CASE REPORT

Spontaneous intramural small bowel hematoma in a patient with acute myeloid leukaemia receiving chemotherapy and nilotinib

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SUMMARY

Spontaneous intramural small bowel hematoma (SISBH) is a rare, acute abdominal condition, with increasing incidence in recent years. Excessive anticoagulation with vitamin K antagonists is the most common aetiology. We report the case of a large acute jejunal intramural hematoma in a patient with newly diagnosed acute myeloid leukaemia receiving chemotherapy and nilotinib. The patient presented with abdominal pain, haematochezia, acute anaemia and thrombocytopenia. CT of the abdomen and pelvis revealed SISBH. The patient was managed conservatively with supportive management and cessation of nilotinib therapy. The patient's symptoms improved, with subsequent CT imaging confirming resolution. This case highlights an uncommon cause of gastrointestinal bleed usually diagnosed only after radiological imaging. A correct diagnosis is important as SISBH usually responds to conservative measures, and may obviate the patient from unnecessary invasive investigations.

BACKGROUND

Spontaneous intramural small bowel hematoma (SISBH) is an uncommon cause of acute abdomen. Although the word 'spontaneous', often used in this context to differentiate from traumatic causes, suggests that there is no underlying aetiology, SISBH is frequently associated with risk factors—most commonly excessive anticoagulation as a result of vitamin K antagonists.¹ The clinical presentation of SISBH can vary from mild abdominal pain to acute abdomen.^{1–3} Diagnosis is made with CT imaging and most cases respond well to conservative management.^{1–4} Our case illustrates the presentation, evaluation and management of SISBH in a patient with a number of established risk factors, including the possible contribution of tyrosine kinase inhibitor (TKI) therapy. A prompt diagnosis in our patient obviated her from further invasive diagnostic and therapeutic investigations. Our case reiterates the presentation and risk factors associated with SISBH, and emphasises the approach to management and good prognosis with conservative measures. Moreover, it offers an interesting discussion point on the propensity for nilotinib to possibly precipitate a bleeding diathesis, not previously described.⁵

CASE PRESENTATION

A 65-year-old woman presented with a 3-month history of progressive light-headedness and generalised weakness. Additional symptoms included aphthous ulcers and gingival bleeding. Her medical history was notable for essential thrombocythaemia (ET) on aspirin and hydroxyurea, osteoarthritis on naproxen as needed, hypertension on hydrochlorothiazide and reflux oesophagitis on pantoprazole. She was a never smoker and rarely drank alcohol. Her family history was unremarkable.

The patient's vital signs revealed a heart rate of 95 beats per minute (bpm), respiratory rate of 21 per minute, blood pressure of 136/89 mm Hg, SpO₂ of 99% on room air and temperature of 37.1°C. Her physical examination was largely unremarkable except for obvious pallor and oral aphthous ulcers. No splenomegaly was noted. Initial laboratory workup revealed the following (reference ranges provided parenthetically): haemoglobin, 4.4 g/dL (12–15.5 g/dL); mean corpuscular volume, 86.5 fL (81.6–98.3 fL); white cell count, $8.7 \times 10^9/L$ (3.5 – $10.5 \times 10^9/L$) with 45% circulating blasts noted on the blood smear; platelets, $24 \times 10^9/L$ (150 – $450 \times 10^9/L$); reticulocytes, 2.77% (0.77%–2.36%); international normalised ratio (INR), 1.4 (0.8–1.2); lactate dehydrogenase, 320 U/L (122–222 U/L); sodium, 133 mEq/L (136–145 mEq/L); potassium, 3.9 mEq/L (3.5–5.0 mEq/L); bicarbonate, 29 mEq/L (23–28 mEq/L); creatinine, 0.7 mg/dL (0.7–1.3 mg/dL). Bone marrow (BM) biopsy was consistent with FAB M2 acute myeloid leukaemia (AML) with 70% BM blasts (CD13+, CD33+, CD117+, CD64–), and Auer rods noted. Molecular studies revealed that she was JAK2–/CALR–/MPL– and FLT-3–/NPM1–/CEBPA–, but had a complex karyotype AML with 17p deletion. She was negative for t(9;22)(q34;q11) translocations and the Bcr/Abl transcript was not present. The patient decided to enrol in a phase II clinical trial after meeting the inclusion criteria for concomitant nilotinib therapy which included evidence of Kit expression (CD117) of myeloblasts $\geq 20\%$.⁶ Therefore, induction chemotherapy (3+7 protocol with cytarabine and daunorubicin, and nilotinib from days 4 to 14) was initiated. In addition, she received multiple platelet and blood transfusions to address her severe anaemia and thrombocytopenia.

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Figure 1 CT abdomen coronal plane demonstrating an intramural hematoma with suspected intraluminal haemorrhage involving a 15 cm length segment of the distal jejunum and proximal ileum causing mild proximal small bowel dilatation.

On day +10 of trial induction chemotherapy, the patient developed acute abdominal pain and moderate-volume haematochezia. At the time of evaluation, her vital signs were notable for tachycardia of 108 bpm, tachypnoea of 29 breaths per minute and blood pressure of 122/58 mm Hg. Her abdominal examination revealed hypoactive bowel sounds and significant periumbilical tenderness with guarding without rebound tenderness. Repeat haemoglobin was 5.8 g/dL decreased from the previous day's reading of 7.8 g/dL, platelet count was $16 \times 10^9/L$ despite multiple transfusions and INR of 1.4. Extended coagulation studies were unremarkable.

INVESTIGATIONS

As part of the diagnostic evaluation, an oesophagogastroduodenoscopy and colonoscopy were considered; however, her refractory thrombocytopenia precluded this testing. After multiple transfusions failed to raise her platelet count after 1 hour, platelet alloimmunisation was confirmed with the presence of anti-HLA (human leucocyte antigen) I antibodies. A CT abdomen and pelvis was performed and demonstrated an intramural hematoma with suspected intraluminal haemorrhage involving a 15 cm length segment of the distal jejunum and proximal ileum (figures 1 and 2) and, red arrow), causing mild proximal small bowel dilatation. No bleeding source was demonstrated.

DIFFERENTIAL DIAGNOSIS

The CT imaging revealed the diagnosis of SISBH. This entity was compatible with the patient's symptoms, and the suspected intraluminal haemorrhage (likely a sequela of the hematoma's rupture) accounted for the haematochezia. The underlying aetiology of the patient's SISBH was less clear. Patient was day +10 of induction chemotherapy (she had completed the traditional induction therapy with daunorubicin and cytarabine) and had 4 days of nilotinib left. The patient was at increased risk of

Figure 2 CT abdomen axial plane demonstrating an intramural hematoma with suspected intraluminal haemorrhage.

coagulopathy due to her AML, induction chemotherapy and severe refractory thrombocytopenia with evidence of alloimmunisation. Another consideration was the possible role of nilotinib, due to the known ability that other TKIs have in inhibiting platelet aggregation.

TREATMENT

A multidisciplinary approach was adopted to our patient's management which included the gastroenterology, interventional radiology and general surgery teams. A conservative approach was agreed on, with continued supportive management with as needed packed red cells (haemoglobin transfusion threshold of 7 g/dL) and platelets transfusions (transfusion threshold of $20 \times 10^9/L$). Due to her alloimmunisation, platelet crossmatch was performed with transfusions performed with products obtained from specific donors. A nasogastric tube was inserted to help with decompression, given the small bowel dilatation noted on CT imaging. Patient was disenrolled from the clinical trial (nilotinib was stopped) given concerns for it being a precipitating factor. An intravenous proton pump inhibitor had also been initiated at the onset of symptoms, empirically treating a possible peptic ulcer bleed—this was stopped once the diagnosis was made.

OUTCOME AND FOLLOW-UP

Our patient's symptoms improved dramatically over the course of the next 3 days, with no further episodes of haematochezia and a stable haemoglobin and platelet count noted. A follow-up CT abdomen and pelvis showed resolution of the intramural jejunal hematoma (figure 3, red arrow).

The patient had a repeat BM biopsy on day +22 of induction chemotherapy (day +14 BM biopsy deferred due to patient's intercurrent illness), which showed refractory AML with 40%–50% blasts in the BM aspirate. Due to our patient's poor performance status, she was felt to be a poor candidate for repeat 7+3 induction chemotherapy; therefore, a trial of cladribine was initiated. Unfortunately, over the remainder of her hospital stay, she developed multiple treatment-associated and disease-associated complications resulting in decline of her functional status to the point of precluding her from further chemotherapy. Eventually, after multiple discussions between the patient, her family and medical teams, the decision was made to enrol her in home hospice.

Figure 3 CT abdomen coronal plane showing interval resolution of the hematoma after conservative management.

DISCUSSION

SISBH is a rare cause of acute abdomen with a varied presentation from mild and vague abdominal pain to intestinal obstruction and acute abdomen.^{1–3} The most common location of haemorrhage is the submucosal layer of the bowel, originating from a small vessel.¹ Intramural, intraluminal, intramesenteric and retroperitoneal haemorrhage can also occur, especially when the duodenum is involved.⁷ Warfarin toxicity is the most common aetiology; however, SISBH has also been associated with a number of haematological disorders such as leukaemia, lymphoma and idiopathic thrombocytopenic purpura, as well as chemotherapy use and vasculitides.¹ Our patient had a number of these including AML, refractory thrombocytopenia with alloimmunisation, chemotherapy (which produced thrombocytopenia as a side effect) and a mildly supratherapeutic INR. Diagnosis requires an extremely high level of suspicion, and is usually not considered until after CT imaging which helps not only making the diagnosis, but also, defining the area of the haemorrhage and revealing possible complications.^{3,4} In the setting of hematoma rupture, imaging typically occurs only after upper and lower endoscopic evaluation; however, our patient's thrombocytopenia precluded endoscopy.

It is noteworthy that our patient had long-standing ET, a chronic myeloid neoplasm most commonly seen in women, with an annual incidence of 2.5 cases per 100 000 in the USA.⁸ Despite indolence for many patients, transformation to AML (2%–3% at 10 years) and bleeding complications (5%–10%, mostly from urogenital and gastrointestinal sources) are significant causes of mortality in ET,⁸ as observed in our patient. The use of hydroxyurea has been reported to increase the risk of leukemoid conversion, especially when associated with 17p chromosome deletions, both factors were present in our case.^{8–10} One of the proposed mechanisms of this increased haemorrhagic risk is platelet hypoactivity which has been described in JAK2V617F-positive patients with ET,¹¹ although our patient was JAK2V617F negative.

Our case illustrated a SISBH presentation and diagnosis in a patient with multiple established risk factors. It showed the

importance of prompt recognition of SISBH, as it can obviate the patient from further invasive diagnostic and therapeutic investigations as most cases respond well to conservative management without short-term complications.^{1,4} Surgery is indicated only if generalised peritonitis or intestinal obstruction develops.² Clinical improvement is mirrored by interval resolution of the hematoma, which occurs within days to weeks from the onset of symptoms. It appears safe to resume anticoagulant therapy in patients whose hematoma appeared as a sequela of anticoagulation toxicity as long as it is administered within the therapeutic range and are monitored adequately.¹

Our patient's refractory thrombocytopenia was an important factor to be considered in her management. Refractoriness to platelet transfusion can be confirmed by failure of the platelet count to increment by $5 \times 10^9/L$ within 1 hour after two sequential ABO-compatible transfusions.¹² Non-immune causes (such as fever, sepsis, bleeding, disseminated intravascular coagulation, drugs, infections or splenomegaly) are most likely and should be explored first. Immune-mediated refractoriness, such as in the present case, can be confirmed with evaluation for antibodies against HLA or platelet-specific antigens.¹³ After alloimmunisation is identified, the use of specific donor after platelet crossmatch may be indicated, illustrated in the present case.

While our patient had multiple risk factors for SISBH, the contribution of nilotinib was also considered prompting the medical team to stop therapy early. Bleeding diathesis is a well-documented side effect of other classes of TKIs, such as dasatinib.⁵ Basic coagulation and platelet aggregation tests have shown imatinib, dasatinib and bosutinib to reversibly inhibit platelet aggregation by impairing arachidonic acid-induced and epinephrine-induced aggregation.¹⁴ However, nilotinib (tested in only nine patients) did not affect platelet aggregation.¹⁴ To our knowledge, there have been no case reports associating nilotinib to bleeding diathesis. One case report described a case of nilotinib-induced diffuse alveolar haemorrhage; however, this was attributed to acute interstitial lung disease rather than an induced bleeding diathesis.¹⁵ It remains to be seen whether nilotinib is truly associated with bleeding diathesis.

Learning points

- Transformation to acute myeloid leukaemia (AML) and bleeding complications are significant causes of mortality in essential thrombocythaemia (ET). While transformation occurs in 2%–3% of cases, the risk of gastrointestinal bleeding is estimated to occur in 5%–10% in both patients with ET and patients with AML.
- Spontaneous intramural small bowel hematoma is an uncommon entity with variable clinical presentations, risk factors predisposing to bleeding can usually be identified, and it is typically diagnosed by CT imaging. Prognosis is good with conservative management, which includes bowel rest and correction of hypercoagulable states.
- Refractory thrombocytopenia is defined as failing to increment platelet count in $5 \times 10^9/L$ within 1 hour, after two sequential ABO-compatible transfusions. Even though non-immune causes are common, immune-mediated processes should be evaluated with specific antibody testing.
- Tyrosine kinase inhibitors have been associated with bleeding diathesis; however, it remains to be seen whether nilotinib follows this class effect.

Contributors GMDR, GPR and TGC made substantial contributions to the conception or design of the work. GMDR drafted the work. GMDR, GPR and TGC revised it critically for important intellectual content, approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

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