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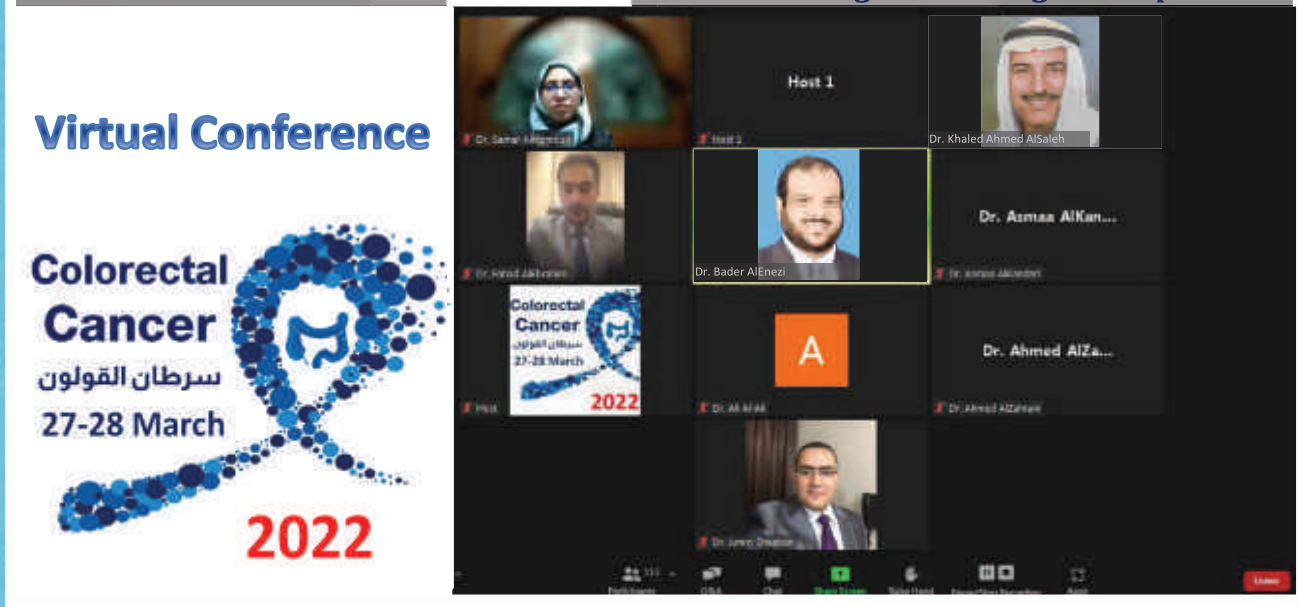

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Original Article

Worse Outcome with Imatinib Mesylate as Neoadjuvant Therapy in Locally Advanced Rectal Gastrointestinal Stromal Tumors: Case Series of Four Patients

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Abstract:

Background: Rectal gastrointestinal stromal tumors are rare and optimal treatment is yet to be defined. The aim of this report is to highlight the possible aggressive behavior of four cases of rectal GISTs treated with neoadjuvant imatinib in a tertiary care medical hospital.

Methods: Four cases of rectal GISTs were retrospectively reviewed for patients demographics, clinical presentation, histology, and imatinib therapy.

Results: GISTs were common in men. Age ranged to symptoms were nonspecific. All cases were initially considered to have locally unresectable. Patients received preoperative imatinib. Course was unfavorable. 3 patients died of progressive disease, and one from infectious complications.

Conclusion: Rectal GISTs may be aggressive and resistant to medical treatment. Thus only early diagnosis may offer the best chance of recovery.

Key words: Rectal – gastrointestinal stromal tumor – neoadjuvant imatinib – resistance.

Introduction

Gastrointestinal stromal tumors (GISTs) of the rectum are uncommon; they represent 5% of GISTs and 0.1% of all rectal tumors[1]. Consequently, their clinical features have not been well studied and optimal treatment strategies have not been well defined, and are yet to be standardized. Surgery remains the cornerstone of treatment in non–metastatic rectal GISTs[2]. However, resection with histologically negative margins is particularly challenging due to the complex anatomic structure of the rectum and the anus and the large size of tumor at the time of diagnosis. Thus, in the modern era, neoadjuvant imatinib is usually used in an attempt to downsize locally advanced GIST and may allow complete resection[3]. In rectal GISTs, the benefit of neoadjuvant imatinib still unknown[4]. In this miniseries, we describe the characteristics and outcomes of four cases of locally advanced rectal GISTs, and we review briefly the existing literature data.

Methods

We reviewed retrospectively 75 patients admitted in our institution for histologically proven Gist, from 2007 to 2011. The information recorded included patient demographics, histology, tumor size, invasion of adjacent structures and treatment. In all 4 patients had a primary diagnosis of locally advanced rectal GIST and were offered neoadjuvant imatinib 400 mg per day after discussion in the joint clinics. Locally advanced'' GISTs were defined by size, the need for multivisceral resection of surrounding organs, anatomic proximity with major vessels. Radiologic response was assessed with computed tomography after 3 months of therapy.

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Results

Case No.	Age/ Sex	Primary symptom	Location	Size per Ct scan (cm)	Invasion of adjacent organs	Histology	IHC Analysis– mitotic index	Reponse to Imatinib at 3 months	2d line treatment	outcome
1	75/M	Burning sensation	Distal rectum	13 x 9	Yes	Spindle cells	CD 117/ CD34 positive – 26/50 HPF	NA	–	Died of local infectious complications
2	51/F	Abdominal pain and disconfort	Mid/Upper Rectum	22 x 17 x 14	No	Spindle cells	CD 117 positive/ CD34 negative– 17/50 HPF	Progression	Imatinib 800 mg	Died of disease spread after 4 months
3	46/F	Vaginal bleeding, pelvic pain	Rectovaginal septum	10 x 7	yes	Spindle cells	CD117 positive/ CD34 positive– 10/50 HPF	progression	–	Died of disease complications
4	39/F	Pelvic pain, tenesmus	Rectovaginal septum	12 x 8,5	yes	Spindle cells	CD 117 positive/ CD34 positive– 7/50 HPF	progression	–	Died of disease complications

Table: Clinicopathologic and molecular features of rectal GISTs from our institution (n=4).
*NA: Not Available. The patient died before tumor response could be assessed.

Discussion

Gastro–intestinal stromal tumors (GISTs) are the most frequent gastrointestinal mesenchymal tumors that arise most frequently from the stomach (60%) and small intestine (35%), while the esophagus, colon and rectum remain uncommon locations[5]. Rectal GIST patients usually have nonspecific symptoms including bleeding, tenesmus together with pelvic pain, or palpable rectal mass during examination[6]. However, since most rectal GISTs arise within the muscularis propria of the intestinal wall, they most commonly have an exophytic growth pattern with the epicenter located well outside the rectum. Thus, rectal GISTs may have unusual clinical presentation, and pose a differential diagnostic challenge to clinicians as they may closely mimic gyneacological[7,8] or urological[9] neoplasms. This is mainly responsible for their diagnosis at a late stage. In this study, the most frequent symptoms were also non specific.

Diagnosis of rectal GISTs is based on digital assessment of the rectum, endoscopy ultrasound guided biopsy[10]. Contrast enhanced computed tomography (CT) is the standard of GIST imaging both for detection and staging[11]. Magnetic resonance imaging (MRI) is useful for liver–specific lesions or patients contraindicated for CT or in cases where CT cannot adequately identify the tumor organ of origin[11]. Positron emission computed tomography is useful in detecting metastases as well as evaluating tumor response to neoadjuvant targeted molecular therapy[12].

While surgical resection for non–metastasized GIST is the standard treatment, the need for preoperative treatment with imatinib is usually required, if the tumor is locally advanced and unresectable or if a reduction in tumor size would significantly enable less invasive and organ sparing surgery[13].

Several studies have reported favorable outcomes of successfully resected rectal GIST after preoperative imatinib[14–16]. Imatinib, a selective tyrosine kinase inhibitor is active in GIST with mutations in the exon 11 and 9 of kit gene and non–D842V PDGFRA mutations. GISTs with exon 13, 14 and 17 mutations of KIT, D842V PDGFR mutations, and BRAF mutations are resistant to imatinib[17]. Some activity of imatinib is seen in succinate dehydrogenase–deficient GIST[18]. Phase II trials of preoperative treatment did not include mutational analysis as a prerequisite for neoadjuvant treatment. Though, only few patients developed tumor progression and none of the authors reported cases of irresectability because of imatinib resistance. Currently, genetic testing of GIST biopsies is a standard of care before preoperative imatinib[22,23]. The optimal timing of surgical intervention in patients undergoing neoadjuvant IM therapy is unclear. Surgery

is generally performed as soon as there is sufficient shrinkage to perform complete resection. This is usually around 6 to 12 months from imatinib onset, given the fact that most of the response to imatinib occurs within 6 months of therapy and the possibility of the development or selection of clones with resistance mutations.

In our series reported here, all the four cases experienced primary resistance to preoperative imatinib leading to disease spread and then death due to complications, suggesting tumors harbored less sensitive mutations to imatinib. Genomic testing could not be performed before starting imatinib as it was not available in our institution at the time. To the best of our knowledge, this is the first reported data in the literature of perioperative failure of imatinib in rectal GISTs. Thus, extensive surgery such as low anterior resection, abdominoperineal resection, or total pelvic exenteration is probably the most appropriate therapeutic option whenever genomic testing or Pet Ct are not available.

Conclusion

Medical literature describing rectal GISTs is scarce and treatment decisions are predicted on the study of gastric and small bowel GISTs. Perioperative imatinib may be promising, but analysis of Kit and PDGFRA mutations is important to determine the possible resistance to Imatinib, and should be incorporated in future studies of neoadjuvant treatment. Our case–series provides evidence of an aggressive clinical course of some rectal GISTs treated with neoadjuvant imatinib, highlighting thus the consequences of delayed diagnostic of rectal GISTs, and the need for further studies to establish the most appropriate treatment strategy.

Declarations

All the authors declare to have no conflict of interest.

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