CASE REPORT

Sphincter sparing resection of a large obstructive distal rectal gastrointestinal stromal tumour after neoadjuvant therapy with imatinib (Glivec)

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SUMMARY

Gastrointestinal stromal tumours (GISTs) are generally rare but are known to be the most common mesenchymal tumours of the gastrointestinal tract. We present a case of a patient who presented with persistent obstructive gastrointestinal and urological symptoms, a sense of incomplete evacuation and bleeding per rectum.

A colonoscopy was performed and a biopsy was taken of a submucosal mass in the distal rectum that revealed a GIST with positive KIT immunostaining. A positron emission tomography (PET)/CT scan showed a large metabolically active distal rectal tumour of 8 cm with macroscopic invasion of surrounding structures.

Neoadjuvant therapy with receptor tyrosine kinase inhibitor imatinib (400 mg orally daily) was initiated and an excellent partial response consisting of a significant decrease in the size of the tumour with complete metabolic resolution was observed within 3 months. Six months after initiation of the neoadjuvant therapy a rectum resection with manual side-to-end coloanal anastomosis was performed. Pathology showed a GIST of 5 cm located 0.1 cm from the distal section plane. Our case shows that in patients with a large invasive distal rectal GIST, neoadjuvant imatinib therapy can facilitate anal sphincter sparing surgery.

BACKGROUND

Gastrointestinal stromal tumours (GISTs) are rare tumours that constitute around 1% of all primary gastrointestinal cancers.¹ Specific mutations in the so-called *KIT* oncogene are the most common cause of the development of this tumour.² Imatinib is an inhibitor of the protein encoded by the *KIT* oncogene and was approved for the treatment of GIST tumours in 2002.³ We present a case of a 40-year-old patient referred to our department with a large GIST in the distal rectum who received neoadjuvant therapy with imatinib. A significant decrease in the size of the tumour was seen after the oral therapy. Consequently, the patient was able to undergo anal sphincter sparing surgery without the creation of an ileostoma. Our case shows that in patients with a large invasive distal rectal GIST, mutilating operations such as abdominoperineal resection and pelvic exenteration can be avoided.

CASE PRESENTATION

A 40-year-old man with an unremarkable medical history presented in another hospital with a history of difficulty of defaecation, perineal pain, a sense of incomplete evacuation and bleeding per rectum

for 2 months. The patient also mentioned a history of intermittent difficulty in micturition with no change in urine colour and odour. On rectal examination, a mass was felt originating from the anterior wall of the rectum.

INVESTIGATIONS

Rectoscopy showed a ventral submucosal mass that was partially ulcerated. Laboratory tests revealed normocytic normochromic anaemia (12.9 g/dL (14–18 g/dL)), tumour markers within normal ranges (carcinoembryonic antigen 0.6 ng/mL (<3.8 ng/mL)) and normal prostate-specific antigen 1.19 ng/mL (<2.00 ng/mL)). To exclude prostate cancer, transrectal ultrasonography was performed and a biopsy was taken that showed no atypia on histological investigation.

A month later, the patient underwent a colonoscopy and a biopsy was taken from the rectum. This time the biopsy showed neoplasia of mesenchymal cells with no visualised mitosis and the presence of the immunological marker CD117 (KIT), indicative of a GIST. Further evaluation with pelvic positron emission tomography (PET)/CT and pelvic MRI showed a large metabolically active rectal tumour with a maximum diameter of 8 cm originating from the anterior wall of the distal rectum with macroscopic invasion of surrounding structures and no evidence of distant metastasis (figure 1).

TREATMENT

Neoadjuvant therapy was initiated with imatinib 400 mg orally daily. The therapy was scheduled for 6 months and would be followed by surgical removal of the remaining tumour. On the 10th day after initiation of the neoadjuvant therapy the patient was referred to our hospital. The patient reported early signs of response as his obstructive symptoms had already disappeared since starting imatinib. A follow-up whole-body PET/CT after 3 months of neoadjuvant treatment showed a remarkable decrease in tumour size to 5 cm in diameter with complete metabolic response. Unfortunately, 4 months after the initiation of neoadjuvant therapy the patient developed generalised erythematous papules with severe itching mainly within 1 h of taking imatinib. The dermatologist was consulted, and topical and systemic treatment of the skin symptoms was started. Owing to the persistence of the skin symptoms, the dose of imatinib was adjusted to 400 mg imatinib orally every other day, which led to better tolerance of the drug, and the operation was rescheduled (Naranjo score = 7).⁴

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Figure 1 First positron emission tomography (PET)/CT scan and MRI. (Left) A transversal cross section of the PET/CT scan showing a large metabolic active tumour. (Right) A sagittal cross section of the MRI showing the compression effect on the rectum, prostate and seminal vesicles.

A preoperative MRI of the pelvic floor performed after 5 months of treatment confirmed a significant decrease in tumour size (figure 2). The lower border of the tumour was at the level of the anal sphincter and there was no macroscopic invasion of surrounding structures. After 6 months of neoadjuvant therapy the patient underwent a rectum resection with manual side-to-end coloanal anastomosis. The mesorectal plane was easily dissected. A Lone Star Retractor was used to perform a sleeve mucosectomy through the anal canal with resection of the upper border of the internal anal sphincter that was still infiltrated by the tumour (figure 3). No ileostoma was created because the anastomosis had a good vascularisation and was traction free.

OUTCOME AND FOLLOW-UP

Postoperative macroscopic examination by the pathologist showed a maximum tumour diameter of 5 cm located 0.1 cm from the distal section plane. Microscopic examination showed negative section planes, no lymphovascular invasion and a mitotic count of 2/50 high power field (HPF). Mutational analysis revealed a p.W557-V559delinsF mutation in exon 11 of the *KIT* gene.

DISCUSSION

What is a GIST?

GISTs are part of the large heterogeneous family of soft tissue sarcomas. GIST cells share some morphological and immunohistochemical similarities with the pacemaker cells of the gastrointestinal tract that regulate peristalsis, the interstitial cells of Cajal.⁵ GIST cells and the interstitial cells of Cajal are therefore thought to have a common ancestry. They can be found in the stomach (51%), jejunum and ileum (36%), colon and rectum

(5–7%), but can also occur extra-gastrointestinally in the mesentery or omentum in rare cases.^{1 6}

Most GISTs are caused by sporadic mutations of the *KIT* or *PDGFRA* oncogene.⁷ The mean age at which they are found is usually between 55 and 68 years, but GISTs can also occur in children with rare hereditary syndromes.⁸ Patients with a GIST usually have non-specific symptoms of gastrointestinal bleeding (33%), abdominal pain (19%), anaemia (9%), abdominal mass (7%) and obstruction (3%).⁹ In our case, a mass was felt in the anterior rectum, which could raise the suspicion of the presence of a prostate tumour. Some authors therefore advocate including GIST in the differential diagnoses of prostate lesions to avoid delayed diagnosis and/or suboptimal treatment.¹⁰

Diagnosis

The diagnostic work up of a symptomatic colorectal tumour often begins with a colonoscopy. A GIST can be seen as a sub-mucosal mass and a biopsy with sufficient tissue sampling can confirm the diagnosis. The biopsy usually shows a spindle, epithelial or mixed cell type. The mitotic count is an important prognostic factor because it is used as a determinant of the aggressiveness of the tumour. Immune histopathology is performed to identify the presence of the CD117 (*KIT*) antigen, which is indicative of a GIST, but can also occur in other malignancies and in normal tissue, such as in the interstitial cells of Cajal.¹¹

A stromal tumour can also be diagnosed on PET/CT imaging; it is usually seen as an exophytic mass that heterogeneously enhances with intravenous contrast because of its high vascularisation.¹² The high anatomic definition of MRI can be helpful in the evaluation of resectability. Contrary to adenocarcinoma, GISTs rarely metastasise to regional lymph nodes and unlike

Figure 2 Preoperative MRI. (Left) A transversal cross section. (Right) A sagittal cross-section. Tumour size 39 mm transverse × 38 mm anterior posterior × 53 mm craniocaudal.

Figure 3 Dissection of the tumour with the Lone Star retractor.

other soft tissue sarcomas, they often metastasise to the liver and peritoneum, and rarely to the lung.¹³ Extra-abdominal metastases are rare but frequently occur during late stages of advanced disease after long periods of treatment with imatinib and other tyrosine kinase inhibitors. Extra-abdominal metastases and multifocal primaries are also associated with the few reported cases of hereditary GIST syndromes (eg, Carney's triad).¹⁴

Prognosis

It is generally accepted that all GISTs with clinical symptoms or a tumour size above 1 cm have the potential to behave malignantly. The determination of the degree of aggressiveness of the tumour is controversial. It has been shown that the Miettinen and Lasota risk classification is the most predictive.^{15 16} This classification is based on the size, mitotic counts and anatomical site of the tumour. Other factors that determine the aggressiveness of the tumour are the presence of synchronous metastasis, rupture during surgery and mutational subtype.^{17–19} Although R0 resection should always be obtained if possible, the microscopic resection margin does not seem to be a crucial predictor of survival.^{7 20–22}

Histopathology and mutational analysis

In approximately 90% of GISTs there is a mutation in the *KIT* gene, leading to overexpression of KIT, a transmembrane stem cell growth factor sensitive tyrosine kinase receptor.² The overexpression leads to constitutional activation of oncogenic cell pathways that are involved in proliferation, with uncontrolled cell growth as a result. The antigen CD117, a part of this tyrosine kinase receptor, is used as a cell surface marker in the identification of GISTs during pathologic investigation.^{2 23 24} Contrary to other mesenchymal tumours, GISTs are almost always negative for desmin and S-100 protein.²⁴

Imatinib

GISTs are unresponsive to chemotherapy and not very sensitive to radiotherapy. The only option for treatment before the introduction of imatinib in clinical practice was total resection of the tumour and its metastases. During early phase 1 and 2 studies, imatinib was found to inhibit the uncontrolled growth of GIST cells that express tyrosine kinase receptors encoded by the *KIT* or *PDGFRA* oncogene.²⁵ Further studies have shown that the metabolic activity of the *KIT*/*PDGFRA* mutation positive tumours can decrease as early as 24 h after initiation of imatinib and the size of the tumour can

decrease markedly in months, as was seen in our case.²⁶ Primary imatinib resistance to neoadjuvant imatinib therapy is found in 50% of *PDGFRA* mutation positive tumours, 33% of wild-type tumours and 9% of *KIT* mutation positive tumours.¹⁸ It is therefore important to identify the exact mutation because certain mutations are non-responsive to tyrosine kinase inhibitors.

Neoadjuvant imatinib increases the chance of successful surgery as smaller tumours can be resected more easily from surrounding anatomical structures and have a decreased chance of rupture during surgery.²⁷ The duration of neoadjuvant therapy is controversial. Neoadjuvant therapy can in theory be continued until the regression of the tumour size or metabolic activity reaches a plateau phase, but the risk of resistance through the development of secondary *KIT* mutations during this stage should be avoided as far as possible.²⁷ Most physicians therefore advocate a neoadjuvant treatment duration of 4–12 months, when the maximum shrinkage and metabolic response of the tumour has been achieved, and the risk of secondary resistance is still low.⁷

Follow-up

Unfortunately, there is limited literature regarding the recurrence and mortality of surgically treated patients with colorectal GISTs who received preoperative imatinib. In a study by Machlenkin *et al*²⁸ of 12 patients with a rectal GISTs, 71% of the patients who underwent surgery after neoadjuvant imatinib and adjuvant imatinib in the case R1 or R2 resection had no clinical or radiological recurrence, and 86% of all patients were alive after a median follow-up of 32 months. In a study by Rutkowski *et al*,⁷ 33 patients operated for rectal GIST after neoadjuvant imatinib showed a 3-year disease free survival rate of 88%. In a recent study, 5 patients underwent laparoscopic intersphincteric resection after neoadjuvant imatinib.²⁹ No recurrence was observed after a media follow-up of 36 months.

It is generally accepted that there is no indication for adjuvant therapy for low-risk rectal GISTs (<5 cm and <5/50 HPF according to the Miettinen and Lasota risk classification). Adjuvant imatinib therapy should be considered in patients with an intermediate to highly aggressive tumour and in the case of a resection with a microscopic (R1) or macroscopic residual tumour (R2).³⁰ Although the GIST in our case can be categorised as a tumour of intermediate aggressiveness according to the NIH classification, the patient was advised not to start with adjuvant imatinib because of poor tolerance of the agent. The patient had concerns about the possibility of suboptimal treatment by not starting adjuvant imatinib therapy, but when confronted with the typical duration of adjuvant treatment of 3 years (or even longer), the patient agreed with strict follow-up.³¹ At 3-month follow-up the patient reported no symptoms of incontinence and had no radiological signs of local recurrence or metastasis.

Learning points

- ▶ Rectal gastrointestinal stromal tumours (GISTs) are rare tumours that can present with gastrointestinal and urological symptoms.
- ▶ Adequate immunohistochemistry of a biopsy is an important diagnostic tool because mutational variants of *KIT* and *PDGFRA* mutation positive tumours are responsive to the tyrosine kinase inhibitor imatinib.
- ▶ Neoadjuvant treatment with imatinib can effectively reduce the size of a GIST and thereby minimise damage to surrounding structures during surgery.

Contributors KHK wrote the abstract, introduction, discussion and learning points; contacted hospitals for more information about the patient's history and wrote the final version of the report. MGO wrote the history of patient; obtained the patient's consent and reviewed the final version of the case report. PS investigated the patient when the patient was referred to University Hospital Leuven; changed therapy doses when the patient reported adverse events and reviewed the final version of the case report. Ad'H operated on the patient; suggested the patient for the case report; and reviewed the final version of the case report.

Competing interests None.

Patient consent Obtained.

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