Sporadic somatic mutation of c-kit gene in a family with gastrointestinal stromal tumors without cutaneous hyperpigmentation

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CASE REPORT

Patient 1
A 79-year-old man was referred to our hospital because of a gastric tumor (Figure 1). He complained of epigastria pain and fullness. There was no cutaneous hyperpigmentation. Histological examination showed that these tumors were GISTs expressing CD34 and CD117. Tumor DNA extracted from paraffin-embedded specimens revealed somatic mutation with a deletion mutation at different codons in exon 11 of c-kit gene after direct sequencing analysis. No germline mutation was detected in DNA extracted from peripheral leukocytes obtained from the father and son. We propose that GISTs could be caused by sporadic somatic mutation in a family without germline mutation and hyperpigmentation.

INTRODUCTION
Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the human gastrointestinal (GI) tract, representing 0.1 to 3% of all GI tract tumors. It has been suggested that a mutation in the juxtamembrane (JM) domain of c-kit contributes to the development of GIST. Furthermore, germline deletion or point mutation of the c-kit JM domain has been shown in a family with GIST and cutaneous hyperpigmentation. GIST-cutaneous hyperpigmentation disease has been used to describe familial multiple GISTs with associated cutaneous hyperpigmentation. Familial GIST is a rare autosomal dominant genetic disorder associated with kit germline mutations. We now report that GISTs could be caused by sporadic somatic mutation in a family without germline mutation and cutaneous hyperpigmentation.

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Key words: Sporadic GIST; Somatic c-kit mutation

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was performed. Histological and immunohistochemical examination revealed advanced high-risk GIST with strong positivity of c-kit and CD34 (Figure 2D). The patient received 400 mg Glivec for 7 months and partial response was illustrated by subsequent abdominal CT. The patient lived with disease for 7 months after surgery.

**Genetic examination**

To determine whether these GISTs showed a genetic defect, DNA was extracted from paraffin-embedded specimen of tumor tissues. Polymerase chain reaction amplification of genomic DNA for kit and PDGFRA was performed and amplification was analyzed for mutations as previously described. Direct sequencing analysis of DNA from patient 1 showed deletion mutation at codon 560 in exon 11, causing a deletion mutant 560 del V (Figure 3B). While direct sequencing analysis of DNA from patient 2 revealed deletion at codons 557-559 in exon 11, resulting in replacement of WKV by C. To determine if the mutation is familial, DNA was extracted from peripheral leukocytes obtained from patients 1 and 2. No mutation was detected in exon 11 of c-kit gene (Figure 3A).

**DISCUSSION**

By histological, immunohistochemical examination, and molecular genetic analysis, this study has uncovered sporadic c-kit somatic mutation in a family with GIST without cutaneous hyperpigmentation. GISTs appear to be related the interstitial cells of Cajal of the mesenteric plexus. These cells are considered as GI pacemaker cells, from the interface between the automatic innervation of the bowel wall and its smooth muscle.

GISTs express the cell-surface transmembrane receptor c-kit with a tyrosin kinase activity and kit oncprotein. There are frequent gain-of-function mutations of c-kit in GISTs. These mutations result in constitutive activation of kit signaling, which leads to uncontrolled cell proliferation and resistance to apoptosis. It has been recently reported that kit activation occurs in all cases of GISTs, regardless of the mutation status of kit. Most GISTs express constitutively activated mutant isoforms of kit kinase or platelet-derived growth factor receptor alpha (PDGFRA), which are potential therapeutic targets for Imatinib mesylate (Glivec).

Figure 1 Pedigree of the family with GISTs without cutaneous hyperpigmentation. Hatched symbols indicate family members with GISTs. Double circles denote multiple GISTs. Squares indicate males and circles indicate females.

Figure 2 A: Abdominal CT revealed gastric GIST at the anterior wall and greater curvature side of high body of the stomach; B: Microscopic findings of the tumor resected. Tumor cells were composed of resacular spindle cells with mild nuclear pleomorphism but no necrosis, expressing strong positive c-kit staining immunohistochemically. (IHC staining, 200X); C: Abdominal CT revealed a gastric GIST measuring 13 cm x 10 cm in size occupying the whole stomach. D: Microscopic findings of the tumor resected. Tumor comprised proliferation of spindle cells with mild nuclear atypia in the myxoid stroma but no necrosis, expressing positive c-kit staining. (IHC staining, 200X).

Figure 3 A. Direct sequencing analysis of DNA from peripheral leukocyte obtained from patients 1 and 2 revealed no mutation in exon 11 of c-kit gene; B. Direct sequencing analysis of DNA from patient 1 showed deletion mutation at codon 560 in exon 11, causing a deletion mutant 560 del V; C. Direct sequencing analysis of DNA from patient 2 revealed deletion at codons 557-559 in exon 11, resulting in replacement of WKV by C.
Gain of function mutations in the JM domain of c-kit contribute to the development of GIST\[2\]. Because normal kit gene is responsible to normal pigmentation, relationships between GISTs and cutaneous hyperpigmentation have been reported before. GIST-cutaneous hyperpigmentation disease has been used to describe familial multiple GISTs associated with cutaneous hyperpigmentation\[3\]. Furthermore, germline deletion mutation of the c-kit JM domain has been shown in tumors and normal somatic cells from a family with multiple GISTs who exhibited perineal hyperpigmentation\[4\]. A single-point germline mutation of c-kit has also been proposed to cause a familial GIST associated with systemic cutaneous hyperpigmentation\[3\]. A germline PDGRF missense mutation could be a second familial predisposing gene\[3\].

We described a rare case report regarding two members in a family with GISTs without cutaneous hyperpigmentation. No mutation was detected in DNA extracted from peripheral leukocytes obtained from the father and son. DNA extracted from paraffin-embedded specimens revealed different somatic mutation with a deletion mutation in the exon 11 of c-kit gene after direct sequencing analysis (deletion mutation at codon 560 versus deletion at codons 557-559 in exon 11). So mutation in the tumor is sporadic somatic but not germline. However, the cause of sporadic c-kit mutation in one family is unknown.

In summary, we propose that GISTs could be caused by sporadic somatic mutation in a family without germline mutation and hyperpigmentation.

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