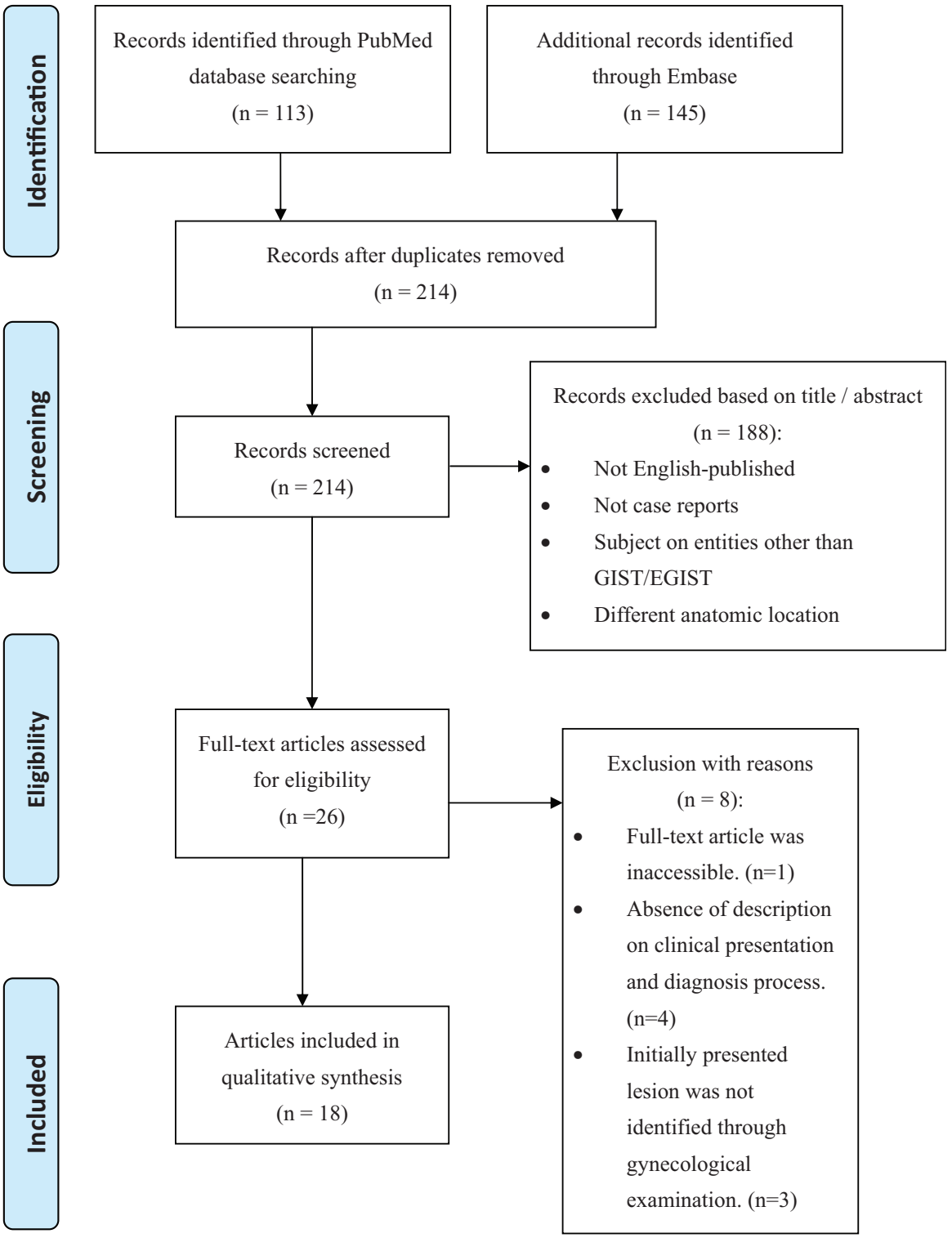

Figure 4. PRISMA flow diagram of literature review.

conducted to identify the similar cases and summarize the clinical findings, initial diagnosis, and treatment plan. The final search was conducted in October 2018. Electronic medical database, PubMed, and Embase were searched for all related literature, using combinations of the following terms: "gastrointestinal Stromal tumor" or "extragastrointestinal Stromal tumor" and "vaginal" or "rectovaginal septum" or "gynecological." Filters were set to find all available English language articles, without limitation on time of publication. Inclusion criteria for the present literature review included case reports, case series, and case characteristic studies, concerning female patients with a diagnosis of GISTs or EGISTs at rectovaginal space (Fig. 4). Two independent reviewers (M Cheng and C-H Liu) selected the identified studies based on the title and abstract. The following

data were collected from all included studies: first author's surname, publication year, sample size, treatment strategies, morphological and immunohistochemical characteristics of the GISTs or EGISTs. We display a flowchart in Figure 1 that summarizes study identification and selection according to PRISMA. Ethics committee approval was not necessary for a systematic review.

The clinicopathological characteristics of previous and the current cases are summarized in Table 1. Only 22 GISTs/EGISTs, including the current case, presenting as vaginal or rectovaginal septal masses have been reported in English since 2004.[4–21] The mean age of patients was 54 years, and the mean tumor size was 6.2 cm. GISTs located in the vagina and retro-vaginal septal space were found in 32% (7/22) and 68% (15/22) of patients, respectively. Cases that received complete resection of tumors and those who had either adjuvant or neoadjuvant targeted therapy included 77% (17/22) and 41% (9/22), respectively. Aside from the current case, a total of 6 patients underwent lesion biopsy at preoperative stage, including 3 new and 3 recurrent cases.[5,6,8,15,16,21] In all new cases ($n = 18$), there were three cases that were precisely diagnosed before definite treatment (3/18,16.7%).[4,6–14,17–21]

4. Discussion

In the current case, we noted an approximate tumor size of 8.5 cm, 7 mitoses per 50 HPFs and tumor rupture under pathological evaluation, and the tumor was defined as a highly malignant GIST according to National Institutes of Health (NIH) consensus classification. Rectal mucosa perforation at the site of lesion was regarded as rapid tumor progression after colonoscopy examination (a 7-day interval). Gastrointestinal stromal tumors (GISTs) from the rectovaginal space are rare and often misleading. The current literature review has shown the low possibility of achieving pretreatment diagnosis. The current case also failed to make accurate preoperative diagnosis.

The clinical manifestations of GISTs originating from rectovaginal space have nonspecific symptoms including bleeding of mass, pain, abdominal distension, and compression effect leading to urinary frequency and constipation. Imaging studies such as computed tomography or magnetic resonance image can provide some clues for clinicians preoperatively. GIST on computed tomography is characterized by well-circumscribed soft tissue mass with heterogeneous density and the low-attenuation parts often suggest necrosis or hemorrhage. Magnetic resonance imaging often shows uniform intermediate enhancement on T1-weighted images and heterogeneous high enhancement on T2-weighted images if necrosis or hemorrhage exists.[17] Although the current case displays the typical features of GIST on computed tomography, these findings were nonspecific, and a pathological proof was essential to confirm the diagnosis.

All previously reported cases demonstrated spindle cells under histologic evaluation, and there were 5 cases (5/21, 24%) having initial diagnosis as leiomyosarcoma or leiomyoma,[5,7,11,12] suggesting the potentially significant diagnostic pitfall before treatment. GISTs and smooth muscle tumors share similar pathological characteristics as fascicular spindle cells. To distinguish GISTs from smooth muscle tumors, conventional histology plus immunohistochemistry might be helpful. Histologically, smooth muscle tumors usually display eosinophilic cytoplasm, whereas GISTs tend to present pale pink cytoplasm in fibrillary pattern.[7] Using immunohistochemistry, leiomyomas and leiomyosarcomas are typically positive for smooth muscle actin, desmin and negative for CD117.[7] Other mesenchymal neoplasms including aggressive schwannomas, angiomyxoma, angiofibroblastoma, and dermatofibrosarcoma protuberans should also be taken into consideration.[7] Schwannomas of rectovaginal septum also show spindle-cell pattern; however, schwannomas are strongly positive for S100 and negative for CD 117.[7] Angiomyxomas and angiofibroblastomas are immunoreactive for actin and desmin, but negative for CD117. Dermatofibrosarcoma protuberans is positive for CD34, which is also seen in the majority of GISTs, but appear negative for CD117.[7] Melanoma and carcinoma should be included in differential diagnosis. Positive CD117 and S100 were frequently presented in melanoma.[22] The current case revealed negative staining of S100 and p40 in biopsy specimen, ruling out melanoma and squamous cell carcinoma, respectively. Furthermore, the absence of pathological finding in cervical conization excluded the possibility of cervical cancer. The diagnosis of GIST was primarily based on immunochemistry, and it was more distinguishable from other mesenchymal tumors by a typical panel of positive immunohistochemical staining including CD117 (95%), DOG1 (98%), CD34 (70%), SMA (50%), S100 (10%), and desmin (5%).[23,24] CD 117 positivity implies the mutation of *KIT* gene, which is a proto-oncogene encoding type III transmembrane tyrosine kinase receptor and a distinctive feature of GISTs. However, it should be noted that CD117 alone is not sufficient to make the definite diagnosis of GISTs, since a number of spindle cell tumors including Kaposi's sarcoma, melanoma also demonstrate immunoreactive CD117.[25] DOG1 displays both high sensitivity and excellent specificity for GISTs, with false positive rate $< 1\%$ in spindle cell tumors[26] The combination use of CD117 and DOG1 staining is reliable in confirming the diagnosis of GISTs. CD34, SMA, and S100 immunostaining act as complementary diagnostic tests if either CD117 or DOG1 staining shows negative result.[25]

The current treatment of choice for vaginal smooth muscle tumors is a margin-free resection of primary tumor and the possible site for uterine sarcoma included,[27] suggesting the variant and individualized extent of surgical excision based on clinical evaluation.[28] On the other hand, the standard treatment for GIST is an en bloc tumor excision with negative margins and segmental resection of the primary site.[29] Regarding the issue of preserving reproductive organs, a precise diagnosis before treatment is relevant for making optimized surgical plan.

The constitutive activation of *KIT* due to gain-of-function mutation is the target of anti-tyrosine kinase therapy.[30–33] Adjuvant imatinib therapy has been shown to improve recurrence-free survival rate for patients with high risk of recurrence after complete resection of primary GIST.[34–39] Several retrospective studies have suggested that the administration of neoadjuvant imatinib may reduce surgical morbidity in patients with advanced primary GISTs,[40–44] which could be potentially beneficial for patients with confirmed preoperative diagnosis.

5. Conclusions

The diagnosis of soft tissue stromal tumors is challenging owing to complex histology and diverse entities. Histological evaluation of biopsy specimens is often inadequate for reaching accurate diagnosis. Therefore, immunochemistry plays a crucial role in

Table 1

Clinicopathologic properties of cases with diagnosis of GIST/EGIST presenting as vaginal/rectovaginal mass.

Author	Age (years)	Size (cm)	Tumor location	Biopsy pathology	Treatment	IHC in surgical pathology			
						CD117	DOG1	SMA	S100
Nasu et al[4] (2004)	54	8.5	R-V sep	ND	Local excision + APR + LN	+	ND	+	–
Ceballos et al[5] (2004)	75	4.5	Vagina	(Recurrence) GIST	Local excision	+	ND	–	–
Weppler et al[6] (2005)	66	8	R-V sep	GIST	Imatinib	ND	ND	ND	ND
Lam et al[7] (2006)	36	4	Vagina	ND	ND	+	ND	–	ND
Lam et al[7] (2006)	48	6	Vagina	ND	ND	+	ND	–	–
Lam et al[7] (2006)	61	8	R-V sep	ND	ND	+	ND	–	ND
Takano et al[8] (2006)	38	7	Vagina	GIST	Local excision + LAR	+	ND	+	–
Hsu et al[9] (2006)	67	9	R-V sep	ND	TAH + BSO + APR + Colostomy + Imatinib	ND	ND	ND	ND
Kim et al[10] (2006)	76	9.5	R-V sep	ND	TAH + BSO + Mass debulking surgery + STI-571 + Imatinib + Novartis				
Nagase et al[11] (2007)	42	3.5	R-V sep	ND	Local excision	+	ND	–	–
Nagase et al[11] (2007)	66	5	Vagina	ND	Local excision + Imatinib	+	ND	–	–
Molina et al[12] (2009)	56	5	R-V sep	ND	Local excision + Radiation	+	ND	+	–
Zhang et al[13] (2009)	42	8	R-V sep	ND	Local excision + Hysterectomy	+	ND	–	ND
Shafiq et al[14] (2009)	59	1.5	R-V sep	ND	Local excision + Hysterectomy + Colostomy	+	ND	+	-
Fregnani et al[15] (2011)	60	2	R-V sep	(Recurrence) Spindle cell	Local excision	+	ND	ND	ND
Pelz et al[16] (2011)	39	8.3	R-V sep	(Recurrence) GIST	Local excision + Imatinib	+	ND	+	–
Vazquez et al[17] (2012)	29	6	R-V sep	ND	Local excision	+	ND	+	–
Munoz et al[18] (2013)	15	2	R-V sep	ND	Transrectal resection + Imatinib	+	+	–	–
Melendez et al[19] (2014)	80	6	R-V sep	ND	Local excision + Imatinib	+	ND	–	ND
Liu et al[20] (2016)	41	8	Vagina	ND	Vagina resection	+	+	–	–
Hanayneh et al[21] (2018)	58	8.9	Vagina	EGIST	Neoadjuvant Imatinib	+	+	–	ND
The current case	78	8.5	R-V sep	Spindle cell	TAH + BSO + Local excision + APR + Imatinib	+	+	–	–

APR = abdominoperineal resection, BSO = bilateral salpingo-oophorectomy, LAR = low anterior resection, IHC = immunohistochemistry, LN = lymphadenectomy, ND = not described, R-V sep = rectovaginal septum, TAH = total abdominal hysterectomy.

distinguishing GISTs from other mesenchymal neoplasms. The combined use of CD117 and DOG1 staining is helpful in making precise diagnosis before treatment. Despite its rarity, GISTs should be considered as one of the possible differential diagnoses in patients presenting with vaginal or rectovaginal septal masses during gynecologic examination with the view of a better surgical plan for preserving reproductive organs and accessibility for targeted therapy.

Author contributions

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Project administration: Peng-Hui Wang.
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Writing – original draft: Min Cheng, Peng-Hui Wang.
Writing – review & editing: Min Cheng, Chia-Hao Liu, Wen-Ling Lee, Peng-Hui Wang.
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