Drug-induced immune-mediated thrombocytopenia secondary to sunitinib in a patient with metastatic renal cell carcinoma: a case report

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\textbf{Abstract}

\textbf{Introduction:} Sunitinib is an oral multi-targeted tyrosine kinase inhibitor approved for first line treatment for metastatic renal cell carcinoma and imatinib-resistant metastatic gastrointestinal stromal tumors. Sunitinib administration can cause myelosuppression resulting in neutropenia and thrombocytopenia. Here we present the case of a patient with metastatic renal cell carcinoma who developed sunitinib-induced immune-mediated thrombocytopenia and who was treated with withdrawal of sunitinib and administration of intravenous immunoglobulin and steroids.

\textbf{Case presentation:} This case report describes a 70-year-old Aboriginal Australian with a diagnosis of metastatic renal cell carcinoma. Three weeks after the initiation of sunitinib he developed epistaxis and was admitted with thrombocytopenia (platelets 7 × 10^9/L) which was found to be refractory to platelet transfusion. Sunitinib was stopped and he was treated with intravenous immunoglobulin and steroids. His platelet count rapidly improved and returned to baseline in three weeks. Only two cases of sunitinib-induced immune-mediated thrombocytopenia have been described in the literature.

\textbf{Conclusion:} Clinicians should have a high index of suspicion for the potential of immune-mediated thrombocytopenia after the initiation of multi-targeted tyrosine kinase inhibitors such as sunitinib. This is a diagnosis of exclusion and can be safely treated by drug withdrawal.

\textbf{Keywords:} Metastatic renal cell carcinoma, Sunitinib, Thrombocytopenia

\textbf{Introduction}

Sunitinib (Sutent\textsuperscript{®}) is an oral multi-targeted tyrosine kinase inhibitor. Sunitinib inhibits members of the split-kinase domain family of receptor tyrosine kinases (RTKs) including the vascular endothelial growth factor receptors (VEGFRs) types 1 and 2 (FLT1 and FLK1 or KDR); platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta); the stem cell factor receptor c-KIT; and the FLT3 and RET kinases. Inhibition of these RTKs results in a reduction in tumor growth, progression, metastases and angiogenesis [1]. Clinically sunitinib is approved for the first line treatment of metastatic renal cell carcinoma (mRCC) and imatinib-resistant metastatic gastrointestinal stromal tumors. Reported toxicities of sunitinib include fatigue, hypertension, diarrhea, vomiting, skin toxicity (hand and foot syndrome), neutropenia and thrombocytopenia [2]. Here we present the case report of a patient with mRCC who developed sunitinib-induced immune-mediated thrombocytopenia and recovered after the withdrawal of sunitinib and immunoglobulin and steroid support.

\textbf{Case presentation} The patient is a 70-year-old Aboriginal Australian with a history of a left nephrectomy in 2005 for clear cell renal cell carcinoma as well as multiple co-morbidities including chronic obstructive airway disease, ischemic heart disease with coronary artery bypass graft, aortic valve replacement on warfarin and gastroesophageal reflux disease. His medications included fluticasone and salmeterol inhaler (250 and 50mcg respectively) two puffs twice a day, furosemide 20mg in the morning, atorvastatin 40mg.
at night, ranitidine 300mg in the morning, and paraceta-
mol 1g daily. Investigation for shortness of breath revealed
multiple metastases in both lungs, the biopsy of which confirmed mRCC. There was no previous history of auto-
immune disease, hematological disorder, liver disease, hu-
man immunodeficiency virus, or hepatitis B or hepatitis C
infection. His baseline full blood count revealed: hemoglo-
bolin 131g/L, white blood cell count 6.4 × 10⁹/L and platelets 294 × 10⁹/L. He was commenced on
sunitinib 50mg/day. The patient did not take any new
medications, herbal or over the counter drugs since his
commencement of sunitinib. There was no evidence of
liver metastases.

A routine full blood count two weeks post-treatment
showed a decline in his platelets to 129 × 10⁹/L, how-
ever, his hemoglobin was 161g/L and white blood cell
count was 4.9 × 10⁹/L. In the third week he developed
epistaxis and was admitted to hospital. His platelets
dropped to 7 × 10⁹/L and his international normalized
ratio (INR) was 2.4. This was reversed with an intraven-
ous vitamin K injection. His sunitinib and warfarin were
stopped. The epistaxis stabilized with nasal packing and
he received a platelet transfusion. His thrombocytopenia
did not respond and his platelet count dropped further
to 1 × 10⁹/L.

On clinical examination there was evidence of orophar-
yngeal petechiae, epistaxis and peripheral ecchymoses.
There was no fever, lymphadenopathy, hepatosplenome-
egaly or neurological signs. Laboratory investigations
included normal renal function tests, electrolytes and
stable liver function tests. Coagulation screening showed
his INR had reversed to 1.1 after intravenous vitamin K,
prothrombin time 12 seconds (11 to 15), activated par-
thromboplastin time 24 seconds (23 to 38) and fibrino-
gen 3.7g/L (2.0 to 4.0). Peripheral blood film
showed thrombocytopenia and no evidence of schisto-
cytosis, spherocytosis or dysplasia. There was no evi-
dence of hemolysis.

Disseminated intravascular coagulation and thrombo-
ctic microangiopathy were ruled out as possible causes
of sunitinib-mediated thrombocytopenia by the results
of the above investigations. Platelet-bound immunoglobu-
lin and a bone marrow aspirate were not performed
when discussed with a hematologist, and the diagnosis
of exclusion, sunitinib-induced immune-mediated throm-
boctopenia, was made. The patient was treated with in-
travenous immunoglobulin 27.5g (0.4g/kg) once daily for
five days with prednisolone 50mg once a day. His platelet
count rapidly improved to 103 × 10⁹/L and returned to a
baseline of 259 × 10⁹/L after three weeks.

Normalization of this patient’s platelet count following
withholding of sunitinib is consistent with the diagno-
sis of immune-mediated thrombocytopenia secondary
to sunitinib.

Discussion

Drug-induced immune-mediated thrombocytopenia is
thought to be a result of antibody production in the
presence of a sensitizing medication, with the antibodies
targeting epitopes on the platelet surface, subsequently
leading to the clearance of the antibody-coated platelets
by the mononuclear phagocytic system. It takes five to
seven days of exposure to produce sensitization in a pa-
tient given the drug for the first time. Although drug-
duced thrombocytopenia is uncommon, it can have
devastating, and even fatal, consequences that can usu-
ally be prevented simply by discontinuing the causative
drug. It is therefore important that clinicians have a gen-
eral understanding of this condition and the drugs that
can cause it. Chemotherapeutic and immunosuppressive
agents typically cause thrombocytopenia by suppressing
hematopoiesis; they can also cause immune-mediated
thrombocytopenia [3]. Drug-induced thrombocytopenia
should be suspected, therefore, in patients treated with
such drugs if there is an acute drop in the platelet level
after exposure.

Thrombotic microangiopathy is another cause of suni-
tinib-mediated thrombocytopenia, reported by Kapiteijn
et al. [4]. Sunitinib is a tyrosine kinase inhibitor that
targets VEGFR-2 and PDGFR-beta, which are both the
major expression subtypes of VEGFR and PDGFR in cap-
pillary vasculature. It is hypothesized that sunitinib acts
via direct anti-VEGFR and anti-PDGFR effects that re-
sult in damage of the capillary endothelium [4].

Sunitinib has been associated with other autoimmune
disorders such as hypothyroidism; therefore, the possi-
bility of an immunologic phenomenon to account for
sunitinib-induced immune-mediated thrombocytopenia
is reasonable [5,6]. However, the exact mechanism by
which sunitinib induces an immune-mediated thrombo-
cytopenia is unknown. In a phase III trial of metastatic
renal cell cancer patients, Motzer et al. reported some
grade of thrombocytopenia in 65 of 375 patients ran-
domized to sunitinib treatment, with eight of the 65
(12%) having grade 3 thrombocytopenia [7].

Renal cell carcinoma is also associated with immune-
mediated thrombocytopenia [8,9]. Therefore, we can-
not rule out the possibility that the immune-mediated
thrombocytopenia was related to renal cell carcinoma.
However, in our case, sunitinib administration after
the diagnosis of renal cell carcinoma resulting in thrombo-
cytopenia resolving completely upon drug withdrawal
is consistent with sunitinib-induced immune-mediated
thrombocytopenia.

There have been two cases of sunitinib-induced im-
mune-mediated thrombocytopenia reported to date. In
both cases patients were treated with intravenous im-
munoglobulin 1g/kg over two days and intravenous tran-
examic acid [10,11].
Conclusion
In this case thrombocytopenia following the initiation of the multi-targeted tyrosine kinase inhibitors, sunitinib, was safely treated by drug withdrawal. When treating patients with these agents clinicians should have a high index of suspicion for the potential of immune-mediated thrombocytopenia which is a diagnosis of exclusion.

Consent
Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
ZA and MG were both involved in the patient diagnosis and management. ZA conducted the literature review and carried out the review of the patient’s medical record. MG participated in the preparation of the manuscript and revised the article for intellectual content details. Both authors read and approved the final manuscript.

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