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Letter

Gastrointestinal stromal tumors with an uncommon primary mutation responded well to imatinib

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, driven by mutations in the proto-oncogene *c-KIT* or platelet-derived growth factor alpha (*PDGFRA*) gene in 85%–90% of cases.[3] Other mutations are rare and have unknown clinical effects. Imatinib, a tyrosine kinase inhibitor (TKI), is used as a first-line treatment and confers a median survival of up to 5 years in 70%–85% of patients with advanced GISTs.[3] This response correlates with the tumor's mutational status. Exon 11 mutations are correlated with a good response, whereas mutations in exons 9, 13, and 17 may result in variable responses to imatinib. Insufficient data regarding the response to imatinib in patients with mutations in the activation-loop domain encoded by exon 17 is available. This mutation is observed in 0.5% of all GISTs.[11] Herein, we discuss the case of a patient with a GIST with a rare proto-oncogene *c-KIT* missense mutation in exon 17 *(*c.2466T > A; Asn822Lys*)*. The patient was treated for 3 months with imatinib, which yielded a partial response (PR).

A man in his 70s presented with melena that had persisted for 3 days. He had a history of treatment with androgen deprivation and enzalutamide for metastatic prostate cancer. He had hypertension and chronic obstructive pulmonary disease, which limited his ability to perform activities of daily living. The patient was an ex-smoker with a family history of lung and ovarian cancers.

Computed tomography (CT) revealed a 46 × 30 mm gastric lesion in the mid-stomach [Figure 1A and B]. Esophagogastroduodenoscopy (OGD) revealed a large polypoid growth in the body of the stomach, extending into the lumen. The working diagnosis was a GIST or leiomyoma. Histology confirmed a morphology consistent with a GIST, with spindle cells and scattered mitotic figures. Immunohistochemistry (IHC) revealed neoplastic cells strongly positive for the *c-KIT* or cluster of differentiation (*CD)117* (transmembrane glycoprotein receptor tyrosine kinase) and "discovered on GIST 1" (DOG-1) [Figure 2]. Further genomic analysis revealed a missense mutation in exon 17 of proto-oncogene *c-KIT*, identified via sequencing as an Asn822Lys mutation. This mutation is mentioned in only a small number of case studies.[11–13] It occurs as a primary mutation or, more commonly, as a secondary mutation acquired through exposure to imatinib, resulting in secondary resistance. No other mutations in this patient were identified in exons 9, 11, or 13 of proto-oncogene *c-KIT,* exons 12 or 18 of *PDGFRA,* or exons 15 of the *BRAF* gene.[1]

The patient was not a suitable candidate for surgical resection because of comorbidities. Therefore, he was administered imatinib (400 mg daily, per oral [PO]) as first-line treatment. The patient tolerated the first 30-day treatment cycle reasonably well. The dose was escalated to 800 mg/day, which was not well tolerated, causing nausea, vomiting, and fatigue. The patient decided to permanently discontinue imatinib because of worsening side effects after the completion of three cycles. Serial CT scans over the next 2 years revealed an unchanged size of the GIST, displaying a ≥15% decrease in tumor attenuation and fulfilling the Choi response criterion for a PR [Figure 1C–F].

Imatinib was permanently discontinued because of adverse side effects. The patient felt better after stopping the treatment and did not want to restart it. CT after 3 months revealed stable disease. The patient remained healthy with no symptoms during 2 years of follow-up.

A GIST is a rare, non-epithelial cancer, comprising 1%–2% of primary gastrointestinal malignancies.[1] It originates from the interstitial cells of Cajal. GIST cells are derived from myeloid stem cells, are positive for the CD34 antigen in 52%–72% of cases, and often express proto-oncogene *c-KIT* (85%–94%).[1] GISTs commonly arise in the stomach, primarily in older patients, with an equal incidence in men and women.[1] It is often incidentally diagnosed. Patients may present with nonspecific chronic symptoms, including pain, bleeding, bowel perforation, and obstruction. Surgical resection remains the treatment of choice for high-risk GISTs, but recurrence is common; therefore, adjuvant TKI therapy is recommended. As low-risk GISTs have a lower risk of recurrence, adjuvant TKI is not usually recommended after their resection.[2] TKIs remain the mainstay of treatment for patients deemed ineligible for surgery.[3] TKIs are also used as neoadjuvant therapy.[3]

Microscopically, GISTs exhibit a spindle cell-type, epithelioid, or mixed morphology.[3] More than 95% of these tumors overexpress proto-oncogene *c-KIT*, owing to mutations in approximately 80% of cases.[3] These mutations cause abnormal activation of the KIT protein, resulting in

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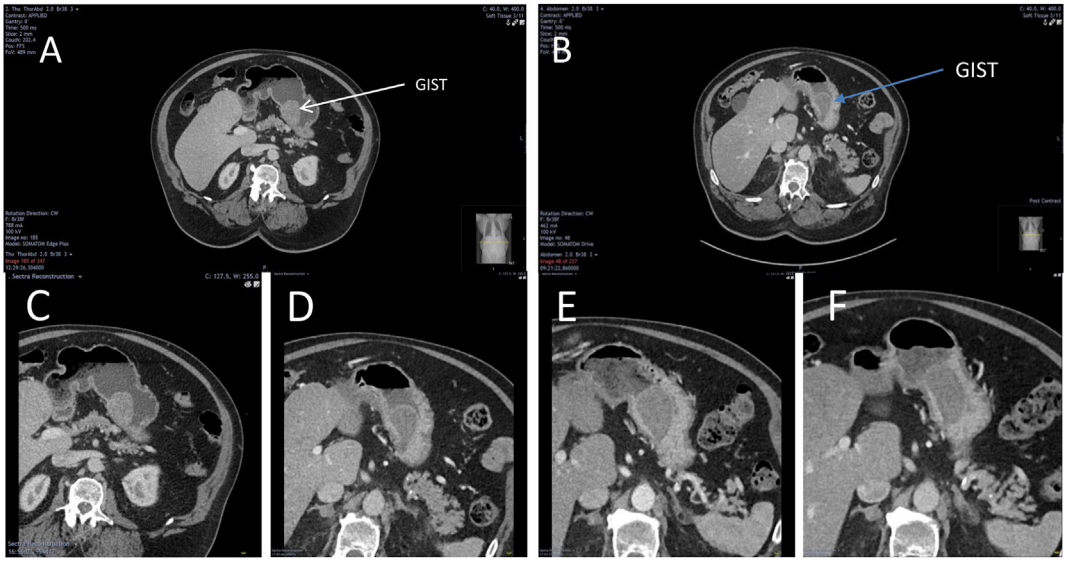

Figure 1. Computed tomography for GIST. An exophytic mass visible within the stomach from the lesser curvature measuring 46 × 30 mm appears relatively well-defined and has no convincing abnormality in the adjacent fat (A and B). The lesion demonstrated a ≥15% decrease in tumor attenuation fulfilling the Choi response criterion for PR in each scan taken 6 months apart (C, D, E, and F). GIST: Gastrointestinal stromal tumor; PR: Partial response.

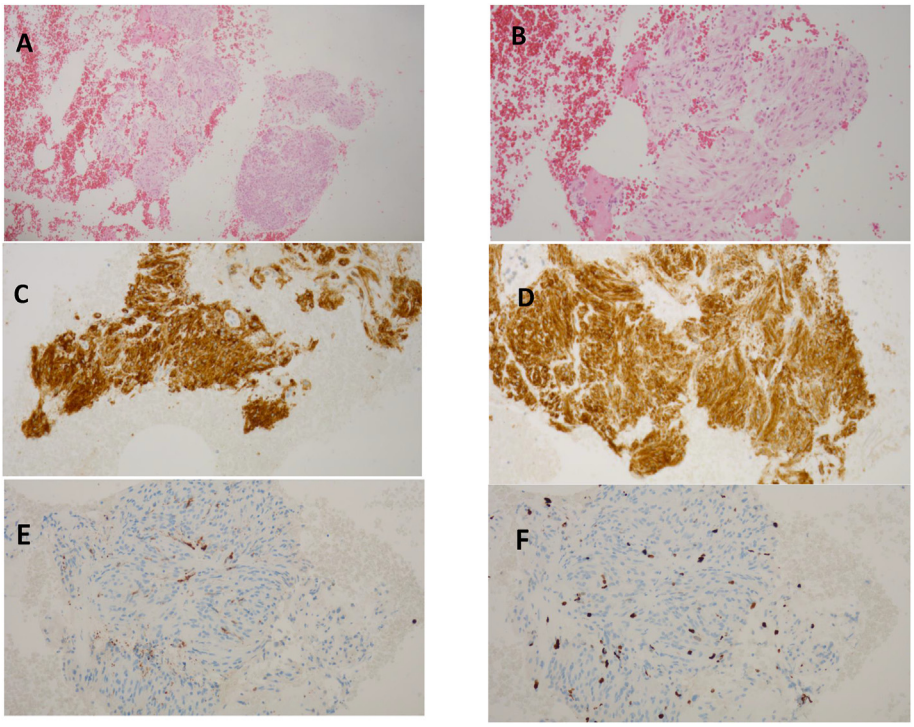

Figure 2. Histopathological patterns of GIST. Spindle cells with lightly eosinophilic, wispy cytoplasm and scattered mitotic figures at medium power (400 × magnification) (A) and high power (1000 × magnification) (B), hematoxylin and eosin staining. IHC revealed cells were positive for c-KIT/CD117 (C) and IHC revealed cells positive for DOG1 (D). Protein S100 expression was negative (E) and MIB-1 was <5% of cells (F). CD117: Cluster of differentiation 117; DOG1: Discovered on gastrointestinal stromal tumor; GIST: Gastrointestinal stromal tumor; IHC: Immunohistochemistry; MIB-1: Molecular immunology Borstel.

ligand-independent oncogenic signaling cascades in the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) serine/threonine kinase 1/mammalian target of rapamycin (mTOR), rapidly accelerated fibrosarcoma (RAS-RAF)/mitogen-activated protein kinase (MAPK), and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways. The activated KIT receptor stimulates the intracellular pathways involved in cell proliferation, adhesion, apoptosis, cell survival, and differentiation, resulting in growth and disease progression.[3] Other molecular alterations include those in *PDGFRA*.[4] GISTs without proto-oncogene *c-KIT* or *PDGFRA* mutations (the wild type) form a heterogeneous group that may have mutations in the succinate dehydrogenase (*SDH*) *complex*, *BRAF*, *RAS*, or neurofibromatosis type I (*NF1*) genes.[5]

Exons 9 and 11 are most commonly mutated in proto-oncogene *c-KIT*, whereas mutations in exons 13, 14, 17, and 18 are uncommon.[6] Exon 9 encodes the extracellular domain of the kinase, and its mutation causes receptor dimerization in the absence of a ligand. Exon 11 contains the primary mutation in 70% of GISTs with proto-oncogene *c-KIT* mutations, which affect the intracellular juxtamembrane domain and alleviate the auto-inhibitory function of the kinase, resulting in abnormal activation.[6] Mutations in exons 13, 14, 17, and 18 affect the kinase domain and are observed as primary mutations in <1% of GISTs. Mutations in exons 13 and 14 affect ATP-binding in the phosphotransferase region, whereas mutations in exons 17 and 18 cause alterations in the activation-loop domain.[6]

The mutational status of a GIST affects the prognosis in terms of the response to imatinib.[7] Information on the effectiveness of imatinib in GISTs with a primary mutation in exon 17 of proto-oncogene *c-KIT* is limited. Studies have yielded inconsistent results. Primary mutations in exon 17 are significantly less common than acquired mutations, demonstrating the preserved activity of imatinib against primary mutations.[8]

It often takes 2–3 months for a GIST to respond to imatinib treatment.[8] For our patient, one complete cycle of 30 days was not long enough to determine whether the tumor had primary imatinib resistance. AAM van der Veldt et al.[9] described a PR as a >10% decrease in one-dimensional tumor size or a >15% tumor attenuation on CT scans, whereas progressive disease (PD) was defined as a >10% increase in size without meeting the PR criteria in terms of attenuation, Choi response criteria for early prediction of clinical outcome. On serial CT scans >2 years, our patient manifested a PR with a >15% attenuation, although the tumor did not shrink. The bleeding ceased, and the patient had a long progression-free survival (PFS). These results support the effectiveness of imatinib treatment for proto-oncogene *c-KIT* exon 17 mutations.

Studies on the effectiveness of imatinib for GISTs with proto-oncogene *c-KIT* exon 17 mutations have yielded contradictory results. In a Korean study, two of 290 patients had a primary mutation in exon 17. Both patients exhibited a PR to imatinib.[10] In another study, a primary alteration in exon 17 was not associated with imatinib resistance, but the numbers were too small to reach a meaningful conclusion.[11] In a xenograft model of a GIST with an exon 17 mutation, intermittent and continuous imatinib treatment both appeared effective.[12]

Spitaleri *et al*[8] and Singeltary *et al*[13] reported on patients with proto-oncogene *c-KIT* exon 17 Asn822Lys-related GISTs who exhibited no response to imatinib. Whether this mutation was primary or acquired was unclear. Loughrey *et al*[14] described a female patient with a deletion in exon 11 and the Asn822Lys mutation in exon 17, in whom the GIST progressed after 12 months of imatinib treatment. A preclinical study of a mouse model of GIST with another mutation in exon 17 (Asp818Tyr) also revealed resistance to imatinib.[15]

The patient had a rare GIST, associated with a primary, intrinsic missense mutation in exon 17 of proto-oncogene *c-KIT* (c.2466T > A; Asn822Lys), and exhibited a response to a relatively short course of imatinib, raising the question of whether this tumor was responsive to imatinib or was simply a type of GIST that would have remained stable even without treatment. Although the tumor did not shrink, but exhibited attenuation on the CT. Moreover, the patient's symptoms improved favoring a true response. TKI-naïve patients may or may not exhibit a response to imatinib. The mechanisms of response and resistance to imatinib need to be understood better to optimize treatment options for such patients.

Authors contribution

All authors took care of the patient. Gilani Shahid contributed to the acquisition, interpretation, drafting, revision, and final draft for approval; Mujeeb Qudsia and Ikram Naima contributed to the initial drafting; Khir Ibrahim approved the final manuscript.

Ethics statement

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that generative artificial intelligence (AI) and AI assisted technologies were not used in the writing process or any other process during the preparation of this manuscript.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

The data that support this case study is available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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