

Case Report

Multiple gastrointestinal stromal tumors with exon 11 mutation of the c-KIT gene in a young male without family history

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Abstract: Multiple gastrointestinal stromal tumors (GISTs) are extremely rare, usually related to specific tumor syndromes such as familial GIST syndrome, neurofibromatosis type 1 (NF1), and the Carney triad. A 27-year-old man came to the hospital for treatment due to watery bloody stool. Abdominal CT disclosed multiple tumors in the gastrointestinal tract. The postoperative pathological examination showed multiple GISTs and diffuse hyperplasia of interstitial cells of Cajal. The c-KIT mutation at exon 11 c.1676T>C (p.V559A) was detected in the paraffin-embedded tumor tissue. He had skin hyperpigmentation from childhood, but had no family history of GIST. This case of multiple GISTs without family history attracted our attention.

Keywords: Multiple GISTs, c-KIT gene, exon 11, family history

Introduction

Gastrointestinal stromal tumor (GIST) is one of the most common primary mesenchymal neoplasms of the digestive system. It is generally believed to originate from undifferentiated stem cells with the interstitial cells of Cajal (ICCs) from the myenteric plexus [1]. Most cases are sporadic, but multiple GISTs are very rare and usually observed only in specific tumor syndromes such as familial GIST syndrome, neurofibromatosis type 1 (NF1), and the Carney triad [2-5]. This case has multiple GISTs in a young male who had hyperpigmented skin lesions accompanied by c-KIT mutation, but he had no family history of GIST. As far as we know, this is the first detailed report of multiple GISTs carried a mutation of c-KIT gene exon 11, had skin hyperpigmentation, but no family history of GIST.

Case report

A 27-year-old male had melanin pigmentation and dark spots on the skin of lips, fingers, toes and groin since childhood, which became darker with the increase of age (Figure 1). He had

no special symptoms other than constipation at ordinary times. The patient began to have bloody stool on August 8, 2019 and three days later he visited our hospital for bloody watery stool with other symptoms of fatigue and transient syncope. Because of the skin hyperpigmentation, the clinical diagnosis was Peutz-Jeghers (P-J) syndrome, but there was no obvious abnormality by enteroscopy. Abdominal enhanced CT showed multiple masses in the small intestine. During the laparoscopy exploration, hard masses occurred multiply on the serosa surface of the greater curvature of the gastric antrum and mesangial area or serous surface of small intestine 15 cm, 35 cm, and 150 cm from the Treitz ligament and 50 cm from the ileocecal junction respectively. Sizes of tumors ranged from 0.5 to 2.5 cm. The gastric wall tumor, small intestine tumor, and partial resection of small intestine were resected completely and then sent for a pathological examination.

Gross examination: (1) Labeled mass of 15 cm from Treitz ligament: a portion of mucosa was 2.0×1.5×1.0 cm, and a gray-white tough nodule was in the submucosa measuring 1.2×1.1×0.8

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Figure 1. The patient had multiple skin pigmentations, especially on the fingers (A), toes (B), lips, and groin.

cm. (2) Labeled mass of 30 cm from Treitz ligament: a mass of tissue was 0.5×0.3×0.3 cm. (3) Labeled mass of 150 cm from Treitz ligament (**Figure 2A**): a polypoid mass with the size of 2.5×2.0×2.0 cm was found on one segment of the intestine, 7.0 cm long and 2.5 cm in diameter, which seemed to involve the whole intestinal wall. Another small gray nodule with diameter about 0.5 cm was seen on the serosal surface of the intestinal wall. (4) Mass of 50 cm from ileocecal junction: a piece of small gray white tissue was 1.0×1.0×0.8 cm. (5) Labeled gastric wall tumor: a piece of small gray white tissue was 0.5×0.4×0.3 cm. Microscopically, spindle cell tumor boundaries were not clear, and the tumors spread horizontally between longitudinal and circular muscles in the adjacent intestinal wall and invaded a nerve tract (**Figure 2B-D**). Number of mitoses was less than 5/50HPF. Immunohistochemical (IHC) results showed that tumor cells expressed diffuse positivity for CD117, DOG-1 (**Figure 2C, 2D**), vimentin, and were focally positive for CD34 and were negative for CK, SMA, and S-100. The index of Ki67 was less than 5%. A

diagnosis of multiple GISTs and diffuse hyperplasia of interstitial cells of Cajal (ICC) was based on the findings described above. Genomic DNA from the tumor tissue was extracted from the paraffin-embedded tumor tissue, and exons 9, 11, 13, and 17 of KIT gene and exons 12, and 18 of the PDGFRA gene were examined (**Table 1**). The results confirmed the mutation (c.1676t>c, p.v559a) in exon 11 of the KIT gene (**Figure 3**), and no mutation was detected in the corresponding exon of PDGFRA gene.

Discussion

GISTs are rare neoplasms, originating from the interstitial cells of Cajal in the gut, which typically occur in the tubular gastrointestinal tract, most commonly the stomach and small intestine, and are less frequent in the colorectum and esophagus. Most of the GISTs are sporadic solitary tumors occurring in elderly patients at a median age of 60 to 65 years. Histologically, these tumor cells have spindled and/or epithelioid patterns, and can be distinguished from

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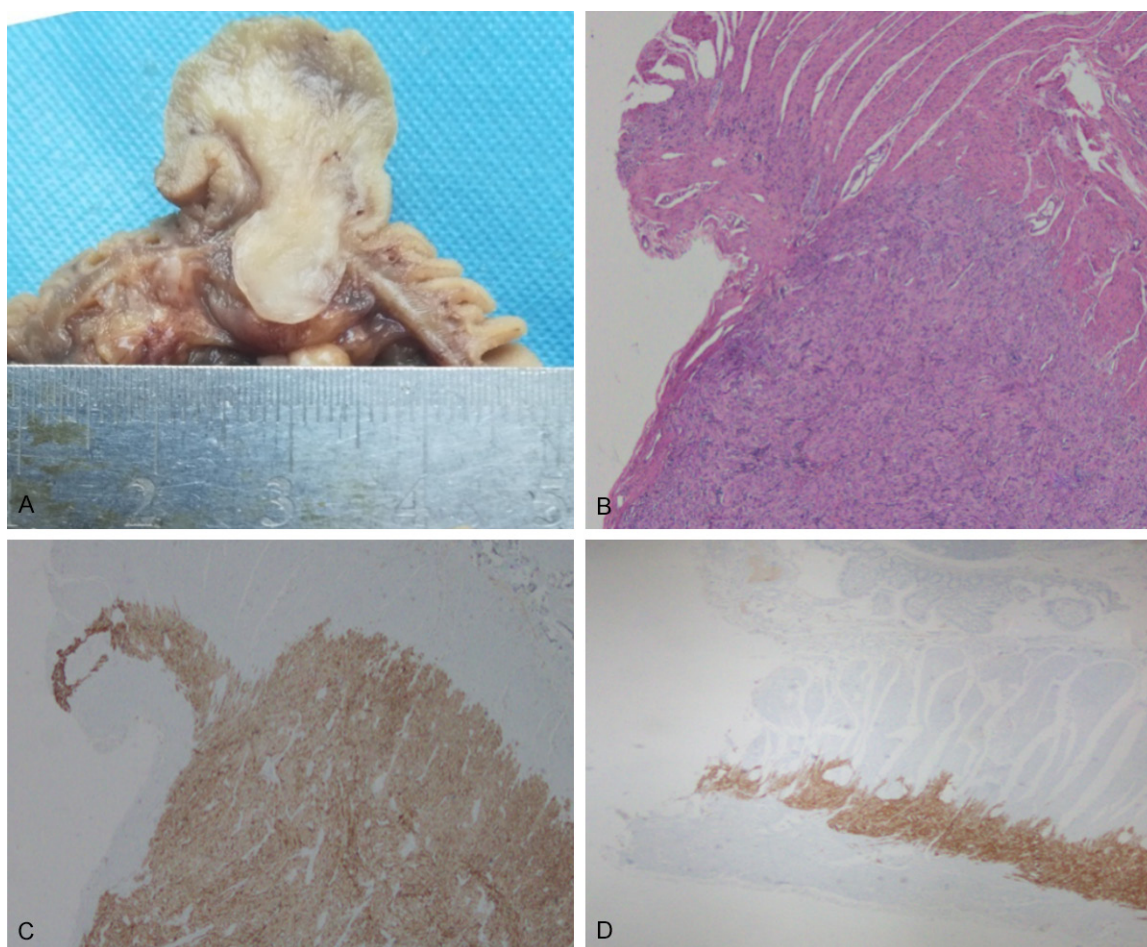


Figure 2. A. A polypoid mass with 2.5×2.0×2.0 cm in size was found on the intestine 150 cm from Treitz ligament, which seemed to involve the whole intestinal wall. B. Spindle cell GIST (H&E, 40×). C. CD117 (+) displayed a GIST tumor and diffuse hyperplasia of ICCs with direct continuity with the GIST masses in the adjacent intestinal wall (IHC, 40×). D. DOG-1 (+) showed Cajal cell proliferation in the whole length of the gastrointestinal examination samples, as well as at the cutting edge of the samples (IHC, 40×).

Table 1. c-KIT/PDGFRα gene mutation detection

| Test | Exon | type of mutation | result of detection |
|-------------|---------|----------------------------|---------------------|
| c-KIT gene | Exon 9 | Repetition, point mutation | Wild-type |
| | Exon 11 | Deletion, point mutation | Mutant |
| | Exon 13 | point mutation | Wild-type |
| | Exon 17 | point mutation | Wild-type |
| PDGFRα gene | Exon 12 | point mutation | Wild-type |
| | Exon 18 | point mutation | Wild-type |

other mesenchymal neoplasms by specific expression of CD117 or DOG-1. Different patients may show different pathogenesis, clinical manifestations, clinical behaviors and prognosis, depending on the particular underlying mechanism. GISTs exhibit a variable biologic pheno-

type ranging from benign to highly malignant. At present, the clear pathogenesis of GISTs is mainly related to c-KIT and PDGFRα gene mutations, while so-called wild-type GISTs appear to be characterized by other oncogenetic drivers, including mutations in NF1, BRAF, RAS, and SDH [5-9]. The most common mutations of c-KIT gene have been found in exon 11 (juxtamembrane domain), followed by exons 9, 13, and 17. The mutation modes includes point mutation, deletion, repetition, and insertion.

CD34 and CD117 are usually both highly expressed in ICC hyperplasia, but small intestinal multiple GISTs with somatic or germline

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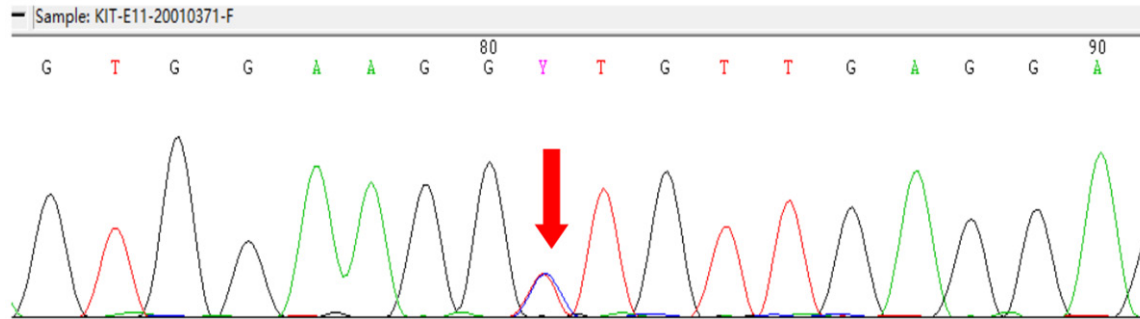


Figure 3. The KIT mutation at exon 11 c.1676T>C (p.V559A) was detected, indicated by the red arrow.

exon 11 mutation of the KIT gene show loss of CD34 expression [10, 11]. The results of IHC in this case are compatible with these previous reports. Most patients with multiple GISTs have a family history, and multiplicity is very rare in sporadic GISTs.

Multiple GISTs have been reported in patients with germline c-KIT or PDGFRA mutations, and in those with NF-1. It has been shown that the pathogenesis of multiple GISTs with pigmentation is mainly related to c-KIT and NF-1 gene mutations. (1) Melanocytic hyperpigmentations in the GIST patients with exon 11 KIT mutations are commonly reported, and either present as hyperpigmentations with a diffuse or patchy pattern or multiple lentigines [12]. (2) The main clinical manifestations of NF-1-associated GISTs are: neurofibroma (disease), cafe au lait spots, pigmentation in groin or armpit, diffuse ICC hyperplasia, and/or gastrointestinal motility disorder [5]. The patient had skin hyperpigmentation from childhood with exon 11 KIT mutation, and the clinical presentation was compatible with multiple GISTs in previous reports. Combined with the research results of a few reported cases [10, 13, 14], it is speculated that the characteristics of multiple GISTs with c-KIT gene germline mutation in exon 11 are as follows: (1) It may be accompanied by skin pigmentation, some of which may be nevus-like; (2) The proliferation of Cajal cells was diffuse in the muscular wall of gastrointestinal tract. ICC cells proliferated into serosal and mucosal surfaces to form multiple tumors, and migrated directly with the tumors; (3) It originated from hyperplasia of interstitial Cajal cells with KIT mutation; (4) The results of immunohistochemistry showed that DOG1 and CD117 were 100% diffuse +, CD34 (±); (5) The

histopathology was a spindled cytomorphology. Various characteristics of this case are compatible with multiple GISTs with c-KIT gene germline mutation in exon 11, but without a family history.

Surgical treatment of these patients is not very effective. Conservative treatment is the key to improve the quality of life and clinical prognosis after diagnosis. The patient in this case had been treated with imatinib mesylate (Gleevec) and the short-term treatment effect was obvious, with improvement of gastrointestinal dysfunction symptoms and reduced pigmentation of skin.

Multiple GISTs with c-KIT gene exon 11 germline mutation without a family history is rare. The clinical manifestations, clinical behavior, and prognosis are not clear. Therefore, systematic reporting and literature review were done for this case, to provide a reference for clinical treatment.

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The case report and any accompanying report pictures were with signed informed consent from the patient's family members.

Disclosure of conflict of interest

None.

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