Gastrointestinal Stromal Tumor with a Novel Mutation of KIT Proto-oncogene

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Abstract

The majority of human gastrointestinal mesenchymal tumors are gastrointestinal stromal tumors (GISTs). Recent reports have shown the existence of gain-of-function mutations in the juxta-membrane domain of receptor tyrosine kinase (KIT) in GISTs. We present a 77-year-old woman with GIST diagnosed by positive immunostaining of cluster designation (CD) 34 and KIT. This case had a novel mutation at codon 576 located in the juxta-membrane domain of KIT. Our results indicate the importance of mutations in this KIT region and suggest the possibility of the existence of other types of mutations in this region in GISTs.

Case Report

A 77-year-old Japanese woman came to us suffering from a gastric tumor. A 6.0×4.5 cm submucosal tumor was detected at the upper body greater curvature of the stomach. Under the diagnosis of a gastric sarcoma, the tumor was surgically resected.

Morphologically, the tumor was located in the submucosa and protruded from the serosa membrane. The section was myxoid and contained a cystic region with a small amount of blood. Histologically, the tumor was comprised of spindle-shaped cells with plump nuclei. Cell density was high and the mitotic index was less than 5 in consecutive 50 high-power fields. The degree of dysplasia was mild to moderate. Immunohistochemically, the tumor was negative for desmin, muscle specific actin, smooth muscle actin, S100, and vimentin staining. However, it was strongly positive for KIT (Fig. 1A) and CD34 staining (Fig. 1B). The genomic sequence of the juxta-membrane region and carboxyl terminus of the KIT proto-oncogene was determined using DNA extracted from the tumor portion of the paraffin-embedded section and peripheral WBC. These regions were amplified by a nested polymerase chain reaction and subcloned followed by sequencing using a dideoxy chain termination method. No mutation was seen in any codon between 550 to 560. However, a point mutation (C to T) at codon 576 which converts prolin to leucin was detected in 4 of the 8 clones investigated (Fig. 2). No mutation was seen in the DNA from WBC.

Discussion

In human GISTs, all the gain-of-function mutations were first thought to be confined within the 11 amino acids (codon 550 to codon 560) (4), and later a deletion mutation at codon 578 was reported as a novel gain-of-function mutation (9). Although a mutation in the KIT tyrosine kinase domain has been shown to be another gain-of-function mutation, it has only been seen in the mast cell neoplasm (10–12). These findings indicate that mutations in the KIT juxta-membrane domain has a...
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Figure 1. Immunostaining for CD34 and KIT. The tumor was positive for both cluster designation (CD) 34 (A) and receptor tyrosine kinase (KIT). (B) Immunoperoxy method (×200).

Figure 2. Sequence of genomic DNA of the KIT proto-oncogene. A point mutation from C to T was detected at codon 576 in the tumor (GIST). No mutation was seen in DNA from WBC. P: prolin, L: leucin, KIT: receptor tyrosine kinase.

WBC

GIST
codon 576

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The case presented in this report was diagnosed as a GIST from the positive staining of CD34 and KIT. However, no mutation was detected within the 11 amino acids or at codon 578, which have been reported previously (4, 9). Interestingly, we found a novel mutation at codon 576 in the KIT proto-oncogene. This novel mutation was also located in the juxta-membrane domain like other mutations. Whether or not this is a gain-of-function mutation is not clear. However, half of the genomic DNA clones from the tumor and all the DNA from the WBC had no mutation in this region. Together with the fact that all mutations in human GISTs have been confined within this region, our findings suggest the possibility that this point mutation is also a KIT gain-of-function mutation. Recently, a germline mutation of the KIT proto-oncogene has been shown in some of the members of familial GISTs by detection of KIT mutation in DNA from WBC (13). However, the present case had no such family history of gastrointestinal tumors nor the
mutation in genomic DNA from WBC.

Although further investigation is necessary to reconcile whether this novel mutation is a gain-of-function mutation or not, our results indicate the importance of mutations in this KIT region and suggest the possibility of the existence of other types of mutations in this region in GISTs.

References