High-Grade KIT-Negative Sarcoma of the Small Bowel in a Patient With Chronic Myeloid Leukemia Receiving Long-Term Tyrosine Kinase Inhibitors

Case Report

A 65-year-old man with a history of hypertension, hypercholesterolemia, and peripheral vascular disease was diagnosed with chronic phase chronic myeloid leukemia (CML) in 1998. He was treated with interferon and cytarabine, which resulted in a complete cytogenetic remission. In August 2000, imatinib (Gleevec; Novartis, East Hanover, NJ) at a dose of 400 mg per day was started for cytogenetic relapse. Complete cytogenetic remission was achieved after 3 months of therapy. Ten years later, cytogenetic relapse reoccurred and imatinib dosing was increased to 800 mg, and then was discontinued shortly thereafter because of adverse effects. Therapy was changed to nilotinib (Tasigna; Novartis) at a dose of 400 mg twice per day.

Eleven months later, the patient developed leg cramps and weakness that were attributed to nilotinib, which was discontinued and replaced with dasatinib (Sprycel; Bristol-Myers Squibb, Princeton, NJ) at a dose of 100 mg once per day. The patient experienced intermittent abdominal pain during the ensuing 4 months, which culminated in hospitalization for upper GI bleeding. Computed tomography (CT) enterography was performed and revealed an enhancing polypoid mass (Fig 1, arrow) at the duodenojejunal junction and retroperitoneal lymphadenopathy. Esophagogastroduodenoscopy demonstrated a medium-sized hemorrhagic mass in the third part of the duodenum.

Endoscopic biopsy revealed a poorly differentiated high-grade malignancy of unknown origin, located mainly in the submucosa. Immunohistochemical staining was positive for vimentin and nega-

tive for epithelial and neuroendocrine markers, lymphoid, myeloid, melanoma, and endothelial markers. c-KIT and CDX2 staining were negative. Serum chromogranin-A (CgA) was 1.5× the upper limit of normal.

Additional staging with positron emission tomography (PET)/CT revealed [^{18}F]fluorodeoxyglucose-avid small bowel foci associated with mass-like formations with standardized uptake values of 12 and 18.3. Confluent retroperitoneal hypermetabolic lymphadenopathy was noted with a maximum standardized uptake value of 19.8. In-111 pentetate scintigraphy (In-111 diethylenetriamine penta-acetic acid) with single-photon emission computed tomography-CT fusion was performed and demonstrated a focus of abnormal radiotracer uptake corresponding to the duodenal tumor.

All of these findings suggested the possibility of a type IV neuroendocrine carcinoma of the small bowel. The patient was not deemed a resection candidate because of evidence of nonregional lymph node metastases. Dasatinib was discontinued and cisplatin and etoposide were initiated in June 2011 on the basis of the established regimen for metastatic high-grade neuroendocrine carcinoma.¹⁻⁴ Abdominal pain and the need for transfusion support persisted after an initial modest improvement. Imaging to assess tumor response revealed progression of disease in all areas. Because of ongoing bleeding, the patient underwent palliative resection of the tumor. Intraoperative findings included an 8-cm tumor (spanning the mid-duodenum to the jejunum) with intraluminal and mesenteric extension, mesenteric vessel involvement, mesenteric lymphadenopathy, as well as liver metastases.

Pathologic examination revealed a 13-cm high-grade malignant neoplasm (Fig 2A) that was composed of sheets of epithelioid cells with abundant eosinophilic cytoplasm, prominent nucleoli, high mitotic activity, and necrosis (Fig 2B, hematoxylin and eosin staining, ×200 original magnification). By immunohistochemistry, the tumor demonstrated positivity for CD34 (scattered cells), vimentin (strongly diffuse), EMA (multifocal; Fig 2C, ×400 original magnification), MNF-116 (scattered cells), CAM 5.2 (scattered cells; Fig 2D, ×400 original magnification), whereas it was negative for INI-1 (retained; Fig 2E, ×400 original magnification), ERG, desmin, DOG1.1, c-KIT, and lymphoid and melanoma markers. Immunostaining for platelet-derived growth factor receptor alpha (PDGFRA) was equivocal.

The final diagnosis was a malignant epithelioid cell neoplasm favoring high-grade sarcoma. One month postoperatively, the patient had follow-up CT imaging that revealed rapid progression of disease with new bilobar hepatic metastases, progressively enlarging lymphadenopathy, and new omental metastases. The patient decided on palliative hospice care in view of his debilitated state and rapid progression of disease.

Additional polymerase chain reaction mutational analysis performed post hoc revealed deletion of *KIT* exon 11^(WK557-8) (Fig 2F) and a concomitant *KRAS* G12V mutation. No mutations were found in *KIT* exons 13, 14, 17, *BRAF* (exon 15 tested), *PDGFRA* (exons 12 and 18) or p53.

Fig 1.

Fig 2.

Discussion

The small bowel is a rare site for primary malignant tumors, with an annual incidence of 2.4 and 1.6 cases per 100,000 men and women, respectively.⁵⁻⁸ In the United States, cancers of the small intestine account for only 0.42% of total cancer cases and 2.3% of cancers of the digestive system.^{9,10} Adenocarcinoma is the most common malignancy of the small intestine, followed by gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and GI stromal tumors (GISTs), with approximate incidences of 37%, 27%, and 23%, respectively.^{9,11,12} Ninety percent of all GI sarcomas are GISTs, with annual incidence rates of 0.17 to 0.24 per 100,000.

A small minority of GEP-NETs consist of poorly differentiated, highly aggressive tumors that are related to small-cell carcinomas of the lung.¹³ Serum CgA, although not to be used as a diagnostic tool, was mildly elevated in our patient. CgA is a part of the granin family of proteins that are found in both endocrine and nervous tissues and can be falsely elevated by a variety of medications and chronic GI conditions.¹⁴

In our patient, octreotide imaging was positive. Many but not all GEP-NETs express somatostatin receptors. CT and magnetic resonance imaging yield 60% to 80% sensitivity for detecting both localized and metastatic GEP-NETs.¹⁵ Increased somatostatin receptor expression can be found in neuroendocrine-derived tissues as well as in activated leukocytes, as in sarcoidosis. In-111 diethylenetriamine penta-acetic acid octreotide imaging, sensitivity and specificity are 80% to 100% for GEP-NETs.^{16,17} PET imaging was positive in our patient, suggesting a rapidly proliferating tumor. PET is useful in poorly differentiated GEP-NETs.¹⁸ Lack of differentiation can occur in grade 3 neuroendocrine carcinomas with a possible lack of CgA; up to 50% of NETs express vimentin alone, with variable classical immunohistochemical staining.¹⁹⁻²¹

Our patient was ultimately found to have a high-grade tumor, most likely a sarcoma of the small bowel, which raised the question of a secondarily tyrosine kinase inhibitor (TKI) –resistant GIST with unusual phenotype.²²⁻²⁴ GISTs are driven by mutations in the *KIT* gene, most commonly in exons 11 and 9, causing ligand-independent activation that drives oncogenic transformation in most cases.²⁵ Notably, GISTs that lack the more common *KIT* gene mutations are often found to have activating mutations in the gene of the homologous membrane receptor tyrosine kinase (RTK) protein PDGFRA. Mutations in these two RTKs, namely *KIT* and PDGFRA, are mutually exclusive. In our case, post hoc analysis demonstrated a discrepancy between immunohistochemical and polymerase chain reaction results.

Imatinib therapy achieves disease control in approximately 80% of patients with GISTs, with most tumors showing a reduction in cellularity and low mitotic indices but rarely showing complete pathologic responses.²⁶ Rarely, differentiation toward a smooth muscle, epithelioid, or even rhabdomyosarcomatous phenotype occurs.²²⁻²⁴ Primary resistance to imatinib as well as secondary progression after prolonged therapy has been associated with novel mutations, usually affecting the domain targeted by imatinib, in both *KIT* and protein PDGFRA RTKs.²⁷⁻²⁹ Our patient was also exposed to dasatinib and nilotinib to treat his CML. Dasatinib is a dual *KIT* and Src kinase inhibitor. It has a greater than 300-fold higher affinity for *BCR-ABL* than imatinib, with less stringent conformational requirements, and is able to bind both active and inactive states of the kinase. Conversely, nilotinib, an ATP-competitive inhibitor of *BCR-ABL*, has a 25-fold-higher binding affinity than imatinib for the inactive state only. Both of these agents have unique affinity profiles for various *KIT* mutations as well as increased binding to double mutants (exon 11/exon 13 or exon 11/exon 17).^{28,30,31} However, neither of these two latter agents

Table 1. Studies Assessing Incidence and Different Types of Secondary Malignancies in Patients Treated With TKIs

References	Indication	TKI	Dosage (mg per day)	No. of Patients	Secondary Malignancies Diagnosed During TKI Therapy
37-40	CML	Imatinib	600	1	Adenocarcinoma of prostate
	CML	Imatinib	400	1	Adenocarcinoma of prostate
	CML	Imatinib	400	1	Adenocarcinoma of prostate
	CML	Imatinib	400	1	Transitional cell carcinoma of urinary bladder
	CML	Imatinib	400	1	Adenocarcinoma of colon
	CML	Imatinib	600	1	SCC (unknown primary)
	CML	Imatinib		1	Prostate cancer
	CML	Imatinib		1	Urinary bladder cancer
35	GIST	Imatinib	400	1	2 malignancies: gastric adenocarcinoma, prostate adenocarcinoma
43	GIST	Imatinib		1	2 malignancies: renal cell carcinoma, gastric carcinoma
36	CML	Imatinib		1	Adenomatoid tumor of the testis
44	CML	Imatinib	400	1	Kaposi's sarcoma
42	CML	Imatinib		832*	1 adrenal gland neoplasm
					1 biliary tract cancer
					1 bladder cancer
					3 breast cancers
					1 CNS
					3 colon cancers
					1 endometrial cancer
					2 lung cancers
					1 NHL
					1 AML
					10 prostate cancers
					2 renal cancers
					1 salivary gland cancer
					2 SCCs
					12 prostate cancers
					10 melanomas
41	CML/MPN	Imatinib/dasatinib/nilotinib/bosutinib		1,445†	8 GI cancers (colon/gastric/esophageal)
					4 GU cancers (urinary bladder/kidney)
					3 thyroid cancers
					4 breast cancers (2 relapse, 2 new)
					2 CLLs
					2 GI cancers (hepatobiliary)
					2 GU cancers (ovarian/uterine)
					2 head and neck cancers
					1 lung cancer
					1 lymphoma
					1 MPN
					1 pancreatic cancer
					1 thymoma
					1 cancer of unknown primary
					25 skin cancers (BCC/SCC)

Abbreviations: AML, acute myeloid leukemia; BCC, basal cell carcinoma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; GU, genitourinary; GIST, GI stromal tumor; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

*Thirty patients were found to have secondary malignancies. Cumulative incidence of secondary malignancies was 3.6%.

†Sixty-six patients were found to have secondary malignancies. Cumulative incidence of secondary malignancies was 4.6%.

has demonstrated sufficient clinical activity against imatinib-refractory GISTs to warrant routine use, with the possible exception of use in the setting of specific secondary mutations, such as in exon 17. Prolonged TKI therapy, especially with several different agents targeting KIT, may lead to a survival advantage and selection of a subpopulation of cells—possibly stem cells—harboring mutations in these two proteins.³² The presence of an activating *KRAS* mutation in our patient's tumor raises the possibility of a novel primary or secondary mutation conferring additional resistance to TKIs,³³ whereas V600E *BRAF* mutation, recently described as one of several gene alteration pathways in GISTs, was not found.³⁴

Our review of the literature reporting secondary malignancies occurring in patients treated with imatinib is presented in Table 1. In our analysis, a cumulative incidence ranging from 3% to 5% of metachronous or synchronous cancers in patients treated with TKIs was found.^{35-41,43-45} In 2011, a multicenter study of patients treated only with imatinib reported no significantly increased risk of second malignancies, with a slightly higher than expected incidence of melanoma, endocrine tumors, kidney cancers, and chronic lymphocytic leukemia.⁴²

In conclusion, the patient case reported here suggests that TKI therapy may have promoted the selection of an anaplastic,

c-KIT-mutated, but low-expressing sarcoma. Although our patient did not have a previously documented GIST, the clinical history, tumor immunoprofile, and molecular data support the diagnosis of dedifferentiation to an anaplastic KIT-negative phenotype, which is a potential diagnostic pitfall.⁴⁶ The underlying molecular mechanisms of this form of tumor progression in GISTs are currently being investigated. Published data regarding secondary malignancies in patients receiving RTK therapy does not document RTK expression or mutational status consistently; therefore, prospective documentation of target protein expression in secondary tumors arising during therapy with TKIs against BCR-ABL is of importance and can help us understand mechanisms of resistance to these agents, especially in the setting of long-term therapy that may extend over years, such as that for CML or GIST tumors.

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