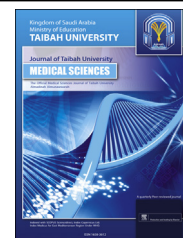




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Case Report

Drug-induced immune thrombocytopenia associated with use of tyrosine kinase inhibitor imatinib



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المخلص

تستخدم مثبطات التيروسين كيناز على نطاق واسع لعلاج مختلف أنواع السرطانات، منذ بدء العمل بها في أواخر التسعينات من القرن الماضي. والآثار الجانبية للإيماتينيب، أحد مثبطات التيروسين كيناز، موثقة جيدا في الأدبيات وتشمل الإجهاد، والطفح الجلدي، وكبت النخاع العظمي، واختلال إنزيمات الكبد. كتبت تقارير عدة عن الآثار الجانبية النادرة من المشرفين على المسوحات التي أجريت في مرحلة ما بعد التسويق، مثل الدكالك القلبي ومتلازمة ستيفن جونسون. في هذا التقرير، نعرض لحالة نادرة لنقص الصفائح الدموية المناعي المرتبطة بالإيماتينيب أدت إلى نزف حاد داخل البطن. مع توضيح موجز لحالات مماثلة من نقص الصفائح الدموية المناعي سببها مثبطات التيروسين كيناز.

الكلمات المفتاحية: نقص الصفائح الدموية؛ مثبطات التيروسين كيناز؛ الإيماتينيب؛ كبت النخاع العظمي؛ نقص الصفائح الدموية الناتج عن العقاقير

Abstract

Since their introduction in the late 1990s, tyrosine kinase Inhibitors (TKIs) have been widely used for the treatment of various cancers. The side effects of the TKI imatinib are well-documented in the literature and include fatigue, skin rash, myelosuppression, and derangement of liver enzymes. Rare side effects have been observed in the postmarketing surveillance and include cardiac

tamponade and Steven Johnson Syndrome. In the present report, we present a rare case of imatinib-associated immune thrombocytopenia leading to severe intra-abdominal bleeding. A brief account of similar cases of TKI drug-induced immune thrombocytopenia (DIT) is also described.

Keywords: Drug-induced immune thrombocytopenia; Imatinib; Myelosuppression; Thrombocytopenia; Tyrosine kinase inhibitor

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Introduction

Tyrosine kinase inhibitors (TKIs) have played an indispensable role in the treatment of various haematological and solid organ malignancies. The blocking pathological tyrosine kinase activity results in the arrest of oncogenic pathway that drives the growth of cancer cells. The first TKI that was introduced was imatinib mesylate, which has been used in treatment of various diseases, including chronic myeloid leukaemia (CML), Ph+ acute lymphoblastic leukaemia (ALL), and gastrointestinal stromal tumours (GIST). These agents are not free from adverse effects. Side effects, such as myelosuppression (or hypo-/amegakaryocytic thrombocytopenia), have been noted to affect up to 45% of imatinib recipients¹ and have also been described for other TKIs such as sunitinib.^{2,3} Clinical trials have shed light on the common

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side effects associated with TKIs; however, rarer side effects, such as autoimmune phenomena, have only become apparent in postmarketing reports (e.g., cardiac tamponade). We present a rare complication of the use of imatinib that caused drug-induced immune thrombocytopenia (DIT) in a patient with a gastrointestinal stromal tumour (GIST) and a summary of similar cases.

Case

A 72-year-old female patient was started on imatinib 400 mg PO daily for an advanced gastrointestinal stromal tumour (GIST) with liver metastasis. Her medical history was unremarkable for any autoimmune, HIV, hepatitis B or C infection or any bleeding disorders. She denied any alcohol use and any history of recreational drug use. Her baseline complete blood count (CBC) revealed the following: white blood cell count (WBC), $6.91 \times 10^9/L$ (normal 4–11); haemoglobin (Hb), 128 g/L (normal 120–160); and platelets, $226 \times 10^9/L$ (normal 150–400). Less than four weeks later after beginning imatinib, she sought medical attention after developing a generalized petechial rash and right upper quadrant (RUQ) pain. On her arrival to the emergency room, her CBC revealed severe thrombocytopenia (platelets $10 \times 10^9/L$), a WBC count of $3.74 \times 10^9/L$ and anaemia (Hb 107 g/L).

Investigations

The possible causes of the acute onset of thrombocytopenia were investigated. Disseminated intravascular coagulation (DIC) and thrombotic microangiopathy (TMA) were unlikely and were excluded based on a normal coagulation profile, a peripheral blood smear examination that revealed

no evidence of schistocytes and normal lactate dehydrogenase (LDH) levels. She was not exposed to heparin prior to admission, and thus it was unlikely that she had developed heparin-induced thrombocytopenia (HIT).

Her next CBC revealed a Hb level of 76 g/L, a WBC of $2.76 \times 10^9/L$ and a platelet count of $2 \times 10^9/L$. Additionally, her reticulocyte count ($103.4 \times 10^9/L$) and immature reticulocyte fraction (33.9%) were both elevated. Due to a strong suspicion of possible intra-abdominal bleeding, she underwent a contrast CT scan of her abdomen, which confirmed intraperitoneal bleeding from the superior intra-renal artery. This finding explained her new onset RUQ pain and the drop in haemoglobin.

Treatment

The patient underwent a successful embolization of the culprit vessel to stop the bleeding. After excluding common causes of acute onset of thrombocytopenia, imatinib-associated immune thrombocytopenia was suspected because this drug had recently been initiated prior to her presentation; thus, imatinib was immediately stopped. Due to the seriousness of the thrombocytopenia (platelet count of $2 \times 10^9/L$ with severe bleeding), treatments of prednisone 1 mg/kg PO once daily, intravenous immunoglobulin (IVIG) 2 g/kg over two days, and supportive transfusion with packed red blood cells and platelets with evidence of refractoriness to platelet transfusions were simultaneously initiated. Additionally, the patient also received a single 2-mg dose of vincristine. Following the cessation of imatinib and the introduction of these immunomodulation measures, her platelet count exhibited an initial recovery within eight days to $31 \times 10^9/L$ and ultimately reached $138 \times 10^9/L$ at the time

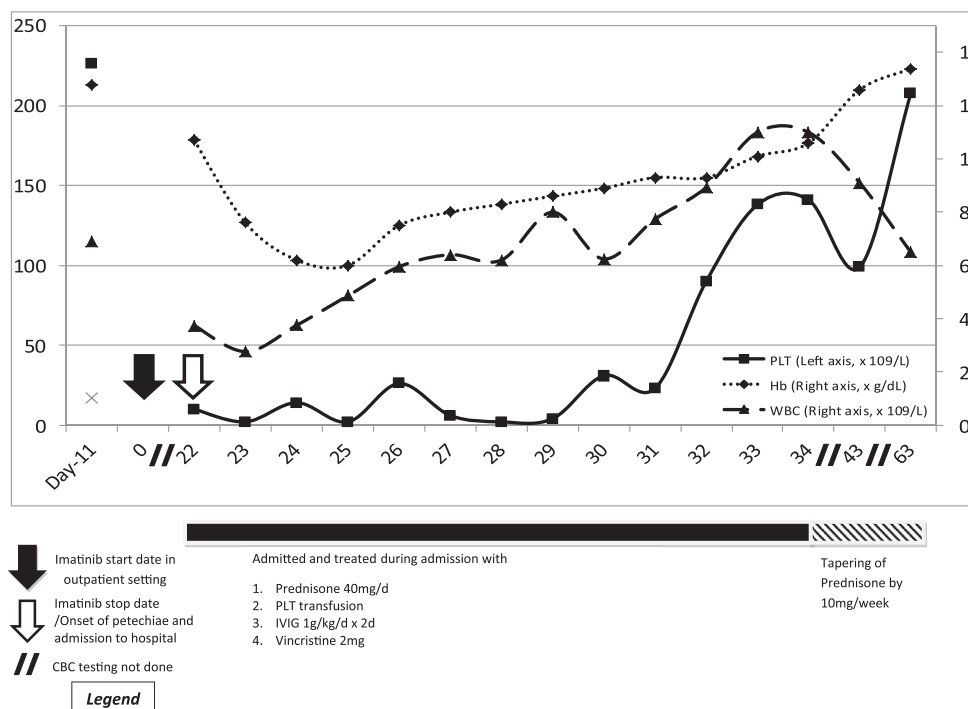


Figure 1: Temporal profile of association between tyrosine kinase inhibitor use, blood counts, and treatments.

of discharge. At this point, she was put on prednisone at a dose that tapered at a rate of 10 mg per week. One month after stopping the corticosteroid, her platelet count was stable at $208 \times 10^9/L$, and there was no evidence of recurrent thrombocytopenia (Figure 1). The Naranjo probability for this sequence having represented a drug-associated adverse drug reaction (ADR) was calculated to be 6 and therefore deemed probable.⁴

Discussion

Several mechanisms have been implicated in drug-induced thrombocytopenia (DIT) including accelerated platelet destruction caused by drug-dependent antibodies,⁵ decreased platelet production,⁶ and reactivity with drug metabolites.⁷ DIT can be benign if the thrombocytopenia occurs without harm and is followed by spontaneous recovery upon discontinuation of the offending drug. Conversely, DIT might manifest with serious results as in the case of heparin-induced thrombocytopenia with thrombosis, which require the initiation of an alternate anticoagulant.^{8–10} The diagnosis of DIT is similar to that of ITP in that they are both diagnoses of exclusion; thus, other causes of thrombocytopenia need to be ruled out.¹¹

Clinical features that might aid differentiation of DIT from other causes of thrombocytopenia include the following: the degree of thrombocytopenia, the presence of bleeding, and the temporal relationship between the onset of thrombocytopenia and initiation of the culprit drug.¹² Other features include immediate platelet transfusion refractoriness¹³ and demonstrable anti-platelet antibodies.¹² Thrombocytopenia is usually severe, and almost invariably associated with bleeding events. Drug imputability is suggested by the temporal association (with consistent post-exposure induction and durable remission after cessation) and specialized (but not widely available) in-vitro demonstrations of the anti-platelet activity in drug-treated platforms.¹²

Although our diagnostic capability for DIT in the present case was limited by the deferral of a bone marrow examination and serologic studies, our patient's case nevertheless exhibited the other elements of DIT, such as the degree of thrombocytopenia and refractoriness to platelet transfusion. Other cases of imatinib use have resulted in immune haemolytic anaemia and DIT.^{14,17} The present case is the second published report of imatinib-induced thrombocytopenia. Although serologic testing for DIT was deferred in this case, Rajappa et al.¹⁸ reported a case of imatinib-associated thrombocytopenia, which was definitive based on four criteria for the diagnosis of drug-induced thrombocytopenia.¹⁵

To our knowledge, there have been five other reported cases of severe thrombocytopenia with TKI administration (Table 1). The majority (80%) were related to the use of newer TKIs (e.g., sorafenib and sunitinib). As in the present case, the onsets of thrombocytopenia were not immediate but were rather delayed (by a mean of seven weeks). Thrombocytopenia is often sufficiently severe to require interventions, such as platelet transfusions, albeit no fatalities have yet been reported. Distinguishing between ITP and DIT can be difficult because some diseases for which TKIs are administered, such as renal cell carcinoma, can themselves be associated with ITP.^{16,17}

Table 1: Review of the literature on tyrosine kinase inhibitor-associated severe thrombocytopenia.

Author	Patient characteristics	Disease	TKI	Onset of thrombocytopenia	Platelet nadir ($\times 10^6/mL$)	Time to recovery after drug cessation	Complication & outcome	Naranjo Scale calculated by authors
Rajappa 2007 ¹⁸	20-year-old man	CML chronic phase	Imatinib	5 months	10,000	15 days	Bleeding necessitating platelet transfusions	8, probable ADR
Tunio 2011 ¹⁹	46 years old male	Renal cell carcinoma	Sunitinib 50 mg/day	8 weeks	15,000	2 weeks	recurrent epistaxis necessitating platelet transfusions	6, probable ADR
Ansari 2013 ²⁰	70-year-old male	Renal cell carcinoma	Sunitinib 50 mg/day	3 weeks	1000	? 3 weeks	epistaxis necessitating platelet transfusions (concomitant warfarin use)	6, probable ADR
Milner 2012 ²¹	61-year-old	Hepatocellular carcinoma	Sorafenib	10 days	7000	—	—	6, probable ADR
Trinka 2008 ²²	52-year-old woman	Breast cancer	Sunitinib 50 mg/day	3 weeks	1000	1 week	epistaxis necessitating platelet transfusions	6, probable ADR

However, a definitive post-cessation resolution (within 1–3 weeks) is most consistent with DIT.

In summary, this updated assembly of cases illustrates DIT of a likely immune nature that is secondary to various TKIs. This ADR requires a high index of suspicion for treating physicians to recognize it and act promptly to mitigate any morbidity or mortality.

Conflicts of interest

The authors have no conflict of interest to declare.

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