Gastric Antral Vascular Ectasia in a Patient with GIST after Treatment with Imatinib: Case Report and Literature Review

Ehab Saad Aldin, Fadi Mourad and Arafat Tfayli*

Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

*For reprints and all correspondence: Arafat Tfayli, Division of Hematology/Oncology, Department of Internal Medicine, American University of Beirut Medical Center, PO Box 11-0236, Riad El-Solh 1107-2020, Beirut, Lebanon.
E-mail: at35@aub.edu.lb

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Imatinib mesylate is a receptor kinase inhibitor approved by the Food and Drug Administration for the treatment of malignant metastatic and/or unresectable gastrointestinal stromal tumors and chronic myelogenous leukemia. Although imatinib is generally well tolerated, certain adverse drug reactions are common. These include gastrointestinal side-effects such as diarrhea, nausea and vomiting, as well as hematological side-effects and other miscellaneous side-effects such as fatigue, edema, dermatitis and dyspnea. We present a previously unreported adverse effect of imatinib, gastric antral vascular ectasia, in a 74-year-old woman with gastrointestinal stromal tumor in remission treated with adjuvant imatinib. Endoscopy performed prior to starting imatinib showed normal gastric mucosa, but 8 months after starting imatinib showed diffuse gastric inflammation. Repeat endoscopy 1 month after discontinuing imatinib showed significant improvement in gastric inflammation.

Key words: gastrointestinal hemorrhage – gastric antral vascular ectasia – gastrointestinal stromal tumors – imatinib – watermelon stomach

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal tumors of the gastrointestinal (GI) tract, with an incidence of 3000–4000 cases per year in the USA (1). They occur in the stomach (70%) and small intestine (10–20%) (2), and occasionally in the rectum, esophagus and colon. About 95% of cases arise in adults over 40 years of age (3), but some occur in children and young adults. The tumor’s aggressiveness and metastatic potential are dependent on its size and mitotic index, making these the most reliable prognostic factors (2).

Surgery remains the standard of care for all resectable non-metastatic tumors. Yet, surgery alone does not always achieve a long-term cure for high-risk GIST patients. Most GISTs express the c-kit oncogene, which codes for the receptor tyrosine kinase (RTK) KIT (CD117) (4). Another RTK whose activation is associated with GISTs is the platelet-derived growth factor receptor α seen in ~3–5% of GISTs, mostly in the KIT-negative tumors (5). Imatinib mesylate is an RTK inhibitor that has been Food and Drug Administration approved for the treatment of chronic myelogenous leukemia and metastatic and/or unresectable GISTs. It was shown to be beneficial in inducing clinical response in that patient population and in decreasing GIST recurrences and/or metastases after primary resection. The most common side-effects of imatinib include abdominal pain, diarrhea, edema, headache, rash, fatigue, neutropenia, arthralgics, myalgias and others (6).

In this case report we present a previously undescribed adverse drug reaction of imatinib in a GIST patient treated with imatinib for 8 months. The patient presented with anemia symptoms and a hemoglobin drop, and was found to have gastric antral vascular ectasia (GAVE) on endoscopy, despite previously having a normal stomach. A few weeks after discontinuing imatinib, repeat endoscopy showed the resolution of GAVE.
CASE PRESENTATION

A 74-year-old woman with osteoporosis and chronic obstructive pulmonary disease (COPD) presented to the American University of Beirut Medical Center (AUBMC) on 1 December 2010 with a 7-month history of fatigue, weight loss, anorexia and abdominal pain. Given her age and smoking history, she underwent a comprehensive malignancy workup, which included complete blood count (CBC), chemistry, carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen, computed tomography (CT) scan of the chest, abdomen and pelvis, in addition to esophagastroduodenoscopy (EGD) and colonoscopy. On CT scan there was a jejunal tumor with four foci of liver metastasis. EGD performed at another medical center showed a small antral ulcer and mild duodenal bulb erythema but otherwise normal gastric mucosa. On colonoscopy there was diverticulosis. All laboratory tests were within normal limits. On 10 December 2010, the patient underwent surgical excision of the tumor and wedge resection of one out of four liver metastases, while the other three were radiofrequency ablated. Pathology confirmed the diagnosis of metastatic GIST (CD117 positive), and imatinib (400 mg/day) was started on 3 January 2011. The patient was asked to continue with her other medications, tiotropium and fluticasone/salmeterol for COPD and vitamin D supplementation for osteoporosis.

The patient was followed up monthly in the oncology clinic. Her weight stabilized after surgery, but she reported fatigue, myalgias, abdominal pain and occasional diarrhea. These were attributed to the use of imatinib, but the patient was asked to continue imatinib at the same dose, as these adverse effects were mild to moderate in severity. Her blood studies on various follow-ups showed mild stable anemia (hemoglobin of 10.1–10.7 g/dl), but other laboratory parameters, including her chemistry panel and liver function tests, were normal on all occasions. Her CT scan of chest, abdomen and pelvis has also been stable and showed no evidence of recurrence or metastasis.

On 23 August 2011 the patient was admitted to AUBMC for worsening of fatigue, pallor, dyspnea and diaphoresis. CBC showed a marked drop in her hemoglobin level, from 10.7 g/dl 1 month earlier to 5.6 g/dl. Her mean corpuscular volume (MCV) was 95 fl. The patient reported no epistaxis, hematemesis or hematuria, but was unsure whether she had melena or not. She has made no dosage changes to any of her medications, and had not started/stopped any medication during this period. The patient’s prothrombin time and activated partial thromboplastin time (APTT) were normal. An anemia workup was initiated and the patient was urgently transfused with four units of packed red blood cells. The workup included a stool occult blood test (tested on three separate occasions), vitamin B12 level, folate level, iron level, total iron-binding capacity (TIBC), iron saturation, unsaturated-binding capacity, transferrin level and ferritin level (see results in Table 1).

Table 1. The patient’s anemia workup

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Unit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12</td>
<td>122</td>
<td>pg/ml</td>
<td>243–894</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>90</td>
<td>pmol/l</td>
<td>179–660</td>
</tr>
<tr>
<td>Active B12</td>
<td>19</td>
<td>pmol/l</td>
<td>19–119</td>
</tr>
<tr>
<td>% Active B12</td>
<td>21</td>
<td>%</td>
<td>10–30</td>
</tr>
<tr>
<td>Iron</td>
<td>51</td>
<td>æg/dl</td>
<td>37–160</td>
</tr>
<tr>
<td>Iron-binding capacity</td>
<td>334</td>
<td>æg/dl</td>
<td>270–450</td>
</tr>
<tr>
<td>Iron % saturation</td>
<td>15.3</td>
<td>%</td>
<td>15.0–50.0</td>
</tr>
<tr>
<td>Transferrin</td>
<td>2.48</td>
<td>g/l</td>
<td>2.00–3.60</td>
</tr>
<tr>
<td>Ferritin</td>
<td>14.3</td>
<td>ng/ml</td>
<td>28–280</td>
</tr>
<tr>
<td>Folate</td>
<td>4.0</td>
<td>ng/ml</td>
<td>Normal, 4.2–19.9; indeterminate, 2.2–4.1; deficient, &lt;2.1</td>
</tr>
</tbody>
</table>

The tests were in favor of an acute and severe GI blood loss (the stool occult blood test was strongly positive in all three samples). While this anemia profile showed vitamin B12 deficiency, the chronic nature of this deficiency rules it out as a cause of the patient’s acute drop in hemoglobin. On 25 August 2011 the patient underwent EGD, which revealed a ‘watermelon’ appearance of the longitudinal antral folds on the patient’s pylorus consistent with gastric antral vascular ectasia (GAVE). On 29 September 2011, ~1 month after stopping imatinib, the patient underwent follow-up...
DISCUSSION

GAVE was first described in 1953 in a patient with chronic anemia (7). Via gastroscopy, the antrum was described as ‘fiery red’ with scattered areas of bleeding and clotted blood. Microscopically, chronic inflammation as well as submucosal edema and dilated veins were described (7). Because the convergence pattern of the longitudinal antral folds on the pylorus, GAVE has the appearance of stripes on a watermelon on EGD, and is often called ‘watermelon stomach’ (8).

GAVE often manifests with a spectrum ranging from chronic occult upper GI bleeding to acute bleeding. Patients often present with iron-deficiency anemia or with an acute drop in hemoglobin. It is estimated that GAVE accounts for up to 4% of all non-variceal upper GI bleeding (8,9).

The pathogenesis of GAVE remains unknown. While more than one-fourth of GAVE patients have cirrhosis (10), GAVE is also seen in patients without cirrhosis, mainly in those with autoimmune disorders (8). It may also be seen in patients with chronic kidney disease, ischemic heart disease, valvular heart disease, acute myeloid leukemia and other disorders (11–13). It is estimated that most patients with GAVE not associated with cirrhosis are female (71%) and have an average age of 73 years (8,11).

Several treatment strategies for GAVE exist. Symptomatic therapy with multiple blood transfusions and fluid resuscitation aims to correct anemia and maintain hemodynamic stability, respectively. In cirrhosis-associated GAVE, correction of portal hypertension with beta-blockers or transjugular intrahepatic portosystemic shunt has not resulted in a reduction in the incidence of bleeding episodes and transfusion requirements (8,14). Other medical therapies that were used, with variable success rates, include corticosteroids (15–17), tranexamic acid (18,19) and thalidomide (20).

Endoscopic therapy remains the therapy of choice for GAVE. Photocoagulation using a neodymium:yttrium-aluminum-garnet laser and argon plasma coagulation have been successful in treating GAVE and abolishing or reducing transfusion requirements (11,21). For intractable cases, surgical antrectomy is the treatment of last resort. While curative, antrectomy is associated with high morbidity and mortality (8).

Although rare, GI bleeding is a well-known complication of imatinib in GIST patients. It is estimated to take place in ~5% of all imatinib-treated patients, possibly due to imatinib-induced tumor necrosis (1,22). The risk of bleeding is highest for duodenal GISTs (26), estimated to be close to 75% of cases compared with gastric GISTs (54%) and ileojejunal GISTs (28%) (23–25).

In this patient, the etiology of the GI bleeding is completely different from the bleeding that complicates 5% of imatinib-treated GIST cases: A 74-year-old woman developed GI bleeding 8 months after her jejunal GIST and liver metastases were treated. The bleeding took place in the stomach, and EGD was diagnostic of GAVE. This complication most probably took place as an adverse reaction to imatinib, as the patient has no underlying medical condition associated with GAVE and had no evidence of it on EGD before starting imatinib. This is the first case report of such an adverse drug reaction in the literature. The resolution of GAVE 4 weeks after discontinuing imatinib further proves that this condition was imatinib induced. In many cases of GAVE, treatment of the underlying cause, such as cirrhosis (by liver transplantation) or scleroderma (by immunomodulatory medications), has led to the resolution of GAVE (10,26).

CONCLUSION

GI bleeding complicates up to 5% of GIST cases treated with imatinib, mainly due to imatinib-induced tumor necrosis. In GIST patients with GI bleeding, the possibility that bleeding is imatinib induced should be entertained even in those after primary tumor resection, as it can be due to the presence of residual tumor or to other less common etiologies, such as GAVE. GAVE may not always cause acute GI bleeding and can present with chronic bleeding and anemia that might be overlooked for other more common causes.

Conflict of interest statement

None declared.

References