Sulfasalazine induced immune thrombocytopenia in a patient with rheumatoid arthritis

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Abstract Sulfasalazine has long been used for the treatment of rheumatoid arthritis and is often chosen as a first-line treatment. Here, we report a case of sulfasalazine-induced autoimmune thrombocytopenia and review the mechanisms behind drug-induced immune thrombocytopenia (DITP) and the approach to its diagnosis and management.

Keywords Rheumatoid arthritis (RA) · Rheumatic diseases · Thrombocytopenia · Autoantibodies · Tissues or models · Hematologic diseases · Blood platelets disorders

Sulfasalazine (SSZ) has been used for the treatment of rheumatoid arthritis (RA) for decades. Given its safety profile (especially lack of teratogenicity), ease of administration and cost, it is often used as first line treatment. Myelosuppression is a recognized side effect of sulfasalazine, as is the development of drug induced-Systemic Lupus Erythematosus (SLE) or SLE-like disease [1], which may also result in blood dyscrasias. Here, we report a case of sulfasalazine induced autoimmune thrombocytopenia, which rapidly settled on stopping the drug, highlighting the importance of considering this rare complication of sulfasalazine therapy. We also review the mechanisms behind drug induced immune thrombocytopenia (DITP) and the approach to its diagnosis and management.

Our patient, a 67 year old Caucasian man, presented with symmetrical synovitis of knees, shoulders, and small joints of the hands. A diagnosis of seronegative RA was made. ANA was negative at time of diagnosis. He was commenced on sulfasalazine, with remission of arthritis 4 months later. His other medication consisted of diclofenac 50 mg, which he took up to twice a day, as needed. Two years after diagnosis, at a routine follow up, it was noted that his platelet count had been steadily declining for 3 months, from an average count of $230 \times 10^9/L$ to $90 \times 10^9/L$. The patient himself was well, without rash, symptoms of bleeding, or history of recent illness and his RA remained in remission. Medication was unchanged. Examination was unremarkable; the patient was afebrile, with no evidence of purpura, or bleeding, and no lymphadenopathy or hepatosplenomegaly.

Repeat platelet count was $87 \times 10^9/L$. Rest of the full blood count, peripheral blood film, and INR (international normalized ratio) were unremarkable. Sulfasalazine was stopped, and the patient continued to take diclofenac as needed.

Immunology testing demonstrated negative ANA, but direct anti-platelet IgM and IgG were positive, consistent with autoimmune thrombocytopenia.

Two weeks after SSZ was stopped, the platelet count had increased to $150 \times 10^9/L$. Three months later, platelet count was steady at $200 \times 10^9/L$, and Anti-platelet IgM was negative. The patient’s arthritis remained in remission, and no further DMARDs were initiated.

Only one case report exists that describes an association of sulfasalazine with autoimmune thrombocytopenia, although that case was also associated with positivity to lupus anticoagulant. [2] Although NSAIDs are a reported cause of thrombocytopenia, in our case, this is extremely unlikely to be the causative drug, since diclofenac was continued while sulfasalazine was ceased, and platelet count still normalized.

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Thrombocytopenia is defined as a platelet count of below 150 × 10^9/L. Prediction of bleeding risk by platelet count is unreliable [3], but generally, platelet counts above 50 × 10^9/L usually do not lead to bleeding, unless platelet dysfunction is also present. At platelet counts of less than 30 × 10^9/L, spontaneous bleeding and purpura may occur, with clinically significant bleeding occurring when count is under 10 × 10^9/L [4]. Thrombocytosis may also be associated with a low platelet count, particularly in heparin-induced thrombocytopenia.

Drug-induced immune thrombocytopenia (DITP) is a rare cause of immune thrombocytopenia, with an estimated incidence of ten cases per million per year [5], and is most common in critically unwell, hospitalized patients. DITP has been reported to occur via at least six different mechanisms [6, 7] (see Table 1).

Testing for specific antibodies for DITP, such drug dependent antibodies can be complex and time consuming, and is available only in a few laboratories. Therefore, a set of clinical criteria have been proposed as a more practical way of establishing the presence of drug-induced ITP based on systematic review of existing literature [8] (see Table 2).

The management of a patient with suspected thrombocytopenia is aimed at establishing the cause, and assessing and treating those with, or at risk of, clinically significant bleeding. History taking includes questioning for evidence of bleeding, constitutional symptoms such as fevers, sweats, weight loss, which may indicate an underlying neoplastic or infective cause for low platelets, and a drug history to look for pre-disposing medications. Examination should look for purpura and other signs of bleeding, as well as hepatosplenomegaly and lymphadenopathy to look for evidence of myelodysplasia.

Initial investigations should include a full blood count, to rule out leukopenia and anaemia. A peripheral blood film is essential, to assess for falsely low platelet count secondary to platelet clumping. Clotting tests such as INR are useful, to assess bleeding risk further, and viral screen for HIV and Hepatitis C should be considered [4].

Management of DITP is to stop the precipitating drug. For those with a platelet count of above 10 × 10^9/L without bleeding, or other risk factors for bleeding, monitoring of the platelet count may be all that is required, with rapid recovery of platelet count within days to weeks as drug is cleared. For those with platelets of less than 10 × 10^9/L, and/or with bleeding, or risk factors for bleeding, such as sepsis, or other blood abnormalities, platelet transfusion is considered [9]. Use of corticosteroids, intravenous immunoglobulins, and plasma exchange, has also been described, but the benefit of these is uncertain [6].

### Compliance with ethical standards

Disclosures None.
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References

1. Gunnarsson I, Kanerud L, Pettersson E, Lundberg I, Lindblad S, Ringertz B (1997) Predisposing factors in sulphasalazine-induced systemic lupus erythematosus. Rheumatology 36:1089–1094
2. Cantarini L, Tinazzi I, Biasi D, Fioravanti A, Galeazzi M (2007) Sulfasalazine-induced immune thrombocytopenia. Postgraduate. Med J 83:e1
3. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B (2000) The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med 160:1630–1638
4. Izak M, Bussel JB (2014) Management of thrombocytopenia. F1000Prime Rep 6:45
5. Aster RH, Bougie DW (2007) Drug-induced immune thrombocytopenia. N Engl J Med 357:580–587
6. Aster RH, Curtis BR, McFarland JG, Bougie DW (2009) Drug-induced immune thrombocytopenia: pathogenesis, diagnosis and management. J Thromb Haemost 7:911–918
7. Curtis BR (2014) Drug-induced immune thrombocytopenia: incidence, clinical features, laboratory testing and pathogenic mechanisms. Immunohematology 30:55–65
8. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, Vondracek T (1998) Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 129:886–890
9. British Committee for Standards in Haematology, Blood Transfusion Task Force (2003) Guidelines for the use of platelet transfusions. Br J Haematol 122:10–23