A rare rectal gastrointestinal stromal tumor with indolent biological behavior: A case study

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Abstract. The overall incidence of rectal gastrointestinal stromal tumor (RGIST) has risen, but it remains a rare disease. Furthermore, tumor rupture is associated with poor prognosis. The present study reported a rare case of RGIST with indolent biological behavior. The biological behavior of this RGIST was analyzed and its malignant potential was evaluated using a guideline-based risk stratification assessment. The patient was diagnosed with a rectal tumor at the Third Affiliated Hospital of Qiqihar Medical University (Qiqihar, China) in April 2020 and a partial resection biopsy was then performed. This resection counts as a rupture. The biopsy confirmed RGIST and the patient refused further examination and treatment due to economic concerns. However, the patient survives with no tumor progression and metastasis until now, May 2022. In conclusion, based on the present case, tumor rupture in indolent RGIST is not necessarily associated with poor outcome.

Introduction

Gastrointestinal stromal tumor (GIST) accounts for 0.1-3% of all GI tumors (1). This type of tumor may occur in any part of the digestive tract but is most common in the stomach (~60% of cases) and least common in the rectum (~5% of cases) (2,3).

The overall incidence of rectal malignancies is as low as 0.6% (4). GISTs are different from other mesenchymal tissue-derived tumors. Approximately 90% of them highly express CD117, as indicated by immunohistochemical staining (5). In terms of morphology, ~70% of GISTs are spindle cell tumors, 20% are epithelioid cell tumors and 10% are mixed cell type tumors (6). In recent years, rectal GISTs (RGISTs) have exhibited certain potential malignant features, and they are characterized by easy relapse following treatment; therefore, RGIST has a poorer prognosis compared with gastric GIST (7). The recently confirmed anorectal GIST cases had a local recurrence rate of 50% (8). Even among patients receiving imatinib treatment, the ratio of RGIST recurrence may still reach 1/3 (9).

The risk stratification assessment results of GIST are closely related to patient prognosis. Globally influential guidelines were retrospectively searched, and search strategies and screening strategies are provided in Supplementary Materials 1 and 2. There is a comprehensive consensus on using tumor size, mitotic index (MI) and anatomical site as optimal parameters for the risk stratification assessment of GIST (10-15). In recent years, the impact of tumor rupture on the risk assessment and prognosis of GIST has been reported several times, but the use of GIST rupture as an independent predictor of prognosis remains controversial (12,16-21). The globally influential National Institutes of Health (NIH) 2008 guidelines included tumor rupture as an independent indicator for the risk assessment of GIST, and it has been proposed that, as long as the tumor ruptures, regardless of tumor size and MI, it is regarded as high risk (12). However, numerous influential studies had limitations, including insufficient sample size of ruptured GISTs (16-21), making it difficult to evaluate the significance of GIST rupture.

Using certain guidelines or prognostic evaluation models, due to the limited sample size of RGIST, its malignant potential and biological behavior cannot be accurately evaluated, which has become a limitation of research (11,16,17). In certain recent guidelines, total area of 5 mm² has replaced 50 high-power microscopic fields (HPF) as the assessment area of the MI, but it is not a worldwide consensus (10-15). The prognosis may reflect the biological behavior of RGIST to a certain extent. The European Society for Medical Oncology...
nancy initially due to the tumor is poorly demarcated from the tumor, which was suspected the possibility of malignancy. The prostate and levator ani muscle were being squeezed by the contrast-enhanced computed tomography (CT) scan and the patient was admitted to the hospital for further examination indicating a rectal submucosal tumor (Fig. 1). Subsequently, the border was clear and there was no ulceration or bleeding on it, suggesting a rectal mass was found 20 mm from the patient's anal margin. The tumor surface was smooth, the colonoscopy. A rectal mass was found 20 mm from the anus. The rectal mass was pliable but firm, the base was wide, the uppermost part was out of reach by abdominal palpation. Digital rectal examination revealed a large mass in the front wall of the abdomen indicated by abdominal pain, bloating and a decrease in a single stool volume than before. While there was no blood in the stools, abdominal pain, bloating and a decrease in stool volume had been noted for 1 year. The patient had a sense of not being clean, indicating for 1 year. Incomplete obstruction is consistent with the patient's symptoms: The patient had a sense of not being clean, and a change in bowel habits with an increased stool frequency (3/4 times a day); no change in the total stool volume over 24 h, and a decrease in a single stool volume than before. The patient had no other complaints except for the incomplete obstruction in defecating. The patient had no history of any past illness.

In terms of physical examination, no obvious mass in the abdomen indicated by abdominal palpation. Digital rectal examination revealed a large mass in the front wall of the rectum ~20 mm from the anus. The rectal mass was pliable but firm, the base was wide, the uppermost part was out of reach by abdominal palpation. Digital rectal examination revealed a large mass in the front wall of the rectum ~20 mm from the anus. The rectal mass was pliable but firm, the base was wide, the uppermost part was out of reach by abdominal palpation. The patient asked for a definitive diagnosis. Therefore, a tissue excision biopsy was performed. The tumor tissue was soft and gray-white. A total of three tumor tissue specimens (from two regions, near the anal opening and the anterior wall of the rectum) were excised; each tumor tissue volume was ~0.5 cm³, with the total volume being 1.5x1x1 cm (1.5 cm³). H&E staining and immunohistochemistry were performed at The Pathology Center of Qiqihar Medical University (Qiqihar, China). Specimens were fixed in 10% formalin at 20°C for 12 h, sectioned at a thickness of 5 µm and stained with hematoxylin for 10 min and eosin for 20 sec at 20°C. Under the microscope, the spindle cells were observed to be densely arranged and uniform in shape. The nuclei were arranged in a palisade shape, there were vacuoles next to the nuclei and mitotic figures of 2 nuclei were able to be observed under the microscope at a magnification of x200 (Fig. 4). For immunohistochemistry, specimens were fixed in 10% formalin at 20°C for 12 h, sectioned at a thickness of 5 µm and followed by dewaxing, rehydration and high-pressure antigen retrieval. Subsequently, they were blocked with 5% normal goat serum (Beyotime Institute of Biotechnology) for 1 h at room temperature. Samples were incubated with the primary antibody overnight at 4°C and with the secondary antibody for 1 h at room temperature. The corresponding antibodies used in the experiments are listed in Table I. Finally, the sections were sealed with neutral gum after staining and the results were observed under a microscope. The immunohistochemistry findings were as follows: CD117(+) the staining was located in the cytoplasm/membrane and the positive rate was 80-100%. Dog-1 (Discovered On GISTs Protein 1) (+), whose staining was localized at the membrane/plasma, is a GIST-specific antibody and was diffusely positive. CD34(+), whose staining was localized in the cell membrane, had a positive rate of 50-80%. Ki67 (1%), whose staining was localized in the nucleus, was used to reflect the proliferative activity of GIST and had a positive rate of 1% (Fig. 5). The histology of the biopsy specimen confirmed RGIST and immunohistochemistry suggested the possibility of receptor tyrosine kinase (KIT) gene mutation. KIT is also known as CD117, and the vast majority of CD117-positive GISTs contain 70-80% of KIT mutations (26).

The RGIST was diagnosed as high risk, according to the 2008 revised National Institutes of Health (NIH) Guidelines (12). A multidisciplinary treatment group was involved in this assessment and the final recommendation was genetic testing followed by preoperative oral imatinib therapy. Abdominoperineal resection or TransAnal Minimally
Invasive Surgery (TAMIS) would be performed according to the tumor response to imatinib. However, the patient refused further examination and treatment due to economic concerns.

The patient was followed up by telephone every 6 months, and the total follow-up time was 2 years. Abdominal CT (from April 2020 to May 2022) suggested that the tumor had shrunk and no lymph node metastasis was found in the lateral rectum, obturator foramen or groin area (Fig. 6). The head and chest CT identified no abnormalities. Furthermore, the patient exhibited no defecation difficulties, hematochezia or other complaints.

Discussion

The ESMO 2022 guidelines propose that radiographic changes in GIST should be considered as tumor reactivity, which indicates the potential of malignancy (10). Tumor size and density may be used as indicators of GIST responsiveness (10). The response of this GIST was assessed using CT. As presented in Fig. 5, the tumor was smaller than previously (April 2020); considering that the tumor tissue had been partially resected during the biopsy, the tumor volume was evaluated as not increased and the density of this RGIST was consistent during follow-up. Therefore, according to the ESMO 2022 guidelines, in the present case, the ruptured RGIST was judged as not having progressed. Furthermore, there was no evidence of metastasis during the follow-ups, indicating that the patient achieved a 2-year progression-free survival (PFS).

Tumor rupture was defined in the ESMO 2022 guidelines as intra-abdominal tumor spillage or fracture, segmental resection, laparoscopic/open incision biopsy, abdominal gastrointestinal perforation, bloody ascites or microscopic transperitoneal infiltrate into adjacent structures (10). The RGIST of the present case was biopsied by an open incision so was considered a tumor rupture. Although there are certain influential guidelines and consensuses supporting the link between tumor rupture and poor prognosis (10,12), whether tumor rupture may be an independent risk factor for the prognosis of GIST remains controversial (16-21). Since tumor rupture is a rare event, the number of cases is not sufficient to meet the inclusion criteria of clinical studies (16,17).

The risk assessment staging of RGIST directly affects the treatment options and prognostic benefits for patients. In the present case, the patient achieved a 2-year PFS with tumor rupture, suggesting that the RGIST is a tumor with indolent biological behavior. However, it was rated as high risk according to the NIH 2008 guidelines, which is clearly inconsistent with its indolent biological behavior. In order to explore the reasons for indolent biological behavior of the RGIST, a review of the main global guidelines was performed, followed by a comprehensive risk assessment of the RGIST in this case. All risk assessment systems (the latest revisions) used in the present study are listed in Tables SI-V. These assessment systems have a comprehensive consensus on using tumor size, MI and anatomical site as the best parameters for GIST risk stratification assessment (11-15). At present, the authority of the NIH 2008 guidelines on the risk stratification assessment of GIST is recognized worldwide, but it appears to not provide a good explanation for the indolent biological behavior of RGIST in the present case. The study by Joensuu et al (16) from 2012 suggested that the identification of mitosis is subjective; the number detected depends on the fixation time of the tissue and the size of the microscopic field, which may affect staging. Mitotic counts are probably best based on per 5 mm² of tumor tissue, rather than per 50 HPF. Certain recent guidelines have agreed with this (Table SI-V). Guidelines developed in earlier years used per 50 HPF as the assessment area [including Armed Forces Institute of Pathology guidelines (AFIP) 2006 guidelines (Table SI) and NIH 2008 guidelines (Table SII)], and the guidelines in recent years gradually replaced per 50 HPF with per 5 mm² [including International Union Against Cancer (UICC) 2016 guidelines (Table SIII) and World Health Organization (WHO) 2020 guidelines (Table SIV)]. The change in the assessment area mentioned in the WHO 2020 guidelines helps to standardize the calculation of the true area of mitosis, since different microscopes have different sizes of high-power fields. ESMO 2022 guidelines also argue that using per 5 mm² as the assessment area may avoid variability. Although the National Comprehensive Cancer Network (NCCN) 2022 guidelines (Table SV) do not change the assessment area of MI, this is enough to indicate that the risk assessment system of GIST has been gradually perfected. Whether there are assessment indicators could be updated to optimize the existing RGIST risk assessment system needs to be confirmed by further research.

Therefore, the RGIST of the present case was evaluated using per 50 HPF or 5 mm² as the assessment area for the MI according to the guidelines. Using per 50 HPF as the assessment area for the MI, the RGIST in this case was rated as stage III intermediate malignant potential using the AFIP guidelines from 2006 (Table SI) (11), stage IV high risk using the revised NIH guidelines from 2008 (Table SII) (12) and moderate risk using the NCCN guidelines from 2022 with a metastasis probability rate of 24% (Table SV) (15). For the present case, two pathologists reassessed the MI as 2/5 mm². Using per 5 mm² as the assessment area for the MI, the...
RGIST was rated as stage II intermediate malignant potential according to the UICC 2016 guidelines (Table SIII) (13) and stage I benign according to the WHO guidelines from 2020 (Table SIV) (14). In conclusion, the RGIST was rated as intermediate risk by category 2 guidelines and high risk by category 1 guidelines before the MI was adjusted. After adjusting for the MI, RGIST was assessed as intermediate risk by category 1 guidelines and benign by category 1 guidelines. The ruptured RGIST in the present case was evaluated using different guidelines with different risk stratification results, and it was only rated as high risk according to the NIH 2008 guidelines. In the present study, the WHO 2020 guidelines were used to evaluate the indolent biological behavior of the RGIST, as the RGIST was not progressing following rupture. Furthermore, the present case reflected the significant heterogeneity in the results of RGIST assessment based on different guidelines, indicating that this case was a rare one.

The RGIST in the present case underwent iatrogenic rupture, which belongs to involuntary rupture in biological behavior, which is different from spontaneous rupture; since GIST originates from mesenchymal tissue, spontaneously ruptured GIST requires to break through the surrounding gastrointestinal wall first, which suggests that the ruptured GIST is more aggressive and has malignant potential. Furthermore, the present case suggested that our understanding of the malignant potential and biological behavior of GIST is not sufficient and further research is required to prove whether there are other independent optimal parameters that may be included in the risk assessment of GIST. Based on guidelines and patient prognostic assessments, it is valid for indolent or low-grade GIST to be diagnosed. The evidence in the present

Figure 2. Contrast-enhanced CT. (A) Arterial phase of enhanced abdominal CT. (B) Venous phase of enhanced abdominal CT. The red arrow points at tumor. CT, computed tomography.

Figure 3. Contrast-enhanced MRI. (A) Enhanced MRI showing the main blood supply of the tumor. (B) Diffusion-weighted imaging of the tumor. (C) Enhanced MRI of the tumor in the coronal plane. (D) Enhanced MRI of the tumor in the sagittal plane. The red arrow points at tumor. MRI, magnetic resonance imaging.
case indicated that it may not be appropriate for indolent RGIST that tumor rupture increases the risk of poor prognosis. Further clinical trials are required in order to demonstrate that the worsening of the prognosis associated with tumor rupture applies to different tumor types (high-risk or indolent). In the future, prospective multicenter cohort studies or randomized controlled trials may be performed to compare the survival outcomes (overall survival, PFS and recurrence-free survival) between ruptured and non-ruptured RGISTs, so as to provide clinical ideas for perfecting the risk assessment system for RGIST.

The ESMO 2022 guidelines explicitly propose genetic sequencing as a class I evidence of prognostic relevance for GIST (10). For instance, GISTs with platelet-derived growth factor receptor A mutations corresponding to D842V are generally associated with a favorable prognosis (10). By contrast, GIST deletions at codons 557-558 of KIT exon 11 are associated with a higher risk of recurrence (27). In the present case, gene sequencing was not performed. However, the pathological evidence was sufficient and the immuno-histochemical results were consistent with the diagnosis of RGIST. The indolent biological behavior of this RGIST may be related to the genotype, which requires further examination and verification after obtaining the patient's consent. In recent years, Ki67 has been repeatedly reported to be associated with the prognosis of GIST (28), but the opposite opinion can be found in the ESMO 2022 guidelines and Ki67 is not part of the established prognostic assessment system for GISTs. Further research is required to resolve this controversy.

The major limitations of the present case are the iatrogenic rupture of the tumor and the refusal of the patient to receive further treatment due to economic concerns, which is a real-world problem. The doctors in primary hospitals were lacking a comprehensive understanding of the standardized diagnosis and treatment of GIST until the release of the first Chinese GIST guidelines in August 2020 (22). Gene sequencing is expensive and thus difficult to perform in the real world, even though it is recommended as a routine checkup item in outpatient clinics in the ESMO 2022 guidelines (10).

If economic issues are not considered, the standardized management for patients is as follows: Gene sequencing is performed first to identify preoperative chemotherapy drugs (e.g., imatinib), adjuvant therapy is administered for at least 6 months (15) and the response is assessed every...
It is recommended to perform R0 resection by transanal endoscopic microsurgery or TAMIS (29), and apply postoperative adjuvant chemotherapy (e.g., imatinib) for at least 3 years (30), with routine follow-up of abdominal CT or MRI every 3-6 months. In most parts of the world, it is not uncommon for patients not undergo standardized diagnosis and treatment due to financial constraints. Therefore, more real-world-based health economics in clinical research are required in order to provide more evidence-based guidelines for the rational allocation and utilization of medical resources and maximize patients' benefits of medical care.

In conclusion, based on the present case, it may not be possible to assume that for indolent RGIST, tumor rupture worsens the prognosis, the confirmation of which may require further clinical trials. Furthermore, this rare case may be able to contribute to perfecting the risk assessment system of RGIST.
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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

JY contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data and manuscript drafting. YL contributed to manuscript drafting. XJS analyzed and interpreted the logical and immunohistochemical findings. SL contributed to the analysis and interpretation of data and reviewed and edited the manuscript. SL and JY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the treatment interventions, images, data collection and submission of this article for publication.

Competing interests

The authors declare that they have no competing interests.

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