Case Report

Two new KIT exon 13 mutations in one gastric gastrointestinal stromal tumor (GIST)

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most frequently mesenchymal tumors found in the gastrointestinal tract. These tumors are usually composed of spindle-shaped cells. More than 80% of GISTs harbor mutations of KIT gene which encodes for an important receptor tyrosine kinase (RTK) type III. Within KIT gene mutations, the mutation of exon 13 is very rare. Here we described a case of GIST in a 42-year-old male which carried two new KIT exon 13 mutations (R634W and N655T). This patient was diagnosed with upper digestive tract hemorrhage and later CT scan revealed a 2.2 cm × 4.0 cm soft-tissue mass on the posterior wall of the stomach. The patient went through a laparoscopic gastrectomy. Following pathological examination revealed this tumor to be a low-risk GIST. Gene sequencing analysis shown that the tumor had two mutations in KIT exon 13, which were not found in the literature. The postoperative course was uneventful and no recurrence was observed after 6 months. Furthermore, we also gave a short review of previously published papers describing KIT exon 13 mutations.

Keywords: Gastrointestinal stromal tumors (GISTs), KIT mutation, exon 13, receptor tyrosine kinase (RTK), digestive tract hemorrhage

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract [1, 2]. The majority of GISTs are frequently localized in the stomach, then the small intestine, the colon-rectum, and the esophagus [3]. GISTs are often consisted of spindle cells, but can also be composed of epithelioid cells or mixed cell types. The majority of GISTs are characterized by KIT or PDGFRA gene mutations. Both KIT and PDGFRA are coding for two important receptor tyrosine kinase (RTK) type III which consist of five Ig-like domains, a transmembrane, a juxtamembrane and two tyrosine kinase domains separated by a kinase insert [4]. The KIT gene mutations are most frequently occurred in exon 11 (60-70% of cases), followed by exon 9 (10% of the cases); exon 13 (1%) and 17 (0.5-1%) mutations are very rare and generally not primary [1, 5-8]. RTK inhibitor imatinib mesylate (Gleevec, Novartis Pharma AG, Basel, Switzerland) can target KIT and show very good effects on sensitive GISTs, therefore this drug serves as the first-line option in the medical treatment of GISTs [9, 10]. Here, we described a case of gastric GIST with double new KIT exon 13 substitution mutations.

Clinical history

A 42-year old male had symptom of melena for three days and also with vomiting of brown-colored stomach contents. This patient went to the hospital and was diagnosed with upper digestive tract bleeding. Chest computed tomography (CT) scan revealed a 2.2 cm × 4.0 cm soft-tissue mass on the posterior wall of the stomach (Figure 1). Together with gastroscopy, both exams were all indicating GIST. After all the above symptoms were restrained, the patient underwent laparoscopic gastrectomy.

Pathologic findings

Grossly, a solid mass was observed, and this tumor had white cut surface measured in 4 cm × 2.5 cm × 2.2 cm size. Pathologically, this tumor had a clear boarder and was locating
After surgical resection, locally recurrence, abdomen spread and/or liver metastasis can often be seen in GISTs. Unresectable or metastasis GISTs are fatal due to their inherent resistance to both chemotherapy and radiation therapy [11]. The median survival duration of patients with metastasis is around 20 months and for those with local recurrence is only 9-12 months [12]. Imatinib mesylate is now the first-line option in the medical treatment of GISTs which targeting KIT and PDGFRA [9, 10].

Our patient went to the hospital due to digestive tract hemorrhage and later was found to have GIST on his stomach wall. The patient underwent laparoscopic gastrectomy and remained health in the 6 follow-up months, no disease recurrence or metastasis was reported.

Based on the pathological analysis, hemorrhage was most likely caused by ulcer on the tumor surface that invaded neighboring blood vessel wall. Notably, digestive tract bleeding was rarely occurring in GISTs. Another characteristic of this case was many T lymphocyte infiltrating in the tumor mesenchyme. Moreover, the tumor in this case was absent of cytoplasmic vacuoles, which are generally present in most stomach GISTs. Whether the specific gene mutations we found influence the tumor pathological and morphological features remained unclear, and needed further research.

Based on literature, mutation rate of KIT gene exon 13 is very rare (1%) and mutations that have been reported are K642E, V654A and T670I [13-15]. GISTs having mutation of K642E were responsive to imatinib therapy. Whereas the V654A and T670I mutations are secondary mutations that caused secondary resistance. All the KIT exon 13 mutations found in the GISTs had poorer prognosis than other KIT exon mutations [16]. In this case, we detected two novel point mutations R634W and N655T, respectively.

Discussion

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and this tumor is characterized by KIT or PDGFRA gene mutations.
most frequent mesenchymal tumors of the gastrointestinal tract and can be identified based on its typical histological and immunohistochemical features. Patients diagnosed with medium and high-risk GISTs carrying responsive mutations will receive tyrosine kinase inhibitors (TKIs) therapy. Therefore finding new KIT gene mutations and understanding drug response of new gene mutations are very necessary. Whether these two new mutations we found are resistant to Gleevec treatment still require further study.

**Disclosure of conflict of interest**

None.
Figure 4. Sanger sequence analysis of KIT exon 13. A. Nucleotide substitution of C to T at position 1920, leading to R to W in amino acid position 634. B. Substitution of A to C in nucleotide sequence of 1964, resulting in amino acid substitution of N to T at position 655. Mutations were arrow indicated.

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References

GIST with two new mutations


