CASE REPORT

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Gastrointestinal stromal tumours: a surprising clinical course – case report and literature review

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Abstract

Introduction. Gastrointestinal stromal tumours (GISTs) are considered the most common mesenchymal lesions of the gastrointestinal tract, despite accounting for less than 1% of cancers diagnosed in this area. They frequently occur in the stomach and small intestine, rarely in the colon and esophagus.

Case Report. The report concerns an unusual case of a patient referred to hospital with abdominal pain and suspected ileocecal intussusception. Ileus was confirmed during diagnostic evaluation. Surgical resection of the tumour mass was performed to release intestinal loops. Based on histology and immunohistochemical staining, GIST was diagnosed. Currently, the patient remains under constant clinical monitoring.

Conclusions. The evolution of gastrointestinal stromal tumours is highly variable. Both the signs and symptoms and tumor localization in the described case are very unusual for this disease. Adequate diagnosis remains critical to implement appropriate therapeutic management.

Key words

gastrointestinal stromal tumours, gastrointestinal tract, intussusception, tyrosine kinase inhibitors

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are the most common neoplasms originating from the mesenchymal tissue of the gastrointestinal (GI) tract, with an incidence of 1–1.5 cases per 100,000 people per year, and an average age at diagnosis of 60 years [1]. Although most GISTs occur in middle-aged individuals, children and young adults may also be affected, and present with the non-hereditary Carney triad or autosomal dominant Carney-Stratakis syndrome [2]. GISTs are rare tumours; most of them are detected incidentally and their true incidence remains unknown [3]. Before the advent of more contemporary diagnostic tools, GISTs were misdiagnosed as smooth muscle tumours [4]. A distinct category of mesenchymal tumours could not be identified until immunohistochemical and molecular diagnostic methods were developed and introduced. GISTs have been shown to arise from the interstitial smooth muscle pacemaker cell (ICC) of Cajal, whose function is to coordinate intestinal motility [5]. GISTs are most commonly found in the stomach (56%), small intestine (32%), colon and rectum (6%), esophagus (0.7%), and other locations (5.5%) [4]. GISTs are currently considered potentially malignant tumours that have an unpredictable evolution.

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CASE REPORT

The case is presented of a 72-year-old female patient with ulcerative colitis who was admitted to the Department of Surgery because of severe paroxysmal abdominal pain and small bowel intussusception suspicion. Abdominal ultrasound scanning, performed on an outpatient basis before admission to the hospital, showed thickened up to 46 mm intestinal loops, 10 cm long, situated in the lower right abdominal quadrant next to the caecum or terminal ileum. Gas-liquid levels suggested intestinal intussusception. The patient was referred to undergo further verification with a computed tomography (CT) scan and urgent hospitalization.

According to the patient's history, the symptoms reported by the patient were non-specific. The pain was accompanied by weakness, nausea without vomiting, bloating and overflow in the abdominal cavity. In addition, 2 days before hospital admission, she had fainted and collapsed. The CT scan of

the head excluded any post-traumatic lesions, and there were no features of intracranial haemorrhage or any other organic alterations in the CNS that could have caused the fainting. It was speculated that abdominal pain might cause transient fainting. During hospitalization, an abdominal and pelvic CT scan confirmed features of intussusception, compression and stenosis in the terminal segment of the ileum, with a risk of acute ischemia (Figure 1). Pathologic tissue structures associated with the ileal loop were also visible (Figure 2). The patient was referred for surgical treatment. A laparotomy was performed. Approximately 30 cm of the small intestine was resected with the creation of side-to-side stapled bowel anastomosis. The bowel fragment was sent for histopathological examination. In the post-operative period, the patient developed Clostridioides difficile infection. Treatment with vancomycin was administered, and subsequent regression of clinical signs and symptoms with normalization of inflammatory markers was achieved. Eight days after surgery, the patient was in a stable condition with normal vital signs and normal abdominal peristalsis. She was discharged home.

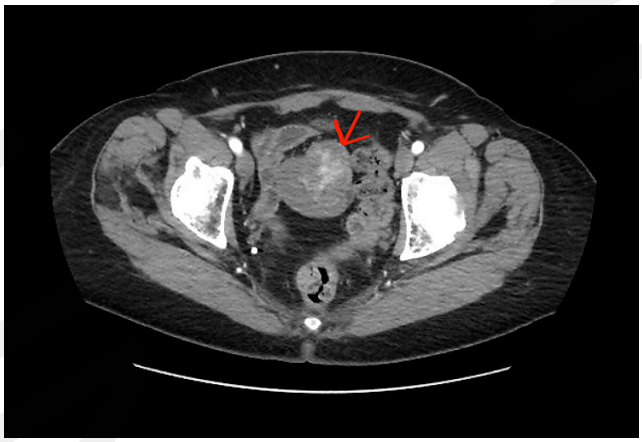

Figure 1. Image of the intussusception on abdominal and pelvic CT scan

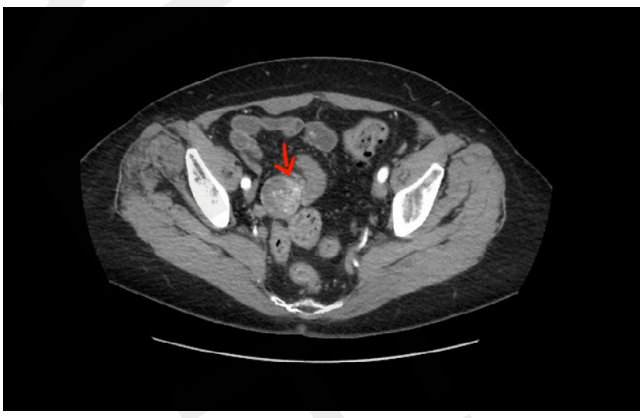

Figure 2. Image of the pathologic tissue structures associated with the ileal loop on abdominal and pelvic CT scan

The results of the pathomorphological examination revealed an 8×4×4.5 cm gastrointestinal stromal tumour (GIST), which had overgrown the muscular layer and emphasized the serous membrane. The neoplasm was composed of spindle cells, richly vascularized with CD 117 (+) expression on immunohistochemical staining, with a KIT point mutation in exon 11. Evaluation revealed the incidence of division figures, mitotic index of 50/dpw: 1. ESMO risk group 3a, intermediate risk of aggressiveness. Surgical lateral margins showed no neoplastic tissue, and radial margins from the serous membrane side showed minimal, focal 0.1mm pT3Nx.

Currently, the patient is undergoing periodic follow-up assessments based on abdominal and pelvic CT scans every 4–5 months for the first 2–3 years, and then every 6 months until 5 years after surgery. Follow-up CT scans showed no GIST recurrence in the postoperative region.. The control CT scan is presented in Figure 3. Similarly, there were no signs of GIST recurrence or metastatic foci in the liver, lymph nodes or other organs. Later follow-up and abdominal ultrasound scanning is required once a year.

Before being admitted to the hospital for intussusception, the patient was under the control of a gastroenterology clinic for ulcerative colitis diagnosed in 2016.

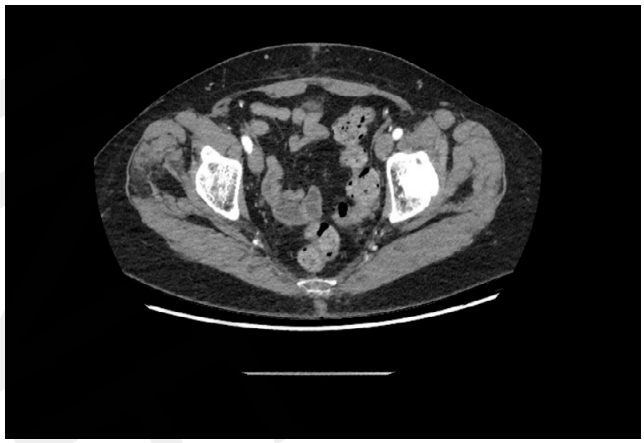

Figure 3.

Less than a year before the diagnosis of GIST, she was admitted to the Department of Gastroenterology for gastrointestinal bleeding from the lower GI tract. During hospitalization, no features of bleeding were observed, and anaemia due to iron deficiency was supplemented intravenously. Endoscopic examinations of the upper and lower GI tract were performed. A colonoscopy revealed an ascending colon polyp, which was removed. The endoscope was inserted into the ileocecal valve without visualizing the distal part of the ileum. Gastroscopy showed numerous small polyps of the gastric fundus and features of mild gastritis. No lesions were found in the small intestine. It also remains important to note that a colonoscopy in this patient performed one year prior to the intussusception, was limited to the ileocecal valve. In situations where the patient's clinical picture remains equivocal, it may be crucial to extend the endoscopy to include imaging of the ileum. This would allow an earlier diagnosis before the tumour caused intussusception of the bowel.

DISCUSSION

Diagnosis and subsequent therapeutic management of gastrointestinal stromal tumours pose a major clinical challenge. The signs and symptoms with which patients present are often non-specific and depend on the location and size of the tumour. They may include early satiety,

abdominal pain and discomfort. However, the most common symptom is gastrointestinal bleeding, which can range from latent anaemia to active bleeding presenting as tarry stools and bloody vomiting [6]. In a review of the literature by Gina Gheroge et al, the rate of bleeding for small intestinal GIST was 28%, while the rate for gastric GIST was much higher, reaching up to 50% [2]. In the presented patient, the bleeding occurred more than a year before the diagnosis of the gastrointestinal stromal tumour, but it was unclear whether it was associated with the GIST tumour or with chronic GI tract disease, i.e. UC. Most GISTs are diagnosed incidentally during an endoscopic examination, or radiological imaging performed for different indications, or on autopsy, without any previous clinical symptoms [7]. Due to its oligosymptomatic and insidious course, up to half of patients develop metastases at the time of diagnosis. They frequently occur in the liver (65% of cases) and peritoneum (21% of cases). Less frequently, they can be found in the bones, lungs and lymph nodes [7, 8]. Symptoms of acute abdomen are not common and are related to large tumours. Moreover, intussusception and obstruction are very rare symptoms, as the tumour usually grows outside the lumen of the gastrointestinal tract. Occasional cases of intestinal intussusception due to GIST have been described in the literature [9, 10].

The diagnosis of submucosal tumours can be a challenge. Endoscopic examination usually reveals a smooth bulge covered with normal mucosa. In an advanced disease, when lesions reach larger sizes, ulcerations may appear. However, endoscopic examinations cannot differentiate between GIST and other subepithelial lesions. The best tool to differentiate submucosal lesions is endoscopic ultrasonography (EUS). The examination can unequivocally identify hyperechoic lipomas, anechoic cysts and varices [11, 12]. However, GIST – similarly to myxomas, neuroblastomas, carcinomas, ectopic pancreas, and lymphoid masses – may present as a hypoechoic solid mass [13]. Tissue samples for histopathological examination and their morphological and immunohistochemical features facilitate an accurate diagnosis, which is critical for further treatment of patients with GIST [14]. Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) is considered the gold standard for diagnosing SEL (subepithelial lesions) [15]. The higher the tumour diameter, the more likely the diagnosis (Table 1) [16].

Table 1. Correlation of SEL (subepithelial lesions) diagnosis with tumour diameter [16]

Tumour diameter	Grade of diagnosis (%)
1–2 cm	71%
2–4 cm	86%
>4 cm	100%

Biopsy is recommended in patients with GIST above >2 cm in size, as they present a higher risk of tumour progression. Confirmation of GIST diagnosis allows selection of the best possible method of treatment, such as neo-adjuvant treatment, and avoid surgery in cases where it is not recommended. For gastric or duodenal submucosal lesions which are below 2cm, EUS-FNA (endoscopic ultrasound-guided fine-needle aspiration biopsy) can be difficult to perform. Often, only small samples can be obtained for histopathological examination. In the majority of patients, only open or laparoscopic excision can lead to confirmation of GIST diagnosis. If tissue samples are unavailable for definitive confirmation of GIST, active surveillance based on periodic EUS checks is recommended [17]. Nevertheless, the optimal follow-up period for small (<2 cm) GISTs without high-risk features has not been established so far, and annual examinations are routinely repeated [18]. According to Ye et al., during a 28-month follow-up period, most small (<20 mm) suspected gastric GISTs did not enlarge (98%), and only 8 lesions (2%) increased in size [19]. Considering the potentially malignant nature of GISTs, surgical resection should be planned in patients who are symptomatic or with a lesion is that is growing [17].

Determining morphological and immunohistochemical features remains paramount in the diagnostic approach to patients with GIST suspicion. According to histopathology, 3 subtypes of tumours are distinguished: the first from spindle cells (70%), the second from epithelial cells (20%) and the third – mixed type (10%) [20]. The most common immunohistochemical GIST markers are KIT, CD 34 and DOG, which are useful when no positive KIT or CD 34 results are found (Tab. 2). Others used in differential diagnosis include SMA, S-100, desmin and keratin [7, 13].

Table 2. Immunohistochemical markers specific for GIST [7, 13]

Marker	Prevalence in GIST
KIT	95%
CD34	60–70%
DOG1	5%

Some genes are resistant to standard treatment; therefore, in order to select an optimal therapy, molecular testing is recommended in all cases of suspected GIST [14, 17]. They include sporadic mutations of the KIT gene (CD 117) or the platelet-derived growth factor receptor alpha (PDGFRA) gene [13, 14, 21, 22]. GIST without detectable KIT or PDGFRA mutations is referred to as the 'wild type'. It is common in paediatric GISTs and is associated with tumour syndromes, e.g. neurofibromatosis type 1 (NF1), Carney's triad (GIST + pulmonary cartilage +-paraganglioma) and Carney-Stratakis syndrome (GIST + paraganglioma). A summary of GIST mutations is shown in Table 3 [20].

Table 3. Molecular classification of gastrointestinal stromal tumours (GIST) and mutation frequency (%) [20]

KIT gene mutations (80%)	PDGFRA gene mutations (10%)	Wild- type (no mutations in the KIT or PDGFRA gene) (10–15%)
Exson 11 (60–70%)	Exson 12 (1–2%)	NF1 mutation (1–2%)
Exson 9 (5–10%)	Exson 14 (<1%)	SDHA/SDHB/SDHC/SDHD mutations (Carney–Stratakis syndrome) (~2%)
Exson 13 (1%)	Exson 18 (5–10%)	Loss of SDH expression (Carney triad)
Exson 17 (1%)		HRAS, NRAS, BRAF mutation

Although mutations provide important prognostic information, assessment of location, tumour size and mitotic index is essential for independent risk stratification in patients with GISTs. These indicators, developed in 2006 by Miettinen and Lasota, are widely used in clinical practice. Localization of GIST in the stomach was associated with a better prognosis in comparison to small intestine and

rectum lesions. Tumour size below 2 cm is also a favourable factor. Gastric GISTs equal or less than 2 cm in diameter have a minimal risk of dissemination, regardless of their mitotic index (0%). This risk increases to 2% for lesions with a diameter of 2–5 cm and a low mitotic index, and to 16% for lesions with a high mitotic index [22]. However, since mitotic index and tumour size are continuous variables, they should be assessed with caution [17]. Nowadays, in addition to the Miettinen and Lasota criteria, the TNM classification and tumour rupture score are used for evaluation. They may provide additional benefits in the diagnosis and treatment of patients with GISTs [7, 20].

Treatment of gastrointestinal stromal tumours depends on tumour size, location and spread. Nevertheless, surgical treatment remains the first therapeutic choice, and is used for localized GIST. Despite the high efficiency of this method of treatment, recurrence and even progression of the disease do occur. Therefore, after surgical resection, follow-up treatment with imatinib for 3–5 years is recommended in patients at moderate to high risk of GIST recurrence [23].

A study summarizing the treatment of advanced GIST found that patients with gastric tumours less than 2 cm could be monitored [24]. However, when lesions up to 8 cm in size are detected, removal by laparoscopy is recommended [23]. Since lymph node dissemination of GIST is rare, routine lymphadenectomy is not performed. When tumours are located in difficult regions, such as the gastroesophageal junction, the duodenal papilla, the junction of the duodenum and jejunum or the rectal sphincter, or tumour size is larger than 10 cm, neoadjuvant therapy is indicated. For this purpose, imatinib is used. The treatment leads to a decline in vascularization and tumour size, and facilitates subsequent tumour resection.

Imatinib is a multitargeted TKI (tyrosine kinase inhibitor) with activity against KIT and PDGFR. Therefore, before administration of this medication, the diagnosis should be confirmed by biopsy. If there is no GIST response to the treatment, misdiagnosis is suspected, which may require a repeated histopathological examination. Tumour resistance to imatinib may be present [23, 24]. Imatinib shows the highest effectiveness in treating GIST with KIT mutations of exon 11 (90%) and 13 (1%), while it is less effective for PDGFR mutations in exons 12, 14 and 18. When a KIT mutation of exon 9 is present, higher-than-standard doses of the drug are used (usually 400 mg twice daily). Imatinib has been shown to own no or limited efficacy for PDGFR mutations in exon 18 of D842V (8%), or in patients with GIST without KIT and PDGFR mutations [25]. Imatinib is used as adjunctive chemotherapy for resectable GISTs. Its administration at a dose of 400 mg/day was associated with an 82% response rate [26, 27].

If the response to imatinib is poor despite an increase in its dose, or if the patient is intolerant of the drug, sunitinib can be used as an option. This is a multidirectional TKI that acts on the tyrosine kinase KIT, PDGFR, vascular endothelial growth factor receptor (VEGFR) and FLT3. It has been shown that about 40% of GIST patients can achieve a long-term response to-sunitinib, especially those with a primary mutation in exon 9.

Regorafenib, a multikinase inhibitor active against KIT, EGFR, as well as a variety of other kinases, can be administered as a third-line treatment after the failure of the previous 2 drugs. In addition, it is used in the treatment of hepatocellular carcinoma and metastatic colorectal cancer [28].

Gastrointestinal stromal tumours may recur or fail to respond to the treatment. For this reason, other multityrosine kinase inhibitors have already been investigated. They include ripretinib, avaptinib, dasatinib, pazopanib, sorafenib, cabozantinib, ponatinib, nilotinib, crenolanib.

Several other therapeutic options for the treatment of GISTs are currently under evaluation, particularly new next-generation tyrosine kinase inhibitors targeting specific secondary KIT mutations. Such drugs include PLX3397, PLX9486 and AZD3229 [29]. It is believed that with the benefits gained from next-generation sequencing, future treatment of GIST will be based on individualized genomic therapy for each patient [30].

CONCLUSIONS

The natural course and evolution of GISTs ~~is~~ are highly variable. Their clinical manifestation rarely includes conditions associated with an acute abdomen, such as intussusception, which occurred in the described patient. Adequate histological, immunohistochemical and molecular diagnosis and early surgical resection are currently considered the most reliable management strategies. Periodic follow-up and monitoring of patients after treatment also remain an important aspect. Currently, there is no consensus on the management of small GISTs.

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