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Rectal Gist in a Latin America Country: A Case Report and Literature Review

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Abstract

We report the case of a 75-year-old female patient with a big tumor in the lower rectum with intestinal obstruction and lower gastrointestinal bleeding history who underwent to laparotomy with tumor biopsy and terminal colostomy at another hospital in Peru. She came to our institution for clinical evaluation with pathology result of rectal gastrointestinal stromal tumor. An extra elevator abdominoperineal resection of the primary tumor was performed with negative margins. A rectal GIST was confirmed by pathology with G2 and mitotic index of 27/50. Immunohistochemistry DOG-1 (+); CD117 (+); CD34 (diffusely positive). Genomic DNA was extracted from the paraffin-fixed tumor sample and the mutation c.1504_1509dupGCCTAT(p.Ala502_Tyr503dup) was detected in exon 9 of the KIT gene. Imatinib 400mg per day for three years was indicated as adjuvant treatment, currently with 12 months of disease-free survival.

Keywords: Case report; Rectal gastrointestinal stromal tumor (GIST); C-KIT mutation; Exon 9.

Introduction

The Gastrointestinal Stromal Tumor (GIST) term was coined by Mazur and Clark in 1983, in reference to non-epithelial tumors of gastrointestinal tract without leiomiosarcoma features [1] arising from the interstitial cell of Cajal or its precursor with malignant tendencies. This rare mesenchymal tumor accounts only for 1-3% of all gastrointestinal malignancies and are predominantly located in the stomach (60–70%). GIST in rectum is extremely rare and represents less than 5 % of all gastrointestinal stromal tumor [2] and 0.1% of all colorectal tumors with an estimated incidence rate of 0.45 persons per million [3,4]. The median age is around 60–65 years old [5], with a similar clinical presentation to rectal adenocarcinoma (rectal bleeding, constipation, abdominal and pelvic discomfort).

Case report

A 75-year old Peruvian female with four months of abdominal pain and lower gastrointestinal bleeding who was initially admitted into emergency from another hospital where a exploratory laparotomy was performed for intestinal obstruction. A rectal tumor without rupture was identified during surgery and a biopsy and terminal colostomy was performed. The patient was then sent to the National Cancer Institute of Peru (INEN)

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with a pathology report of rectal GIST **Figure 1**. Rectal examination on admission showed a rectal tumor at 3 cm from the anal verge that occupied 80% of circumference. The MRI showed an extensive solid lesion of 7.6 x 9.3 cm, large isointense in T1, iso – hyperintenste in T2 with necrotic areas, restricting diffusion, exophytic, located in posterior and right lateral and posterior aspect of median and lower rectum, contacting mesorectum and levatorani muscle with positive Circumferential Resection Margin (CRM). No metastatic disease was found **Figure 2.**

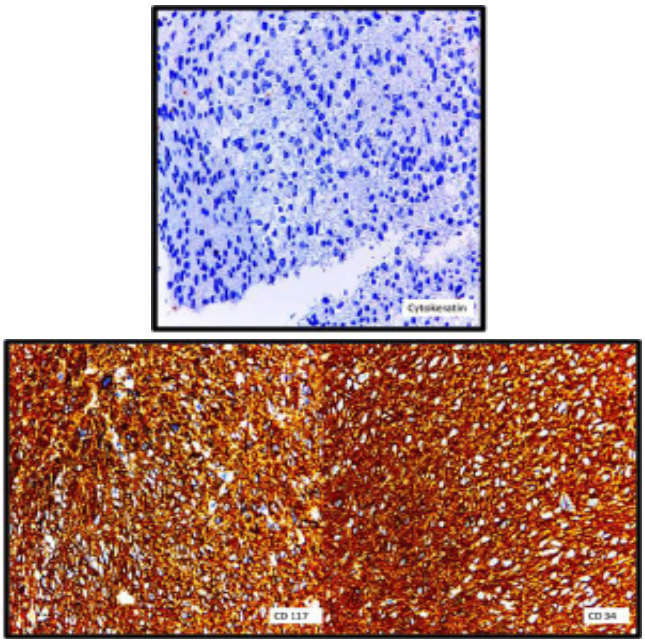

Figure 1: The biopsy prior to abdominoperineal resection showed a spindle cell proliferation, with bland nuclei and eosinophilic cytoplasm and inconspicuous nucleoli. The stain for Cytokeratin AE1/AE3 was negative, which favored the mesenchymal nature of the neoplasm. Staining for CD117 and CD34 was diffusely positive, thus favoring a gastrointestinal stromal tumor. Confirmation with DOG-1 was not performed in the biopsy.

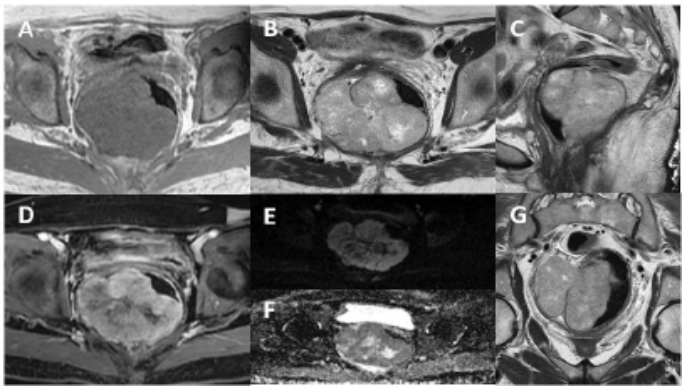

Figure 2: A, B, C and **G**, Axial T1 weighted MR and Axial, Sagittal and Coronal T2 weighted MR respectively shows a large isointense mass in T1, iso – hyperintense in T2, with well-defined edges, is observed, located in the pelvic region, which compromises the posterior and right lateral wall of the median and lower rectum contacting mesorectum and levatorani muscle, with a predominantly exophytic component with the presence of a small intraluminal component. The tumor mass compressed and displaced the rectum to the left and displaces the uterus superiorly. No lymphadenopathy is observed.
D, Post contrast Axial Fat-Suppressed T1 weighted MR shows solid component of the mass enhanced heterogeneously. **E, F**: Diffusion weighted imaging show hyperintense solid component and a low ADC indicating restricted diffusion

An extra elevator abdominoperineal resection of the primary tumor performed on May 2019; pelvic examination under anesthesia demonstrated a tumor at 3 cm from the anal verge with wide base depending of the right and posterior side of the rectum **Figure 3.**

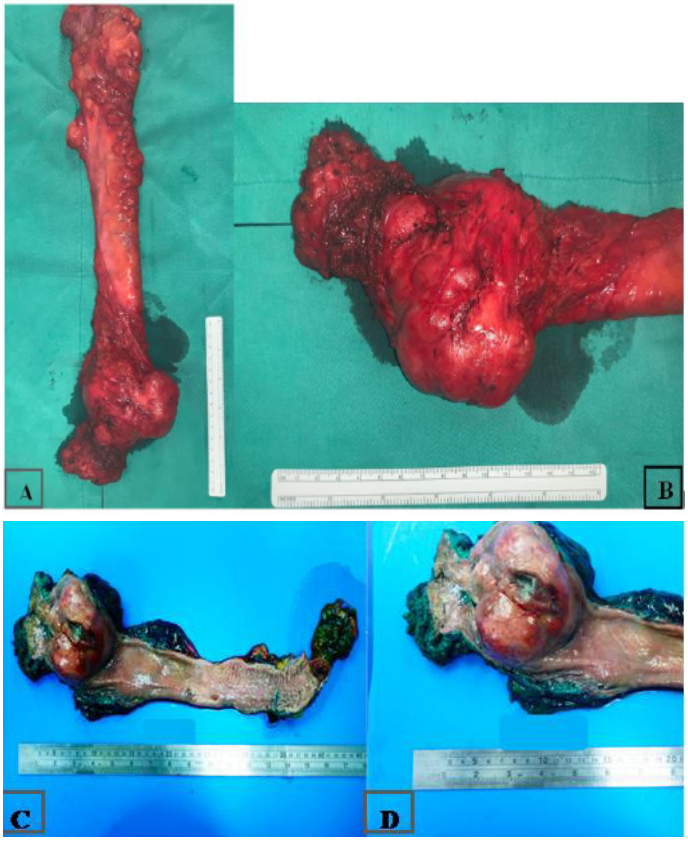

Figure 3: A. Surgical specimen of extra elevator abdominoperineal resection.
B. Tumor on inferior rectum, of 8x7cm, well-defined edges, prevalence of exophytic component
C. On gross examination, the tumor was a fleshy, tannish-brown, multilobular, well circumscribed mass of 8.0 x 7.0 x 6.5 cm, centered in the muscularis propria of the rectum with ulcerated mucosa.

The final pathology reports a tumor size of 8 x 7 cm with free margins, the closest was the distal margin at 4.5 cm. The pathology confirmed fusocelular subtype of rectal GIST with mitotic index of 27/50, G2, and 30% of necrosis. No metastatic lymph nodes were found (0/53). The final pathologic stage was pT3N0. Immunohistochemistry showed DOG-1 (+) and CD117 (+) **Figure 4.**

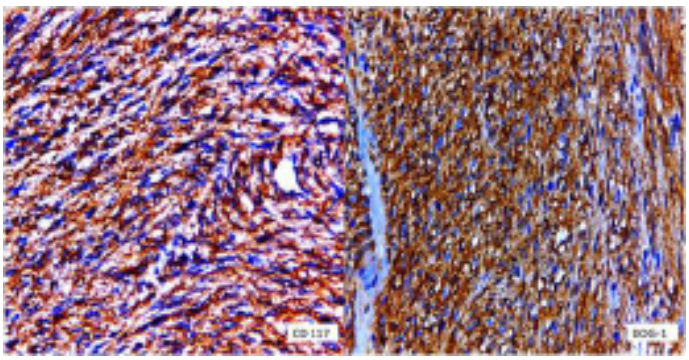

Figure 4: Inmunohistochemical stain for CD117 was positive and specific DOG-1 was diffusely positive.

The medical oncologists began adjuvant treatment at 10 weeks post-surgery with Imatinib 400 mg per day for three years treatment according to the NCCN guidelines. There is no evidence of recurrent disease by imaging studies till the date of the last follow up (12 months).

Mutational analysis of the affected tissue was only available after the start of the patient's adjuvant treatment due to the recent implementation of this test in our hospital. Genomic DNA was extracted from the paraffin-fixed tumor sample and a Sanger sequencing reaction was performed from exons 9, 11, 13 and 17 of the KIT gene and exons 12, 14 and 18 of the PDGFRA gene. The mutation c.1504_1509dupGCCTAT(p.Ala502_Tyr503-dup) was detected in exon 9 of the KIT gene.

Discussion

Gastrointestinal stromal tumors located in the rectum are extremely rare and represents an adverse prognostic factor, irrespectively of tumor size. Rectal GIST is characterized by large tumor mass with well-defined margins and predominantly extra luminal location. The epicenter of the tumor is located well outside the rectum in most cases [6].

There is one study in our country that reviews the clinic-pathological and survival features in gastrointestinal stromal tumors that shows frequency according to organ location been stomach the most frequent (56.3%), and only four cases in rectum (3.9%). The factors associated with longer survival were optimal surgical treatment, small tumor size, tumor stage, low mitotic index, asymptomatic patient, no tumor recurrence, no metastasis and no cancer association. Nonetheless, the characteristics and particularities of rectal GIST are not mentioned [7].

The origin of the tumor is determine by MRI, and allows an adequate evaluation of the surgical pelvic floor, involvement of adjacent organs and circumferential resection margin (CRM). Rectal GIST is isointense to skeletal muscle on T1 weighted images and hyperintense on T2 weighted, with heterogeneous pattern of enhancement as our case, and calcifications and bleeding areas in some cases [8,9]. Despite having a big tumor size, there was no radiological evidence of metastatic lymph node disease. This is an unusual finding for rectal adenocarcinoma; beside the presence of intramural degeneration signs with cystic changes, hemorrhage and calcification should exclude the possibility of lymphoma [6].

The European Society of Medical Oncology (ESMO) reaffirm that surgical resection is the ideal treatment in all resectable rectal GIST patients, but there are no surgical strategies discussed. The surgical approach is technically challenging related to the anatomy, near the sphincter complex, with risk of tumor rupture and positive margins [10]. Malignant stromal tumors are 10% of all GISTs. They metastasize primarily by blood and peritoneal seeding; metastatic lymph node disease is not common. This is the reason why total mesorectal excision (TME) is not mandatory, especially for small tumors with optimal surgical free margins in local resections.

A Low Anterior Resection (LAR) or an Abdominoperineal Resection (APR) should be performed if the rectal tumor is located below 5cm from the anal verge because the high risk of positive CRM [11]. Other authors recommend both surgical approaches depending on the tumor size (>2 cm) and the distance from the dentate line [12]. Otherwise, Local Tumor Resection (LTR) with sphincter preservation surgery should be performed (transvaginal, trans anal or trans perineal) [13].

The surgical treatment does not differ per each subtypes of GIST, however, a complete resection in rectum is difficult because the reduce space in the pelvis and the tumor size. Some studies concluded that there is no difference between de surgical technique between Local Tumor Resection (LTR), low anterior resection and abdominoperineal resection in terms of Recurrence Free Survival (RFS) and Overall Survival (OS) [14]. However, elderly patients, tumor size, mutations status, presence of lymph node disease, high mitotic rate and positive resection margins, perioperative tumor rupture and no neoadjuvant treatment with imatinib are major risk factor for worst survival [4].

Around 90% of GIST are related to gain-of-function mutations in KIT and PDGFRA genes [15,16]. A duplication in exon 9 of the KIT gene was found in our patient. This is the second most frequent related to GIST [17] and are related to primary non-gastric GIST, usually in small intestine and less commonly in rectum [18]. The importance of performing mutational analysis in all patients with GIS has therapeutic implications improving survival in relation to Imatinib dose [19].

GISTs without mutations in these genes are called wild-type GIST (WT-GIST) and may have different clinical behavior as resistance to treatment with tyrosine kinase inhibitors. Most frequently, GIST appears sporadically and some cases related to hereditary syndromes such as Neurofibromatosis 1 or Carney-Stratakis Syndrome [20].

GIST is a well-circumscribed mass of highly variable size (from <1.0 mm to > 20.0 cm) macroscopically. In larger lesions, the cut surface may show foci of hemorrhage, cystic change or necrosis [21]. GIST has a wide microscopically morphological spectrum. Tumors consist of uniform spindle cells or epithelioid cells arranged in lobules. Nuclear pleomorphism is rare. Cytoplasm is eosinophilic and cytoplasmic vacuoles are common. Vessels are typically inconspicuous and there might be a myxoid or myxochondroid background.

“Skeinoid” fibers, which are coarse, wire-like collagen bundles, are present in small bowel examples. Poor prognostic factors are extension into mucosa and tumor necrosis. There is also a so-called “pediatric-type”, which is a SDH-deficient GIST. These tumors have a plexiform growth, are commonly epithelioid and present with lymph node metastasis [22].

Small intestinal and colonic GIST have usually spindle cell morphology, with diffuse sheets or vague storiform arrangement of cells. Rectal GIST most frequently feature spindle cell morphology [21].

The vast majorities of GIST have kit mutations and are CD117/c-KIT stain positive (95%). About 70% of GIST express CD34, which can also be included in a diagnostic panel. DOG-1 is another antibody that was discovered using gene expression profiling and is also expressed by most GIST (>99%). Most KIT negative/DOG1 positive GISTs are gastric or extra visceral GISTs and harbor a PDGFRA mutation [23-24].

Histologic grading is important in soft tissue sarcoma staging but not well suited for GIST, because these tumors have aggressive features despite having low mitotic rates [25]. The grade is determined entirely by mitotic activity in GIST staging: GX: Grade cannot be assessed, G1: Low grade; mitotic rate ≤5/5 mm2 and G2: High grade; mitotic rate >5/5 mm2.

GIST can recur many years after initial excision; thus, these tumors have even potential for distant metastasis. Nevertheless, the National Institutes of Health (NIH) develops a consensus criteria for risk stratification in 2002. This criteria uses the tumor size and mitotic count pathological factors for a recurrence risk: very low, low, intermediate and high. In 2008, Joensuu proposed a modified version of the NIH risk assessment system which included tumor rupture and primary tumor site.

This system classifies patients with small (≤5 cm), non-gastric GISTs and mitotic counts >5 per 50 HPF and those with non-gastric tumor sizes between 5.1 and 10 cm and <5 mitosis per 50 HPF as having a high risk of recurrence. These criteria are shown in the table below: [26].

Table 1: Joensuu criteria for GIST risk assessment.

Risk category	Tumor size (cm)	Mitotic Index (per 50 HPF)	Primary tumor site
Very low	<2	≤5	Any
low	2.1-5	≤5	Any
Intermediate	2.1-5	>5	Gastric
	<5	6-10	Any
	5.1-10	≤5	Gastric
High	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>10	Any
	>5	>5	Any
	2.1-5	>5	Non-gastric
	5.1-10	≤5	Non-gastric

Rectal GIST neoadjuvant treatment indication is usually for complete resection with negative margins (R0) and for sphincter-sparing surgery, however, there is limited evidence based data regarding the treatment and its safety. The low incidence of rectal GIST and the lack of evidence for large-scale prospective studies, neoadjuvant treatment, surgical approach, resection scope and prognosis are still controversial [10].

Conclusion

GIST tumors are rarely located in the rectum and optimal treatment for rectal GIST is controversial due to the extremely low incidence of the disease.

Surgical treatment with free margins is a good option for patients with resectable primary rectal GIST.

Surgical approach and type of surgery have no significant impact on the prognosis and survival.

Performing mutational analysis in patients with GIST it is important for decision of immunotherapy.

Highlights

The first case report of a rectal GIST in our institute.

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