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Report of a Case of Total Wild-type Gastrointestinal Stromal Tumor

Bingcong Zhao[1], Yahong Li[1], Wenjian Xu[2], Zhijuan Guo[2] and Ming Liu[3*]

[1]*College of Graduate, Inner Mongolia Medical University, Hohhot, Inner Mongolia, 010110, P. R. China.*

[2]*Department of Pathology, Inner Mongolia Autonomous Region Cancer Hospital, Hohhot, Inner Mongolia, 010000, P. R. China.*

[3]*Department of General Surgery, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, 010000, P. R. China.*

***Correspondence:**
Ming Liu, Department of General Surgery, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, 010000, P. R. China.

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Keywords
Gastrointestinal stromal tumor, Pelvic tumors, Abdominal CT scan, Surgery.

Introduction
Gastrointestinal stromal tumor (GIST) is the most common non-directional differentiated mesenchymal tumor of the gastrointestinal tract [1]. KIT and PDGFRA genes are mutatedin 90% of GIST patients. However such mutations do not take place in about 10% of patients with GIST, namely WT-GIST patients [2]. Imatinib is a kind of TKIS, which can inhibit related pathways in KIT and PDGFR gene mutations [3-5]. It is also the main targeted drug for GIST treatment, but the curative effect is poor for WT-GIST patients. The recurrence rate is still high after taking this medicine. Thus, it is clinically significant to study the incidence and medication of this kind of special cases.

Case Presentation
A 60-year-old female was hospitalized at our hospital because of "pelvic tumor resection for 1 year and reexamination found pelvic abdominal mass for 3 days". Pelvic mass resection was performed (at another hospital and intraoperative condition was unknown) in 2016. Postoperative pathology was diagnosed as pelvic peritoneal stromal tumor, and imatinib 400mg/d was taken orally after surgery. In September 2017 and September 2018, the patient had a second recurrence and underwent pelvic tumor resection. Postoperative pathology and immunohistochemical examination were performed and the tumor was diagnosed as spindle cell mass (Figure 1a). Positive expressions of CD34 (Figure 1b), CD117 (Figure 1c) and Dog-1 (Figure 1d) were detected. Genetic test showed that exons 9, 11, 13, 17 of c-kit gene and exons 12 and 18 of PDGFR-α gene were total wild type, as shown in table 1. Imatinib 400mg/d was taken orally after surgery for drug therapy. She was admitted to our hospital for reexamination in April 2019. Abdominal CT scan of the abdominal cavity and pelvic cavity suggested that multiple solid masses were found in the pelvic cavity and a small amount of fluid was accumulated in the abdominal cavity and pelvic cavity (Figure 2). Multiple pelvic masses were resected again, and the removed specimens were shown in Figure 3. Postoperative pathological diagnosis of spindle cell malignancy, combined with the results of the previous twice pathological examinations, was considered as stromal tumor. Sunitinib is recommended to be taken 50 mg/d orally for drug treatment after surgery.

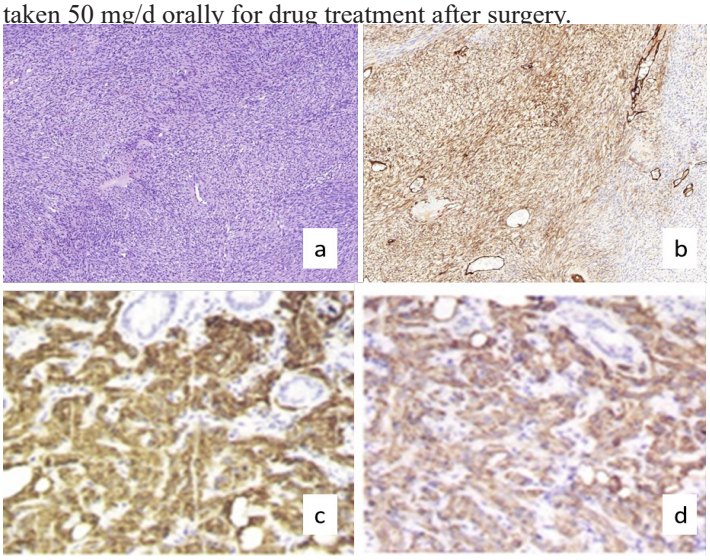

Figure 1: Postoperative pathology and immunohistochemical examination were performed. (a) The tumor was diagnosed as spindle cell mass with HE staining sections (en vision staining ×200). (b) Positive expressions of CD34 (en vision staining ×200), (c) CD117 (en vision staining ×400) and (d) Dog-1 were detected (en vision staining ×400).

	Mutation site	Type
c-KIT	Exon11	wild
	Exon9	wild
	Exon13	wild
	Exon17	wild
PDGFRa	Exon12	wild
	Exon18	wild

Table 1: Detection of genetic mutation of c-KIT/PDGFR-α.

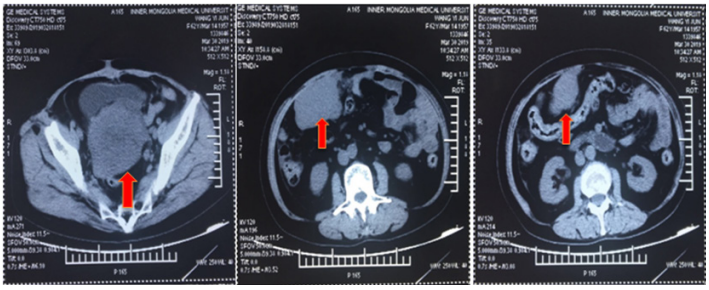

Figure 2: Multiple masses were found in the pelvic cavity and abdomen, which differ in size.

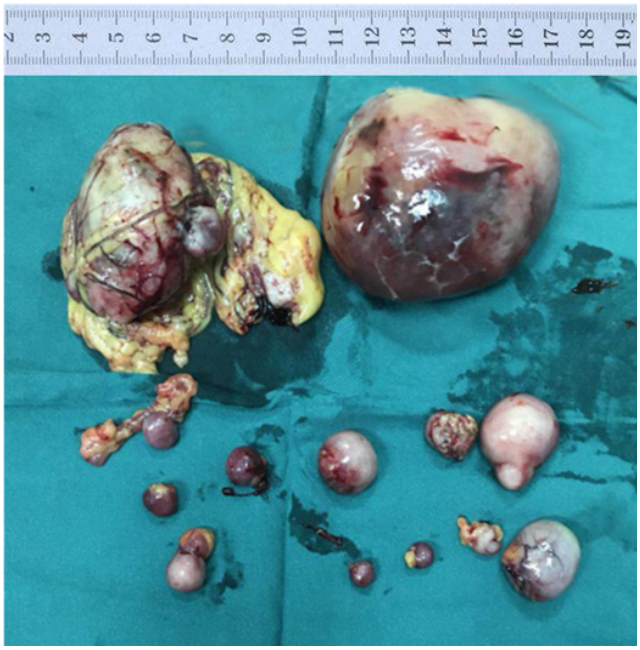

Figure 3: Surgically removed specimens.

Discussion

GIST mainly occurs in the gastrointestinal tract but can also occur outside this area. The primary locations are 50% to 70% in the stomach, 25% to 35% in the small intestine, and 5% to 10% in the colorectum. About 5% of the cases occur outside the gastrointestinal tract (such as omentum, retroperitoneum, and pelvic cavity) [6]. It is a relatively rare case of WT-GIST in this case that the location of primary tumor is in retroperitoneal outside the gastrointestinal tract. Clinically, there is still lack of effective therapeutic targets. Complete surgical resection of the lesion is the best treatment for this type of GIST at present. And 1-3 years of postoperative treatment with imatinib for patients with genetic mutations can reduce the recurrence rate and improve the cure rate, but the postoperative treatment for total WT-GIST is not satisfactory.

GIST is the most common mesenchymal tumor in the gastrointestinal tract. The annual new incidence is about 2 in 100,000, but only 10% of patients with WT-GIST were diagnosed. The patient presented in this paper is total WT-GIST, and the multiple surgical resections of the lesion and the postoperative adjuvant treatment with imatinib had not been satisfactory. Although it is still lack of a complete clinical treatment plan and prognosis evaluation criteria for the classification of the risk of WT-GIST, some progress has been made on the pathogenesis of WT-GIST. Tumorigenetic mechanisms between the wild type and the mutant GIST are different, so it is classified as WT-SDH deficient GIST, BRAF mutant GIST, NF1 mutant GIST and quadruplenegative WT-GIST clinically. SDH deficient GIST, which is more common in women, is mainly found in the stomach with Carney-Stratakis syndrome and Carney triad.It is generally believed that this is caused by SDH expression defects [7]. Pantaleo [8] indicates that miR-139-5p, 455-5p and let-7b signals characterized by overexpression of IGF1R may be important therapeutic targets for KIT/PDGFRA WT-SDH deficient GIST. BRAF mutant GIST mostly occurs in the elders and the location of its onset is concentrated in the small intestine. In this group of patients, most of the genetic expression is the mutation at the V600E site of exon 15 [9]. NF1 deficient GIST is characterized by a small gender difference in its onset, which is mostly manifested as multiple lesions. Because of NF1 gene mutation, neurofibromatine protein lost its function as a tumor suppressor, and this lead to tumorigenesis [10,11]. The pathogenesis of the quadruple negative WT-GIST is not related to above mentioned genetic pathway abnormalities, and it may have been caused by multiple genetic level abnormalities [12].

The wild-type patients are prone to develop primary drug resistance to imatinib, one of first-line drugs in GIST's therapy. In addition, most patients will develop secondary resistance after long-term treatment with imatinib, so it's necessary to further study the treatment of primary and secondary resistance in wild-type patients. Patients resistant to imatinib with exon 9 mutation often have good sensitivity of sunitinib, thus sunitinib can be used as second-line drugs for patients with failed imatinib treatment. However, it is found that sunitinib was prone to adverse reactions like hypertension, heart disease and hypothyroidism [13]. The combination of new targeted drugs such as Pazopanib [14], Dabrafenib [15], Crizotinib [16]may reduce the resistance of imatinib, but this still has to be proved by further clinical trials.

Conclusion

WT-GIST is a rare type with significant different biological behavior of the tumor among individuals. For resectable WT-GIST, surgical resection is still the most important treatment method. Since these patients are primarily resistant to imatinib, the treatment of WT-GIST patients, especially the treatment after drug resistance, provides a new direction and challenge for the research related to GIST.

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