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Neoadjuvant Imatinib in a Gastrointestinal Stromal Tumor of the Rectum: Report of a Case

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Abstract
Gastrointestinal stromal tumors (GISTs) are rare tumors of the gastrointestinal tract, and of these, GISTs involving the rectum are uncommon. This report describes a case of effective neoadjuvant therapy for a rectal GIST expressing the c-kit gene, where a laparoscopic ultralow anterior resection was successfully performed, thus preserving the anus. A 57-year-old woman visited our hospital due to constipation and was found by a digital examination to have a soft mass on the right wall of the rectum. Computed tomography revealed an 8.0 × 5.0-cm mass with an unclear margin adjacent to the rectum. A biopsy specimen was positive for CD34 and the c-kit gene product, but it was not positive for smooth muscle actin or S-100 protein, and thus the tumor was diagnosed as GIST. An abdominoperineal resection is generally essential for large rectal GISTs; however, she refused this operation. Neoadjuvant treatment with Imatinib decreased the tumor size (4.0 × 3.5 cm) and the anus was preserved by a laparoscopic ultralow anterior resection with direct coloanal anastomosis. She had no evidence of disease for 24 months postoperatively. To preserve the anus, a rectal GIST expressing the c-kit gene is best treated with Imatinib as neoadjuvant therapy.

Key words Gastrointestinal stromal tumor · Imatinib · Laparoscopic ultralow anterior resection · Coloanal anastomosis

Introduction

A colorectal gastrointestinal stromal tumor (GIST) is a rare tumor that accounts for only 0.1% of all colorectal cancers, and its annual incidence has been estimated at 0.45 per million persons.[1] The prognosis of GIST is poor, with a complete surgical excision being the only effective therapy. Such surgery makes it difficult to preserve the anus in patients with a large rectal GIST.

We herein report a patient with a GIST expressing the c-kit gene arising in the rectum, who received neoadjuvant therapy (Imatinib: Glivec; Novartis, East Hanover, NJ, USA) and thereafter underwent a laparoscopic ultralow anterior resection with direct coloanal anastomosis.

Case Report

A 57-year-old woman visited our hospital complaining of constipation, and was found by a digital examination to have an elastically soft mass on the right wall of the rectum. Her past medical history was unremarkable and she was not taking any medication. Standard laboratory tests of serum and urine showed no abnormalities. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were within the normal limits. Rectal endoscopy showed an approximately 4-cm submucosal tumor located 1 cm above the dentate line. Computed tomography revealed a mass in the rectum (8.0 × 5.0 cm) but did not show any evidence of either pelvic lymphadenopathy or distant metastasis (Fig. 1). A barium enema revealed no irregular mucosal pattern from right to posterior wall in the rectum. Magnetic resonance imaging (MRI) revealed a lobulated tumor exhibiting intra- and extramural growth, on the right wall of the rectum. The biopsy specimen was positive for CD34 and the c-kit gene, but not for smooth muscle actin or S-100 protein. From the results of these examinations, a rectal GIST was diagnosed. The patient declined our recommendation to undergo an abdominoperineal resection (APR) with a colostomy. She was therefore started on Imatinib at 400 mg once daily.

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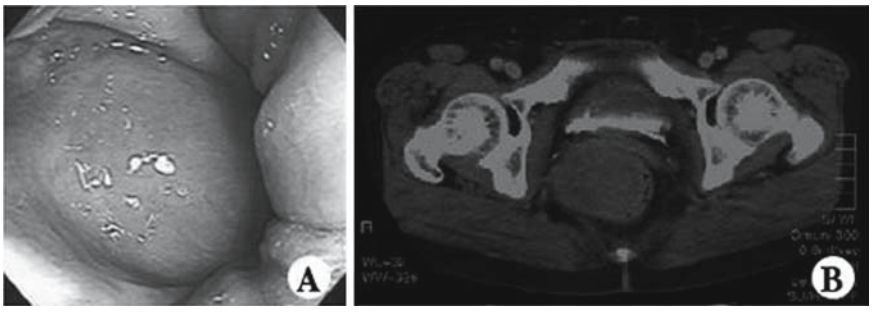

Fig. 1A,B. Image opinion before Imatinib administration. **A** Colonoscopy revealed an approximately 4-cm smooth mass located 1 cm on the oral side from the anal verge. **B** Computed tomography revealed an 8.0-cm mass in the rectum but did not show any evidence of pelvic lymphadenopathy

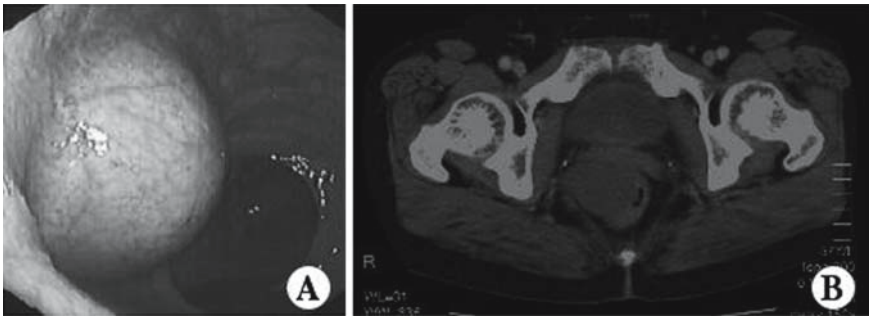

Fig. 2A,B. Image findings after Imatinib administration. **A** Colonoscopy revealed an approximately 2.5-cm smooth mass located 2 cm on the oral side from the anal verge. **B** Computed tomography revealed a 4.0-cm mass in the rectum

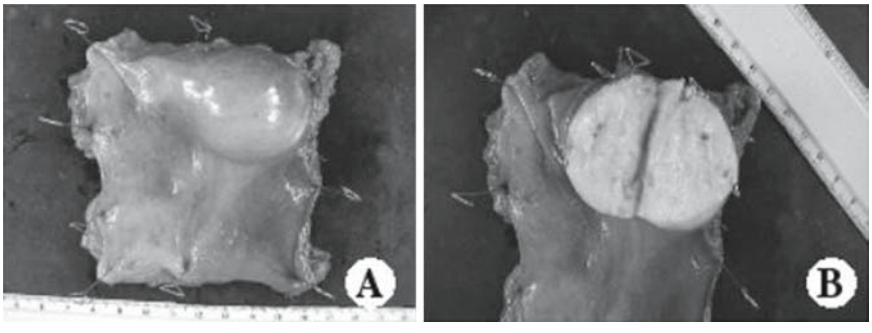

Fig. 3A,B. Resected specimen. **A** Macroscopic findings of the resected specimen measuring 4.5 × 4.0 × 3.6 cm in size. **B** A cross-section revealed a white mass with some yellowish softening

During this treatment regimen, she did not experience any side effects. After 6 weeks of Imatinib therapy, repeat rectal endoscopy, computed tomography (CT) and MRI showed a decrease in size of the rectal mass (4.0 × 3.5 cm), and that the tumor was located 2 cm above the dentate line (Fig. 2). She therefore underwent a laparoscopic ultralow anterior resection with direct coloanal anastomosis after 8 weeks of therapy with Imatinib. During surgery, we used four trocars and performed the total mesorectal excision with anal sphincter preservation.

The tumor, which measured 4.5 × 4.0 × 3.6 cm, involved the rectum extensively. The mass was solid and white with some yellowish softening on the cut sections (Fig. 3). A microscopic examination revealed a spindle-shaped-cell tumor originating from the muscularis propria of the rectum. The tumor showed extensive hyalinized areas with sparse, scattered tumor cells containing small, condensed nuclei. Prior to Imatinib treatment, the tumor revealed a mitotic rate of 5/50 high-power fields (hpf) and a 10% proliferative index in comparison to a post-treatment mitotic rate of 0/50 hpf and a proliferative index far less than 1% (Fig. 4). On immunohistochemical examination, CD34 and c-kit positive staining cells were not seen throughout the tumor. The resection margins were uninvolved on all sides, and there was no lymph node metastasis. The patient's postoperative course has been satisfactory and no recurrence has occurred during the 24-month period without Imatinib treatment.

Discussion

The specific GISTs constitute the largest group of mesenchymal tumors in the gastrointestinal tract, whereas true smooth muscle tumors are rare, except in the esophagus and the muscularis mucosae of the colon and rectum.[2] Gastrointestinal stromal tumors occur most commonly in the stomach and small intestine, but a

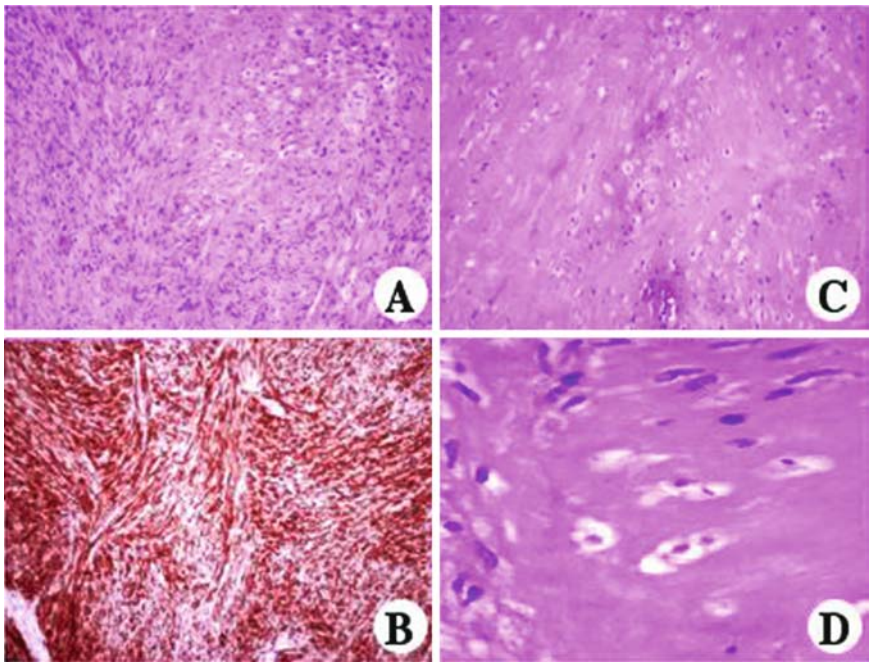

Fig. 4. A The biopsy specimen showed spindle cells with mitosis. **B** Immunohistochemical staining for c-kit was positive. **C,D** After Imatinib treatment, the tumor showed extensive hyalinized areas with sparse, scattered tumor cells containing small, condensed nuclei

small series of comparable tumors has also been reported in all other parts of the tubular gastrointestinal tract, including the rectum and anus.[3] A complete surgical resection with an en bloc (R0) resection of the tumor and surrounding normal tissue is the treatment of choice for GISTs,[4] followed by surveillance for metastatic disease. Chemotherapy and radiation therapy are not effective modalities of treatment. Case reports of rectal GISTs often describe treatment with a radical resection or an APR of the rectum.[5,6] The pathologic, ligand-independent, constitutional activation of c-kit tyrosinase kinase is a strong candidate for the pathogenetic mechanism of GIST. Currently, c-kit expression is the most specific marker for GISTs.[7] Imatinib, a selective tyrosine kinase inhibitor, blocks the constitutive activity of c-kit in GIST cells, and an arrest in proliferation and apoptotic cell death then ensue. Imatinib's effectiveness was first described in 2001, when its use resulted in a dramatic improvement in a patient's multiple metastatic lesions.[8] The phase II trial leading to its approval showed a partial response rate of 53.7% and a 27% stable disease rate after a median follow-up of 24 weeks after the onset of response.[9] However, only few reports have so far described using Imatinib as a neoadjuvant therapy. The present patient declined the initial surgery consisting of an APR procedure with colostomy. The tumor biopsy specimen expressed c-kit, and therefore we decided to administer Imatinib as a neoadjuvant therapy. The morphologic findings of extensive sclerosis and hyalinization with scattered, shrunken tumor cells of a previously viable cells show us the effectiveness of Imatinib. These findings may indicate that Imatinib occupies the ATP-binding site of the target kinase receptor while preventing subsequent autophosphorylation, and thereby leading to the onset of apoptosis and a decreased proliferation. Tumor size consequently decreased, and the patient was able to undergo preservation of the anus by a laparoscopic ultralow anterior resection with direct coloanal anastomosis. Currently, there is no standard operative method, and we selected a super low anterior resection in order to perform total mesorectal excision (R0) of the tumor and surrounding normal tissue. We did not continue Imatinib as an adjuvant therapy following surgery because this is currently not standard practice.

Endoscopic surgery has gained worldwide acceptance in clinical practice. It has become increasingly feasible not only for abdominal surgical procedures but also for thoracic and soft tissue procedures. Recently, GISTs have been shown to be successfully resected by laparoscopic surgery. However, the present case is the first report of a rectal GIST resected by laparoscopic surgery, following downsizing of the GIST due to neoadjuvant therapy.

An optimal method for treatment of a primary GIST based on clinical evidence is required. With the introduction of Imatinib, a potential paradigm shift in the management of GISTs has thus been proposed.[10] Resectable tumors should still undergo a complete R0 resection, but unresectable tumors may be downsized with Imatinib and then re-evaluated for resectability. Our experience suggests that the downsizing of tumors with Imatinib is possible, thus permitting less invasive surgery, a concept being explored in a Phase II study of

neoadjuvant Imatinib mesylate in patients with primary or recurrent, potentially resectable, GISTs. In conclusion, we suggest that in unresectable cases requiring APR for rectal GIST, a better approach may therefore be to administer Imatinib as neoadjuvant therapy.

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