Dear Sir,

A 24-year-old female presented with acute onset of multiple petechial skin rashes all over the body along with subconjunctival hemorrhages in both eyes and hematuria for 2 days. Hematological investigations showed hemoglobin of 6.5 g/dL and platelet count of $10 \times 10^9/L$ with normal total leukocyte count of $5.82 \times 10^9/L$. Peripheral blood film did not show any atypical cells, and a subsequent bone marrow biopsy was also normal. She was receiving anti-tubercular therapy (ATT) namely rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) for the past 2 weeks for tubercular pleural effusion. Her platelet count was $228 \times 10^9/L$ at the time of diagnosis of tuberculosis and before starting ATT. She had no other comorbidities. She did not have coagulopathy and antinuclear antibody & indirect Coomb test were negative. She was tested negative for hepatitis B, hepatitis C, and human immunodeficiency virus serology. Serum Vitamin B12 and folic acid levels and ultrasonography of the abdomen were also normal.

A possibility of drug-induced thrombocytopenia (DIT) was kept, and all the four anti-tubercular drugs were stopped. However, platelet counts did not improve even after giving transfusion of multiple random donor platelets and single-donor apheresis platelets, rather her platelet count decreased further up to $5 \times 10^9/L$. A possibility of immune-mediated peripheral destruction of platelet was kept, and she was given oral prednisolone ($1 \text{ mg/kg/day}$) and the platelet count improved to $100 \times 10^9/L$. After 7 days of steroid induction with resolution of the bleeding manifestation. A diagnosis of ATT-induced immune-mediated thrombocytopenia (DIT) was made, and all the four anti-tubercular drugs were stopped. Her platelet count was $325 \times 10^9/L$ on ATT 7 days after stopping steroid, and she did not have any further recurrence of thrombocytopenia.

Tuberculosis remains a difficult-to-treat disease due to various side effects of ATT. As ATT is taken for a longer period of time, regular and prolonged monitoring is required for various side effects such as drug-induced liver injury, thrombocytopenia, peripheral neuropathy, and optic nerve damage. Thrombocytopenia has been reported with all the first-line ATT drugs, mainly isoniazid, rifampicin, pyrazinamide, and ethambutol. It is infrequent but can be a potentially detrimental side effect.

DIT is yet underrecognized and challenging to diagnose entity. Two main mechanisms of DIT are non-immune and immune mediated. Non-immune mediated DIT is usually predictable and anticipated like chemotherapy-induced myelosuppression, dose and duration dependent like linezolid, and may also interfere with the release of megakaryocyte like bortezomib. Immune-mediated DIT is mostly of rapid onset, is unpredictable, and is dose and duration independent. Various proposed mechanisms for DIT are hapten-dependent, drug-glycoprotein complex related, drug-specific, immune-complex mediated antibody formation, autoantibody formation and ligand-induced binding site creation. New platelet formation may also be suppressed by antiplatelet antibodies by immune-mediated mechanism. Platelets get attacked more commonly than neutrophils or red blood cells by drug-dependent antibodies for unspecified reasons.

George et al. proposed criteria for DIT for defining association between drug and thrombocytopenia. Four criteria are: (i) the suspected drug must precede thrombocytopenia with complete and sustained recovery of the thrombocytopenia after withdrawal of the suspected drug, (ii) the suspected drug should be the only drug used prior to the onset of thrombocytopenia and/or other drugs are continued or reintroduced after discontinuing the suspected drug with a persistent normal platelet count, (iii) possible alternative etiologies for the thrombocytopenia are excluded, and (iv) recurrence of thrombocytopenia after reintroduction to the suspected drug. When all the four criteria are met, the level of evidence is definite. It is probable, when the first three criteria are met; it is possible, when only the first criterion is met; and when even the first criterion is not met, it is unlikely that the suspected drug is responsible for the thrombocytopenia. Rifampicin, isoniazid, pyrazinamide, and ethambutol all are known to cause DIT, and rifampicin is the leading cause among them. Laboratory detection of drug-dependent antibodies can be invaluable. However, various issues hindering the development include absence of standardization and lack of validation across a variety of drugs with inaccessibility at all main laboratories. The mainstay of treatment is stopping the offending medication. Various therapies used in life-threatening bleeding include intravenous immunoglobulin therapy, plasmapheresis, or platelet transfusions. Corticosteroids have been found to

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be ineffective in the treatment of DIT.[8] However, corticosteroids can be lifesaving in patients with severe DIT where immune-mediated mechanism is suspected, like in our case. With this article, we would like to stress upon that though withdrawal of the offending drug is the first-line management for DIT, immune-mediated DIT should be suspected when there is no improvement of platelet count even after platelet transfusion and withdrawal of the offending drug, and management with corticosteroids may be beneficial in this case.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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