



Multivisceral Resection by Abdominal-Perineal Approach of a Recurrent Extra-Gastrointestinal Stromal Tumor: A Case Report

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Abstract

Gastrointestinal Stromal Tumors (GIST) are a rare heterogeneous group of non-epithelial neoplasms which originate from gastrointestinal mesenchymal tissue. Very rarely, these tumors arise from extraintestinal site. In these cases they are defined as Extragastrointestinal Stromal Tumors' (EGISTs). The most common sites are the omentum, the mesentery and the retroperitoneum. EGISTs represent 1% of all GIST.

We report a rare case of a recurrent EGIST of the Rectovaginal Septum (RVS) considering that identification, incidence, tumor behavior, and surgical treatment is still debated.

In July 2004 a 43-year-old woman underwent local excision for EGIST of RVS in another hospital. Adjuvant Treatment (AT) with Imatinib and a follow-up every 4 months was scheduled. In February 2011 Local Recurrence (LR) occurred. Low anterior resection of the rectum extended to the lesion was undergone. Imatinib was resumed with closed follow-up. In April 2017 a second LR of the vaginal canal occurred. A new pharmacological trial based on Sunitinib and Masitinib was started. In June 2018 by CT scan and pelvic-MRI, a third LR closed with the neo-rectum and the vagina's distal portion was identified. Clinically the patient presented a voluminous and painful mass of the perineal region and Rectovaginal Fistula (RF) with loss of stool. By the Multidisciplinary Team (MDT) meetings debulking surgery was planned and performed through a multivisceral resection of the LR by three Surgical Teams (ST) with a combined abdominal-perineal approach. MDT and specialized ST are mandatory in the management of these rare tumors that must be provided in cancer center.

Keywords: Extragastrointestinal gist; Multidisciplinary team; Multivisceral resection; Imatinib

Introduction

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal tumors in gastrointestinal tract. GISTs develop from the interstitial cells of Cajal and are generally characterized by oncogene mutations of the KIT gene [1,2].

The most common sites are: The stomach (50% to 70%), small intestine (20% to 30%), and others (<10%), including esophagus, colon, rectum and extra-gastrointestinal sites [3].

GISTs outside the gastrointestinal tract are defined to as Extragastrointestinal Stromal Tumors (E-GISTs), comprising only 5% to 7% of GISTs [4].

GISTs are the paradigm of a cancer that requires a multidisciplinary management and approach, targeted diagnosis and therapy [5].

GISTs or E-GISTs rarely occur in the gynecological tract, and are very difficult to distinguish since their origins are unclear [6]. To the best of our knowledge, few cases of primary E-GIST have been reported arising in the rectumvaginal septum. In this study, we present a rare case of

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rectumvaginal septum E-GIST.

Case Presentation

A 57-year-old patient with no comorbidity and previous diagnosis of E-GIST of the rectumvaginal septum came to our surgical department.

She was already treated by surgery and pharmacological therapy in no referral cancer center.

By physical exam the emission of loose stools and air from the vagina was reported. Clinical history began at the age of 43 (July 2004) with tenesmus (rectal "weight") and pain.

The patient carried out clinical instrumental tests in another hospital; a pelvic mass of the rectumvaginal septum was described by CT scan.

In July 2004 she was undergone by a transanal approach to local excision of the lesion. The histological and Immunohistochemical (I.H.C.) report was GIST of rectum with a prognosis more aggressive; number of mitosis >5 per 50 High Power Fields (HPF); tumor size >2 and <5 cm.

The patient started adjuvant treatment with Imatinib 400 mg twice/daily until 2009 according to the various therapeutic schemes and was subjected at close follow-up.

In February 2011 the patient reported tenesmus and rectorrhagia. CT scan total body and the pelvic MRI showed a 5 cm lesion in the rectum. The adjuvant treatment (Imatinib) was resumed with an excellent response and volumetric reduction of the mass demonstrated by CT scan and MRI. After that patient underwent low anterior resection, Colo-J Pouch Anal anastomosis and covering stoma.

Pathological report outcome was GIST of 3.2 cm (mitosis 12×50 HPF; exon mutational analysis 11). The patient continued Imatinib with absence of disease during the follow-up. In April 2017, at CT scan there was evidence of a solid oval lesion at the level of the lower third of the vaginal canal. The lesion was biopsied resulting as GIST.

Then a second line of a new pharmacological trial based on Sunitinib and Masitinib was proposed and accepted by the patient. After a screening phase, she was initiated on the protocol and randomized to Masitinib.

After 3 months a disease progression was detected by MRI with an increase in the vaginal lesion. The patient was followed only by an oncologist and started Sunitinib 12.5 mg three/daily with her consent.

In June 2018, a large solid mass of 4.5 cm \times 5 cm at the rectumvaginal septum emerging at the level of the pelvic floor was detected by MRI and TC.

This mass had contiguity with the neo-rectum and the distal portion of the vagina (Figures 1a-1c).

The patient started Regorafenib therapy, with no clinical benefit. Finally, in October 2018 the patient was addressed to our surgical department. During the physical exam, a painful solid mass of 5 cm covered with hyperemic skin was evident in the perineal region. Vaginal exploration showed an extrinsic compression of the perineal mass and the presence of fecal material in the vagina (Figure 2).

The patient was evaluated by the Multidisciplinary Team (MDT): Urologist, gynecologist, radiologist, oncologist, colon-rectal surgeon

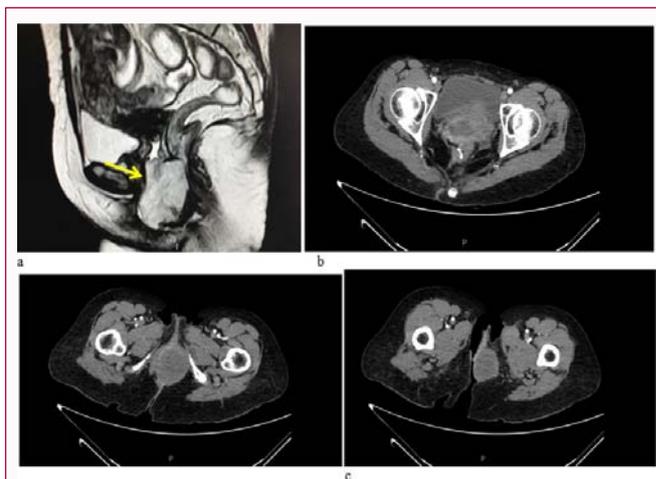


Figure 1: The imaging shows the location of the rectovaginal septum GIST. a) Sagittal (T2W) MRI show the mass (arrow) located in the vaginal-rectal space and protruded from the anterior rectal wall. b, c) CT scans result of transvaginal ultrasound show that the tumor protruded from the posterior of the lower vaginal wall.

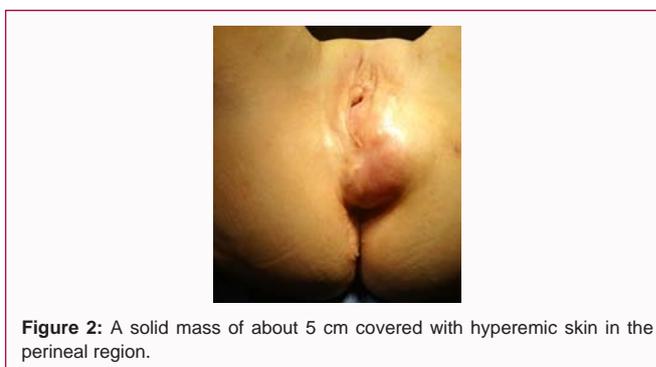


Figure 2: A solid mass of about 5 cm covered with hyperemic skin in the perineal region.

and plastic surgeon. MDT represented an important role in this challenging clinical. The long history of the patients has been widely evaluated.

Several recurrences, several lines of pharmacological treatment with side effects, disease progression, symptomatic mass at risk of systemic sepsis and local progression were taking into account for planning a surgical procedure with radical intent.

The American Society of Anesthesiologists (ASA) score was three. Three surgical teams' colorectal surgeons, gynecologist and plastic surgeons were in different phase involved.

Treatment

Abdominal phase: The surgery began with a median re-laparotomy followed by a complex viscerolysis. The abdominal phase consisted of a left end-colostomy. The closure of the laparotomy was reinforced by the use of a supra-fascial prosthesis of bovine pericardium.

Perineal-pelvic phase: An enlarged vulvectomy was performed and a section of the posterior vaginal wall about 2 cm from the cervix falling on healthy tissue. This bulky tumor about 12 cm was fragile, infiltrating the J-pouch and crops out on the left perineal skin. The colon detached itself from the posterior wall of the vagina always on healthy tissue. Excision of the anus and removal of the mass. The reconstructive phase performed by plastic surgeons consisted of a double V-Y sliding flaps and reconstruction of the perineum (Figure



Figure 3: Intraoperative images of the reconstructive phase by team plastic surgeons.

3). Operative time was 420 min. Clavien-Dindo score was II.

Outcome and follow-up

The patient was discharged on 15th post-operative day in good clinical condition, carrying a bladder catheter. The specimen consisted of: Tumor with a colo-vaginal fistula, the posterior vaginal wall, the neo-rectum and anus. Macroscopic findings of the specimen: As a knot of 10.2 cm × 6 cm × 6 cm of whitish when cut and with adherent skin lozenge of 9 cm × 5 cm.

The microscopic findings was a GIST of the colo-anal anastomosis, mitotic index higher than 5/5 mmq (34/20 HPF); positive immunohistochemistry for CD117 e CD34, negative for S100, desmin, actin ML and SOX10. According to Miettinen risk stratification: High degree. Surgical margins were free of tumor.

The patient resumed therapy with Imatinib 400 mg twice/daily. After absence of disease for 4 months, a CT scan revealed osteomedullary recurrence disease with lytic lesions of the posterior pillar of the root and left ischial bone and contralateral ischium. MRI of the spine confirmed the lesions highlighted on the CT scan. Moreover other secondary lesions were found at the level of all lumbar metamers with slight compression of the vertebral specimen with the absence of myelomalacia and other lesions at the level of the sacrum, Ischia pubic branches and bilateral femoral cephalic regions.

Local radiotherapy for analgesic purposes were associated with pain pharmacological therapy. The patient died 15 years after the first surgery and after 11 months from our surgical procedure.

Discussion

Gastrointestinal Stromal Tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract [6], typically arising in the wall of the stomach or small intestine [7].

GISTs comprise around 1% of all primary Gastrointestinal (GI) cancers [8]. They occur in the GI tract in 80%, while 10% in the retroperitoneum and pelvis. Most EGIST is related to metastases of primary GIST. Primary EGIST is very rare; the sites are: The omentum, mesentery, retroperitoneum and recto-vaginal septum with clinic-pathologic and molecular features similar to GISTs [1].

Rare cases of omental, mesenteric localizations have been described, as well as at the genital apparatus, appendix and gallbladder. All these are classified E-GISTs. The incidence of E-GISTs is reported to be approximately 10% or less of all GISTs [7,9].

The location in the rectumvaginal septum is rare and often misleading. Only a few cases are reported in the literature [7,10-13].

Many reviews reported have shown the low possibility of achieving a pretreatment diagnosis [6].

Our case is a multiple recurring E-GIST of rectumvaginal septum. In the first surgery there was no accurate preoperative diagnosis and the resection margins have not been described.

The histology of our patient at the first surgery showed intratumoral coagulation necrosis, classifying the lesion as unfavorable prognosis with aggressive behavior.

The clinical manifestations of the rectumvaginal septum can be asymptomatic, non-specific symptoms including bleeding of mass, pain, abdominal distension, and compression effect leading to urinary frequency and constipation, as in the case reported by Vazquez et al. [14], Dimofte et al. [15] and Cheng et al. [6].

In our case the atypical manifestations were tenesmus and pain; clinical and radiological diagnosis is challenging.

Histology and I.I.C. are needed for the diagnosis. The first diagnosis is based on morphological aspects and the second is positivity for the anti-KIT antibody (CD117) [9,16-18].

Approximately two-thirds of patients with a conventional GIST have a c-kit mutation at exon 11. The incidence of E-GISTs mutated at exon 11 is reported to be approximately 40% to 50% [9,16,18] and our case presented an exon 11 mutation. The exon 11 mutation is associated with a better prognosis.

On the other hand, some authors propose that E-GISTs are more aggressive than GISTs [11]. E-GISTs are characterized by considerable size usually with a high mitotic number, making them high risk tumors [9]. Tumor necrosis, nuclear atypia, tumor histology and mutations in the KIT tyrosine kinase gene seem to impact negatively in the tumor behavior [7].

Genetic analysis of c-kit gene mutation is the best predictor for response to Imatinib. In patients who developed resistance and intolerance for Imatinib a second-line tyrosine kinase inhibitor, Sunitinib is currently a treatment of choice. Anyway more recently, Regorafenib (third-line multikinase inhibitor) was approved as a treatment for patients with advanced GISTs, which developed resistance to either Imatinib or Sorafenib treatment [19].

Sunitinib and Regorafenib can be used in advanced GISTs after treatment failure with Imatinib [20]. In this case the patient performed a first-line treatment with Imatinib, subsequently due to the side effects a second-line experimental treatment was accepted with Sunitinib.

In some cases with metastasis or recurrent disease under treatment with Sunitinib or Regorafenib, the role of debulking surgery is still debated.

In the literature there is only a certain amount of emergency interventions. It should be considered that in these cases the tumors are advanced and resistant to standard treatment, so the potential benefit of the surgery is unknown [5]. Our patient came to our observation in an emergency situation with rectovaginal fistula and recurrent local infections. The patient's clinical case was widely discussed during the MDT meeting who decided to perform debulking surgery with radical intent.

GISTs have a indolent clinical course with a tendency to recurrence locally or present metastases even after 20 years [3,7].

The surgery is the definitive treatment. The aim of surgery is to obtain R0 resection to the maximum extent [20]. Lymphadenectomy

is not required because lymph node metastases occur infrequently (<10%) [10,11].

However, despite the complete resection with negative margins, biologic behavior of GIST is aggressive, and the patients show high local recurrence rates (60%) [10,11].

In consideration of the tendency of GIST to extra-parietal extension and peritoneal diffusion, careful manipulation of the tumor is crucial. In fact, its rupture is considered a negative prognostic factor for relapse and seeding peritoneal [3].

According to The NIH (National Institutes of Health) consensus criteria reviewed by Joensuu et al. [21], affirm that tumors spontaneous rupture or during surgery tumor rupture worsens the prognosis. Also the incomplete resection is a negative prognostic factor on Overall Survival (OS) [5,22].

Preoperative diagnosis and radical intervention with negative margins are fundamental to avoid recurrence. The presented case did not have an accurate preoperative diagnosis at the first intervention. Furthermore, in 2004 there was no treatment planning and no discussion of the case in a MDT. This case is not very clear, given that enucleation probably did not completely contain the tumor. In fact at the first surgery in 2004 in a no referral cancer hospital, a local trans-anal excision of the lesion was performed. The pathological report was poor "structured"; indeed the negative margins have not been described.

Unlike in 2018 in our cancer center the case was discussed in the MDT. In limited localized progression disease the patients could be undergone to a debulking surgery [5].

Sugar backer proposed aggressive surgical procedures for the treatment of loco-regional relapses and peritoneal metastases. These strategies are peritonectomy and multivisceral resection to remove all macroscopic tumors [5].

The enlarged resections to the adjacent organs, the infiltrating neoplasm, must guarantee the complete removal of the primary tumor.

In generalized progression of disease (the disease is progressing at multiple sites while on drug therapy) the surgical intervention is not indicated and does not seem to prolong survival so cytoreductive surgery is not recommended [5].

In the absence of a direct connection with a luminal gastrointestinal structure, it is difficult to ascertain the true risk of recurrence and progressive disease.

In 15 years the patient has been undergone to three surgical operations, therapy with imatinib and experimental protocols for side effects to imatinib.

The 1-, 3- and 5-year overall survival rates of E-GIST patients were 91.7%, 61.1% and 48.9%, respectively. The 1-, 3- and 5-year recurrence-free survival rates were 72.2%, 28.9% and 19.3%, respectively.

Compared with a conventional GIST, an E-GIST is considered to have a less favorable prognosis [11]. Despite the survival described in the literature, our patient had a 15-year overall survival from first diagnosis in 2004. The patient was 7-year disease free from recurrence from the first and the second surgery.

Many guidelines suggest that managing GISTs requires a

multidisciplinary approach [5]. In clinical practice guidelines relating to GIST management, National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) claim that a MDT of physicians is mandatory for the successful treatment of GIST [23].

Moreover the role for individual core team workers is highlighted, defining a role for each specialist for each scenario [5].

In fact, in our department, the MDT defined the best diagnostic and therapeutic pathway. The surgical procedure, carried out by 3 surgical teams, achieved several advantages of multidisciplinary management: Optimizing timing of surgery, organ-sparing, reducing recurrent disease and extension of survival for the patient enhancing response to targeted treatment [19,23].

Conclusion

The diagnoses of masses of the vaginal septum and the rectum-vaginal septum are more difficult and rare. Pelvic-MRI is useful for local staging, restaging and follow-up. The aim is to perform targeted therapy and the preservation of reproductive organs when possible.

Cancer center and MDT are mandatory for achieving the best treatment by the best timing for all tumors, especially if rare as our case. The standard treatment for E-GIST is surgery to achieve R0 resection with free margins. As in our case, the multivisceral resections are also possible in localized progression disease and in emergency case. Pharmacological therapy has a key role to reduce tumor size, to perform conservative surgery preserving organ function. In our case the MDT with three teams accomplished the best treatment for the patient with multiple E-GIST recurrence performing a combined and radical (i.e. R0) approach.

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