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Gastro Intestinal Stromal Tumor of the Rectum Associated with Liver Cirrhosis: Case Report and the Review of Literature

Review of Literature

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Introduction

Gastro intestinal stromal [GIST] tumor are rare mesenchymatous tumors, they develop frequently in the small intestine, stomach, more rarely the esophagus, colon and rectum [1].

GIST's origin was thought to be smooth muscle or neurogenic for years. In nineteen eighty three, Mazur and Clark suggests that GIST represent a distinctive and unique group of neoplasm with their own biological behavior [2].

The rectal localization of gist is rare, it constitutes approximately 5% of all Gist, and symptoms are usually not specific such as lower bleeding or abdominal pain [3].

For resectable GIST, the main treatment is surgery. However, metastasis as well as recurrence is frequent even with complete surgical resection [4].

We report a case of a 73 years old patient presented with inguinal hernia revealing a rectal GIST as well as liver cirrhosis; the purpose of our report is to describe rectal gist presentation, its radiology aspect, overcome therapeutic challenges due to the patient's cirrhosis.

Observation

A 73-year-old man, with no medical history, was referred to our department for the investigation of an inguinal hernia, the patient denied any history of hematochezia or constipation or abdominal pain.

An ultrasound sonography was performed and revealed a dysmorphic liver, portal hypertension and a pelvic tumor measuring 119x103x90 mm [Figure 1].

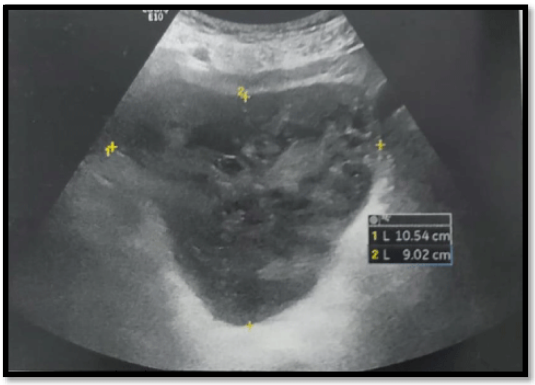

Figure 1: Ultrasonography revealing a pelvic mass

The tests results showed: Hb = 8.3 g / dl, Hematocrit = 26.9%, VGM = 72.4 fl, Platelets = 74000 /mm3, Leukocytes = 2000 g / l, PT = 66%, urea: 0.6 g/L creatinine: 22.2. The diagnosis of liver cirrhosis was retained; hepatitis serology revealed HVB and HVC co infection, antiviral treatment was started.

Concerning the pelvic tumor, a CT scan was performed revealing a large pelvic heterogeneous hypo dense mass between the bladder and the rectum measuring 99x100x113 mm with no adenopathy nor metastasis lesion [Figure 2-4].

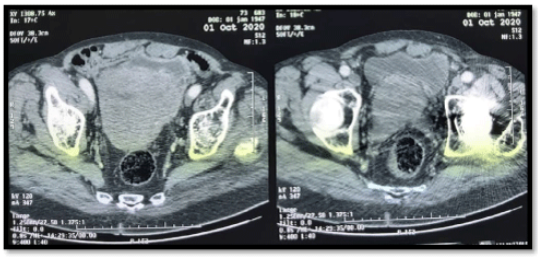

Figure 2: CT scan showing a large pelvic tumor

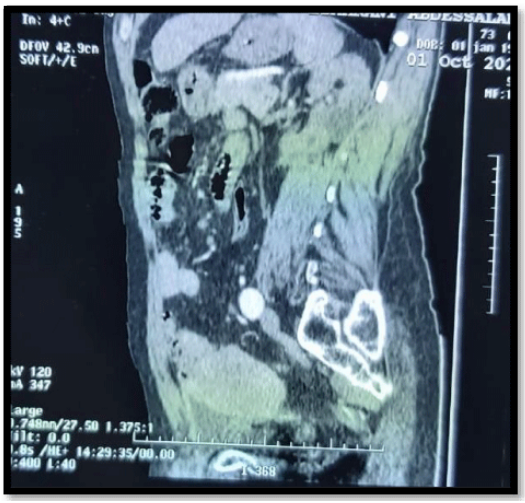

Figure 3: CT scan showing a large pelvic tumor

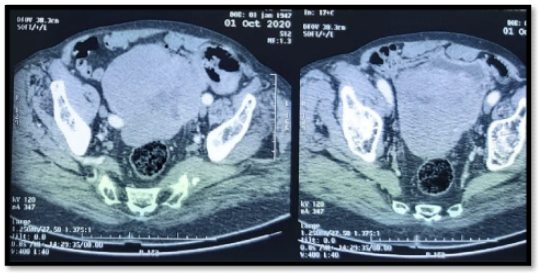

Figure 4: CT scan showing a large pelvic tumor

An endoscopic ultrasonography [EUS] showed hypo echoic heterogeneous rectal mass, we then performed fine needle [22G] aspiration with collection of sampling for histology and cytology. Pathological examination revealed rectal gastro intestinal stromal tumor [GIST] [CD117 antibodies were positive at a 100%, muscle specific actin antibodies were positive].

The rectal GIST greatest dimension was more than 10 cm and was therefore staged locally advanced, the patient was suffering from liver cirrhosis with a performance status at 3, and the decision was to propose the patient for Neoadjuvant tyrosine kinase inhibitors [Imatinib] at the standard dose of 400mg/d and monitor the tumor's size.

Considering Imatinib hepatic toxicity, it was decided to follow the patient closely, controlling hepatic tests as well as looking for any sign of decompensated cirrhosis.

Discussion

Gastrointestinal stromal tumors [GISTs] are believed to originate from interstitial cells of Cajal or related stem cells. They are specific [PDGFRA mutation-driven or Kit [CD117]-positive]. mesenchymal tumors of the GI tract [5].

It has become important to identify GISTs since specific pathogenesis targeted treatments are available [6].

Spindle cells, epitheliod cells and sometimes pleomorphic morphology are characteristic histologic features of GISTs, nuclear atypia and multinucleation are also found in pathological examination and are encountered more often in epitheliod GISTs [7].

There are 4 categories depending on immuno histo-chemical findings and based on differentiation [8].

- Smooth muscle cells differentiation
- Neural elements differentiation
- Smooth muscle cells and neural elements differentiation
- No differentiation

Fourteen and a half per million has been estimated as the annual incidence of GIST in Sweden, and as 11 per million in Iceland, in the united states, the annual incidence is estimated at approximately 5000 cases per year [9–11].

GISTs arising from the rectum or anal canal comprise approximately 5 percent of all GISTs, they occur more often in male patients [71%] who are between 50 and 60 years old [12].

Rectal GISTs proven Immunohistochemically are rare with only some previous in the literature.

GIST's treatment of choice is complete surgical resection [R0] of the tumor as well as normal tissue surrounding. Standard chemotherapy isn't effective on GISTS [13].

Rectal GIST treatment is challenging because of the bony pelvis and the anatomic constraints. For many years, Rectal GIST was often treated with radical resection, such as abdominoperineal resection or total pelvic exenteration. However, in the late years, transanal, transvaginal or transabdominal approaches as well low anterior resection have been adopted [14].

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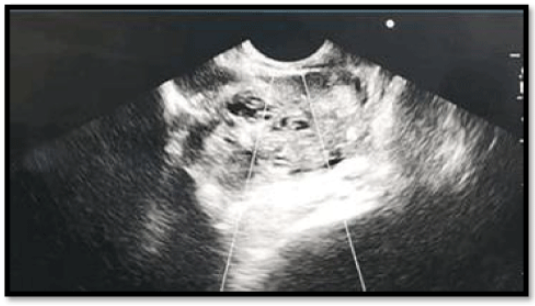

Figure 5: Echo endoscopy aspect of rectal GIST

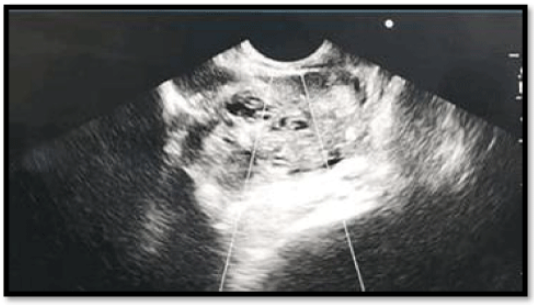

Figure 6: Echo endoscopy aspect of rectal GIST

Majority of GISTs are due to mutations in the KIT [75%] or PDGFRa [10%] oncogenes and often respond to tyrosine kinase inhibitor [15].

Risk stratification systems were developed in order to identify the risk of recurrence and metastasis, these systems are more commonly used than standard staging schemes in GIST management [16].

Initially, the first variables to be taken into consideration for risk assessment in GISTs are tumor size and mitotic index in the first risk stratification system [the National Institutes of Health [NIH] consensus classification system] [Figure 7,8] [17].

Risk category	Size (cm)[a]	Mitotic count (/50 HPF)
Very low risk	<2	<5
Low risk	2–5	<5
Intermediate risk	<5	6–10
	5–10	<5
High risk	>5	>5
	>10	Any mitotic rate
	Any size	>10

NIH National Institutes of Health, *GIST* gastrointestinal stromal tumor, *HPF* high-power field

Figure 7: NIH consensus criteria for risk stratification in GIST (20)

Tumor location was proven to be a prognostic factor; it was therefore included into another stratification risk system known as Mittinen Lasota/ Armed Forces Institute of Pathology [M-L/AFIP] classification system. [5,12,18,19].

Group	Tumor parameters		Patients with progressive disease during follow-up and characterization of malignant potential			
	Size (cm)	Mitotic rate (/50 HPF)	Gastric GIST		Small intestinal GIST	
1	≤2	≤5	0%	Very low if any	0%	Very low if any
2	>2, ≤5	≤5	1.9%	Low	4.3%	Low
3a	>5, ≤10	≤5	3.6%	Low	24%	Intermediate
3b	>10	≤5	12%	Intermediate	52%	High
4	≤2	>5	0%	Low*	50%	High*
5	>2, ≤5	>5	16%	Intermediate	73%	High
6a	>5, ≤10	>5	55%	High	85%	High
6b	>10	>5	86%	High	90%	High

GIST gastrointestinal stromal tumor, *HPF* high-power field
Adapted with permission from Miettinen and Lasota
* Denotes tumor categories with very small numbers of cases that are insufficient for prediction of malignancy potential

Figure 8: Miettinen-Lasota/ Armed Forces Institute of Pathology suggested guidelines for assessing the malignant potential of gastric and small intestinal GIST (18)

The aim of these systems is to determine the risk of recurrence, so patients can be managed accordingly, and propose pharmacological intervention with imatinib therapy. However, there are no clear consensus as to which patients should be considered for adjuvant imatinib therapy currently exists [16].

Achieving negative resection margins [R0] as well as preserving organ are the optimal therapeutic goals in GIST surgery. However, in reality, the situation is less distinct because of other indentified variables like size of tumor, mutation, tumor location and relative risk associated with microscopically involved [R1] resection margins, especially in the imatinib therapy era [21].

The European Society of Medical Oncology [ESMO] guidelines state that in rectal GIST patients, surgical resection should be considered in all rectal GIST patients [22].

The surgical approach in rectal GIST should be considered because of its challenging nature, related to the site of origin in the rectum, and its relation to the sphincter. Different surgical procedures can be proposed in rectal GIST resection depending on risk stratification and tumor size such as, local tumour resection [LTR] including transanal excision, transanal endoscopic microsurgery and transperineal approach for resection of the anal canal. Two other common surgical procedures can also be proposed: low anterior resection [LAR]. and abdomino-perineal resection [APR] [23].

Patients with a locally advanced GIST, with borderline resecability just like our patient, because of proximity to vital organs, or because of a big size or a high mitotic rate, usually are indicating radical mutilating resections, and therefore require specific management [21].

Imatinib has proven to be effective in the treatment in metastatic GIST, it led then to believe that it could be also beneficial if used as a neoadjuvant therapy in patients with locally advanced GISTs [24,25].

The potential advantages of neoadjuvant imatinib are cytoreduction in order to facilitate R0 resection, the potential for organ preservation, less invasive surgical approach and a tendency to render the tumour less hypervascular and fragile with attendant decreases in the risk of intra-operative bleeding or disastrous tumour rupture [26,27].

Mitotic rate response

Cavnar and et al [14], in a study analysing rectal GIST management in the imatinib era showed that neoadjuvant therapy with Imatinib, there were a considerable response in tumor size, pathologic aspect and mitotic rate. This study showed as well that the imatinib era was associated with more rectal and sphincter preservation.

Hepatotoxicity due to Imatinib can cause an aggravation of the patient's condition, and may alter therapeutic plan, Han and al., in their recent study tried to determine the underlying mechanism as well as factors responsible for imatinib induced hepatotoxicity [28].

Han and et al [28], showed in their study that liver disease or HBV infection as well as daily imatinib dose greater than 400 mg were important factors related to hepatotoxicity.

Multivariate analysis showed that patients taking Proton pump inhibitors [PPIs] and patients with liver disease or HBV had an approximately 2.1 and 5.2 fold increased hazard of hepatotoxicity compared to those not taking PPIs and without liver disease or HBV, respectively [28].

Yuan and et al [29]. compared the efficiency and safety while using Imatinib at the dose of 300mg/d in patients with GIST who didn't tolerate the standard dose of 400mg/d, and showed that the lower dose could provide sufficient plasma Cmin, disease control and lowered side effects, especially hematologic and hepatic toxicity.

Lowering Imatinib dose could be a good alternative in our patient, considering the presence of hepatic toxicity factors [HVB, liver disease], associated with close monitoring of hepatic function.

Some prospective studies of patients with pre-existing mildly abnormal liver function tests [AST>ULN, bilirubin ≤1.5× ULN] regardless of the underlying cause have shown that imatinib can be safely used in these situations. [30,31].

It is however mandatory to closely follow these patients to identify early any liver function deterioration [32].

William James Kane and et al [33] proposed n 2019 an algorithm in rectal GIST management [Figure 9,10].

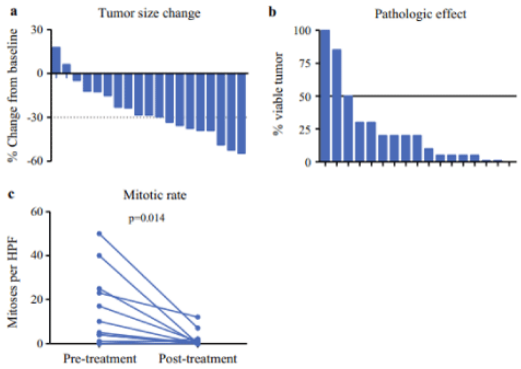

Figure 9: Response to neoadjuvant imatinib in rectal gastrointestinal stromal tumor (GIST). Waterfall plots are shown representing : a.Tumor size change b. Pathologic response c.

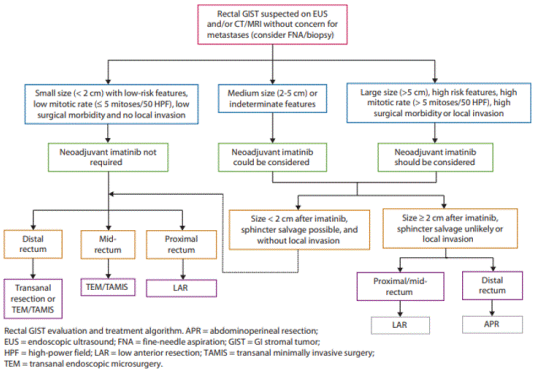

Figure 10: Evaluation and treatment algorithm

In conclusion, it appears that patients with locally advanced rectal GIST, just like our patient, after reviewing literature, should be proposed for imatinib neoadjuvant therapy. It is as well mandatory to look for hepatic toxicity factors and take them into consideration in post treatment follow up in order to prevent the patient's aggravation.

Conclusion

To conclude, we report a locally advanced rectal GIST, symptoms are the same as those of other rectal tumors, they can also be lacking. Therapeutic management depends on size, mitotic index and the presence or not of metastasis.

Surgical resection has been considered for many years as a first line curative therapy, however, when GIST are locally advance, or when localization indicates radical and mutilating procedures, peri operative Imatinib can be proposed as neoadjuvant or adjuvant therapy.

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Our case report shows as well, that is important to look for factors related to hepatotoxiciy in order to prevent or at least detect early any drug induced toxicity that could worsens patients' prognosis.

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