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[Case Report] Familial gastrointestinal stromal tumor with Fingers with zebra-like pigmentation

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Funding: This clinical research was performed with research funding from the following: Japan Society for Promoting Science for TH (Grant No. 19K09840), START-program Japan Science and Technology Agency for TH (Grant No. STSC20001), and the National Hospital Organization Multicenter clinical study for TH (Grant No. 2019-Cancer in general-02), and The Japan Agency for Medical Research and Development (AMED) (Grant No. 22ym0126802j0001), Tokyo, Japan.

Potential competing interests: No potential competing interests to declare.

Abstract

Clinical studies to date have revealed that gastrointestinal stromal tumors (GISTs) are predominantly sporadic. The occurrence of GIST associated with familial syndromes is very rare, with most cases showing wild-type KIT and platelet-derived growth factor alpha (PDGFRA). To date, only 30 kindreds worldwide have been reported with a GIST associated with the germline KIT pathogenic variants. The efficacy of imatinib, a multityrosine kinase inhibitor, in GIST patients with germline KIT variants has been largely unreported. Therefore, the results of clinical trials regarding the efficacy of treatment with tyrosine kinase inhibitors in GIST patients with the germline KIT variants are unclear. As a result, imatinib treatment in GIST patients with the germline KIT variants is not yet recommended. This paper describes a 32-year-old male patient with a germline W557R pathogenic variant with advanced GIST throughout the upper stomach and cutaneous hyperpigmentation. The treatment with imatinib showed long-term regression of the GIST.

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Keywords: KIT, GIST, Cancer genetic test.

Gastrointestinal stromal tumors (GISTs) are intestinal mesenchymal tumors that arise from pacemaker cells called Cajal cells, which play a role in gastric motility.[1] KIT proto-oncogene (*KIT*), also known as cluster of differentiation (CD)117, is important for the development of Cajal interstitial cells, mast cells, and melanocytes.[2] Familial GIST is a rare autosomal dominant disorder, with only a few affected families worldwide; it is mostly caused by germinal *KIT* pathogenic variants in approximately 75%–80% of cases.[3] The KIT ligand (KITLG)/c-kit and KRAS proto-oncogene (KRAS)/mitogen-activated protein kinase (MAPK) pathways have been identified as important pathways in controlling pigmentation.[4] Here, we report a case of familial GIST with a novel germline pathogenic variant within exon 11 of *KIT* gene, which was detected using cancer genome testing. Additionally, we report a young adult male patient who presented with gastric subepithelial lesions accompanied by skin hyperpigmentation and was subsequently diagnosed with multinodular GIST with a pathogenic variant in exon 11 of *KIT* gene. The imatinib administration, a tyrosine kinase inhibitor has been identified as a useful targeted therapy for *KIT* pathogenic variants. The patient is currently being treated with imatinib.

A 32-year-old male patient underwentpyloric-side gastrectomy for a gastric tumor. Additionally, reconstruction was performed by suturing the remnant stomach on the cardiac side and the duodenum (Billroth I method). Pathological analysis of the resected tissue revealed spindle-shaped atypical cells that were intricately arranged in an east-like manner (Figure 1A). Mitotic counts were <5 per 50 high-power fields (Figure 1A). Recent clinical research has revealed that stained tissue sections of GISTs show positive results for *KIT* (CD117, 95%) and deleted-in-oral-cancer-1 (DOG1) (almost exclusively associated with GIST).[3] Immunohistochemical staining results of the resected tissue sections were negative for desumin, α-smooth muscle actin (α-SMA), and CD34 and positive for c-kit (CD117) and DOG1 (Figure 1A). He was diagnosed with stage IIa undifferentiated adenocarcinoma. In the following year, he presented with chief complaints of abdominal pain and anorexia. Contrast-enhanced computed tomography (CT) revealed a submucosal tumor in the upper stomach, a tumor in the liver, and multiple tumors in the abdominal cavity (Figure 1B).

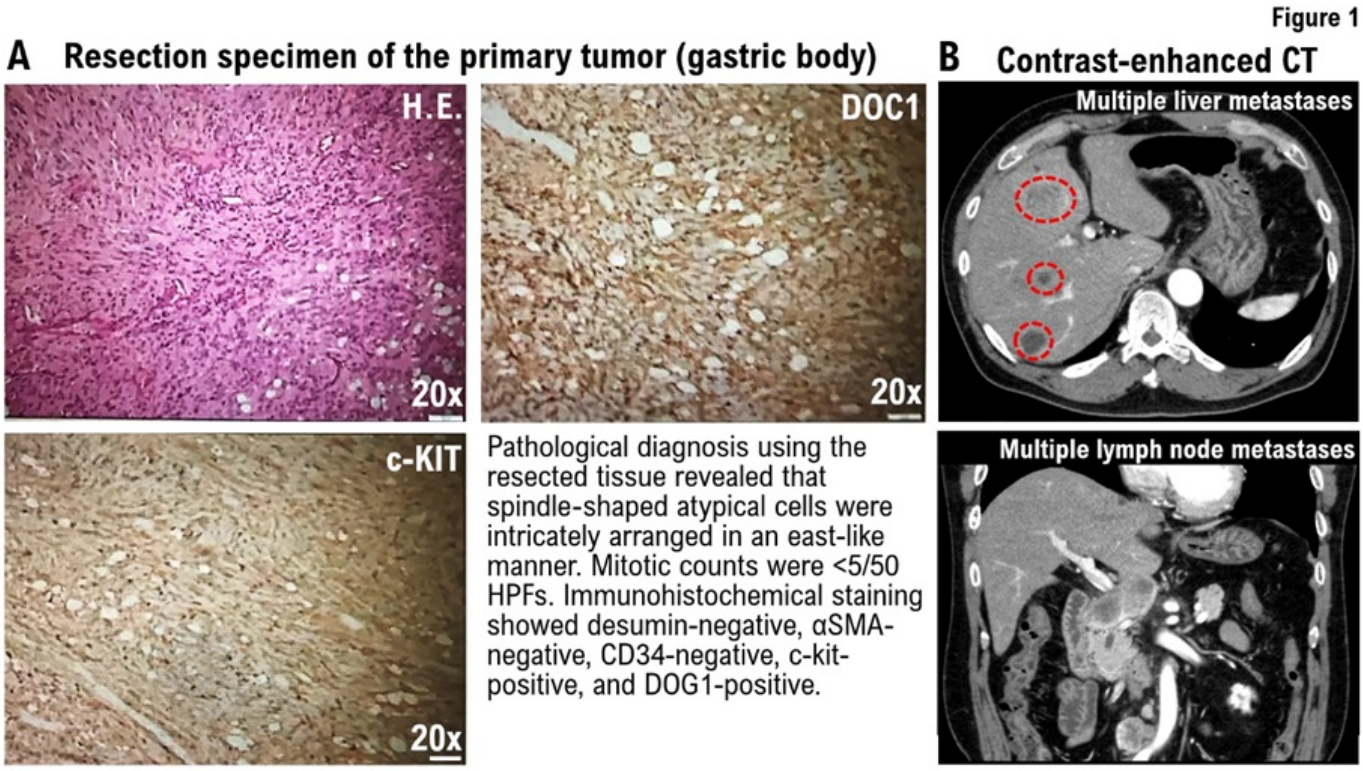

Figure 1. The results obtained by pathological examination and contrast-enhanced computed tomography (CT) examination.

A. The results obtained by pathological examination. Magnification 20x. Scale bar = 100 μm

B. The results obtained by contrast-enhanced CT revealed a submucosal tumor in the upper stomach, a tumor in the liver, and multiple tumors in the abdominal cavity. Liver metastases of GIST are indicated by red dotted lines.

A recent report revealed that a *de novo* genetic variant in *KIT* gene caused atypical lentiginosis and hyperpigmentation in pediatric patients or young adults.[4] Zebra-like dark pigmentation was observed throughout the patient's body (Figure 2).

Figure 2

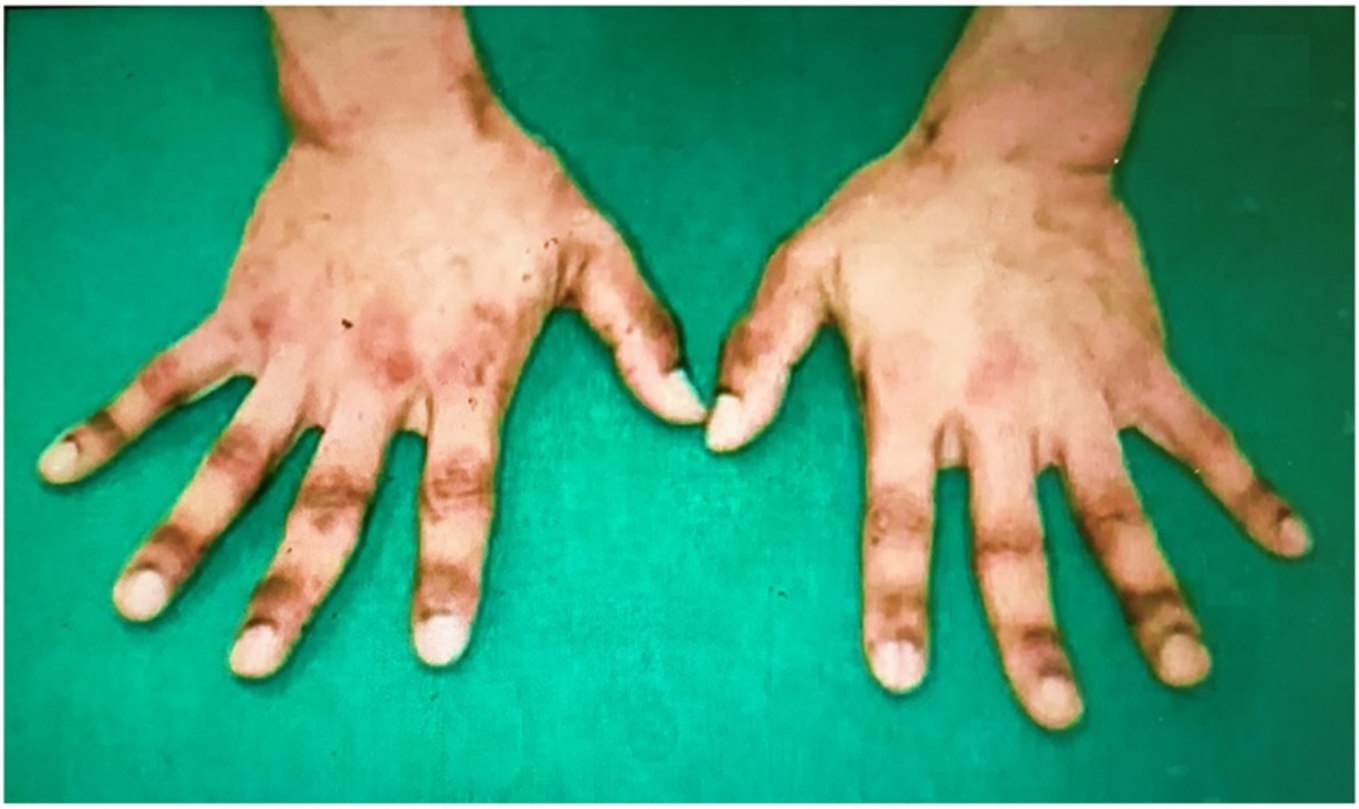

Figure 2. Back before treatment with imatinib mesylate. The backs of both hands with zebra-like pigmentation.

A cancer genetic test (FoundationOne® CDx tissue, Foundation Medicine, Inc., Cambridge, MA, USA) was performed on samples of the upper-stomach tumor resected using a gastroscope. It revealed a pathogenic variant (W557R) located within exon 11 of *KIT* gene (allele-fraction = 0.5798), and the results were verified using the ClinVar# human genome database (Supplementary Figure 1). The *KIT* pathogenic variant (W557R) detected using FoundationOne® CDx testing may have a germinal mutation based on the allele-fraction value obtained from the cancer genetic testing. The patient was diagnosed with familial multinodular GIST based on his clinical findings and familial history of malignant tumors (Supplementary Figure 2). Activated form of KIT caused by a pathogenic variant promotes the synthesis of melanin pigment, and pigmentation is observed (Supplementary Figure 3).

The tumor cell models were later developed for the rapid screening of candidate agents and the investigation of potential malignant tumor mechanisms. Signal transducer and activator of transcription tyrosine kinase domain c-kit, a receptor tyrosine kinase (CD117), is involved in intracellular signaling, and a mutated form of c-kit plays an important role in the development of some malignant tumors. c-kit signaling independently activates three signal pathways, namely phosphatidylinositol-3 kinase (PI3K)/AKT (protein kinase B), KRAS/MAPK/extracellular signal-regulated kinase (ERK), and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways (Supplementary Figure 4).[5] The PI3K pathway activates anti-apoptosis genes, resulting in cell survival. The MAPK/ERK pathway controls the activation of genes involved in cell proliferation. The JAK/STAT pathway is associated with cell proliferation. Therefore, the

KIT pathogenic variants significantly activate the PI3K/AKT, MAPK/ERK, and JAK/STAT pathways, which could be inhibited by imatinib, a tyrosine kinase inhibitor.[5] Thus, imatinib administration has been identified as a useful targeted therapy for *KIT* pathogenic variants. The patient is currently being treated with imatinib, a tyrosine kinase inhibitor. A clear pathological reaction has been seen after surgical treatment.

In clinical practice, pathogenic variants detected by cancer genome testing can be used to diagnose malignant tumors and select new therapeutic agents for many patients with advanced malignancies. To the best of our knowledge, this is the first report of the *KIT* W557R pathogenic variant in familial GISTs, adding to our understanding of the disease's pathogenesis and providing valuable information for precision treatment.

Acknowledgements

We thank all medical staff for clinical research at Kyoto University Hospital and the National Hospital Organization Kyoto Medical Center.

Funding

This clinical research was performed with research funding from the following: Japan Society for Promoting Science for TH (Grant No. 19K09840), START-program Japan Science and Technology Agency for TH (Grant No. STSC20001), and the National Hospital Organization Multicenter clinical study for TH (Grant No. 2019-Cancer in general-02), and The Japan Agency for Medical Research and Development (AMED) (Grant No. 22ym0126802j0001), Tokyo, Japan.

Competing Interest statement

The authors state No competing interest.

Ethics approval and consent to participate

This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 08, 2019, and Kyoto University School of Medicine (Kyoto, Japan) on August 17, 2019, with approval codes NHO H31-02 and M192. The completion numbers for the authors are AP0000151756, AP0000151757, AP0000151769, and AP000351128. As this research was considered clinical research, consent to participate was required. After briefing regarding the clinical study and approval of the research contents, the participants signed an informed consent form.

Clinical Research: A multi-center retrospective observational clinical study of subjects who underwent cancer genomic medicine at a cancer medical facility in Kyoto, Japan.

This study was reviewed and approved by the Central Ethics Review Board of the National Hospital Organization Headquarters in Japan (Tokyo, Japan) on November 18, 2020, and Kyoto University School of Medicine (Kyoto, Japan) on August 24, 2022, with approval codes NHO R4-04 and M237.

All participants agreed to take part in the present study. We have obtained Informed Consent Statements from people participating in clinical studies.

Author contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Conceptualization, T.H. and I.K.; Writing-Original Draft, T.H. and I.K.; Writing-Review & Editing, I.K.; Visualization, T.H. and I.K.; Supervision, T.H. and I.K.; Funding Acquisition, T.H. and I.K.

Footnotes

[#] ClinVar[#]; The National Center for Biotechnology Information (NCBI) advances science and health by providing access to biomedical and genomic information. ClinVar is a database provided by NCBI as a freely available archive that collects information about human genomic diversity and associated diseases.

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