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Boiten, H.J.; Amini, S.; Wolfhagen, F.H.J.; Westerweel, P.E.

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SHORT REPORT

Adalimumab-induced platelet antibodies resulting in severe thrombocytopenia

Henk-Jan Boiten[1] | Sufia Amini[2] | Frank H. J. Wolfhagen[3] | Peter E. Westerweel[1]

[1]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands

[2]Department of Internal Medicine, Haga Hospital, The Hague, The Netherlands

[3]Department of Gastroenterology and Hepatology, Albert Schweitzer Hospital, Dordrecht, The Netherlands

Correspondence
Henk-Jan Boiten, MD PhD, Albert Schweitzer Hospital, Department of Internal Medicine, Albert Schweitzerplaats 25, 3318 AT, Dordrecht, The Netherlands.
Email: henkjan_boiten@hotmail.com

Anti-tumour necrosis factor-α (TNFα) agents are effective in diseases including Crohn's disease but may cause cytopenias. The mechanisms involved in anti-TNFα agent-induced thrombocytopenia are scarce. We report a 73-year-old male with Crohn's disease for which he currently used adalimumab, an anti-TNFα agent. He had received mesalazine and infliximab before the treatment of adalimumab. No comorbidities were present. Routine laboratory tests revealed a deep thrombocytopenia (thrombocytes 24 × 10^9/L), after which adalimumab was discontinued. Bleeding symptoms included cutaneous haematomas and mild epistaxis. Direct monoclonal antibody-specific immobilization of platelet antigens revealed autoantibodies specific to glycoprotein IIb/IIIa and glycoprotein V platelet receptors. There was no bone marrow suppression. Other causes of the thrombocytopenia were ruled out. The platelet count normalized after adalimumab discontinuation. No further interventions were required. Monitoring thrombocyte levels after initiating anti-TNFα agents is recommended, which could lead to prevention of this potentially fatal phenomenon.

KEYWORDS
adalimumab, antibodies, immune thrombocytopenia, platelets

1 | INTRODUCTION

Anti-tumour necrosis factor-α (**TNFα**) agents are effective in the treatment of Crohn's disease (CD) and ulcerative colitis but may cause adverse effects including cytopenias.[1] Anti-TNFα-induced thrombocytopenia, although not common, is a recognized side effect. However, the exact mechanisms involved in anti-TNFα thrombocytopenia are unknown. We therefore present a case of **adalimumab** (anti-TNFα agent)-induced immune thrombocytopenia in a patient with CD in whom we were able to demonstrate drug-induced platelet antibodies. Moreover, we discuss the proposed mechanisms involved.

2 | METHODS

A 73-year-old male was diagnosed with CD in 2016. Colonoscopy at that time revealed a mild chronic inflammation of his sigmoid for which he was initially treated with **mesalazine**. No comorbidities were present. Infliximab was started 1 year later but, after 14 weeks of treatment, the patient developed polyarthralgia, myalgia and weight loss after which the **infliximab** was stopped. Analysis revealed a lupus-like disease with positive antinuclear antibodies and anti-double-stranded DNA, although these antibodies were also detectable prior to infliximab treatment. Seven months later, a colonoscopy showed significant chronic, active colitis of the distal sigmoid with ulcerations. Due to the formation of antibodies against infliximab, adalimumab was started. Adalimumab treatment was started with 160 mg subcutaneously at week 0, followed by 80 mg at week 1 and was then maintained on 40 mg every 2 weeks. His polyarthralgia and myalgia resolved and his weight stabilized. As part of monitoring the therapy laboratory tests were performed 4 weeks after treatment with adalimumab (after 3 injections). These tests revealed a deep thrombocytopenia (thrombocytes 24 × 10^9/l) after which adalimumab was discontinued. His only other medication at this time was

The authors confirm that the Principal Investigator for this paper is P.E.W. and that he had direct clinical responsibility for patients.

mesalazine, which had been used for several years during which thrombocyte levels had remained stable. Bleeding symptoms included cutaneous haematomas and mild epistaxis. There were no bleeding symptoms requiring immediate intervention. He denied any drug and alcohol abuse. Physical examination revealed no fever, hepatosplenomegaly or lymphadenopathy.

Besides the thrombocytopenia, the complete blood count showed a mild and stable normocytic anaemia (haemoglobin 13.05 g/dL, normal 13.5–17.5) with unremarkable leucocyte count and differentiation, and low C-reactive protein. Thrombocyte counts in citrate anticoagulated blood excluded EDTA-induced pseudo thrombocytopenia. Levels of folic acid, vitamin B12, iron, liver enzymes and renal function were all within normal ranges. Protein electrophoresis showed no monoclonal protein. Peripheral blood smear revealed rouleaux formation and macrothrombocytes. A bone marrow aspirate and biopsy showed hypercellularity with an increased number of megakaryocytes with normal morphology, consistent with intact megakaryopoiesis. Erythropoiesis and myelopoiesis were unremarkable. Direct monoclonal antibody-specific immobilization of platelet antigens revealed autoantibodies specific to glycoprotein IIb/IIIa (GPIIb/IIIa) and glycoprotein V (GPV) platelet receptors. The thrombopoietin level was normal (10 units/mL, normal 4–32).

Platelet count improved 6 days after cessation of adalimumab (platelet count 71 × 10^9/L) without further intervention and increased to 139 × 10^9/L in 2 weeks. A fully normalized platelet count (platelet count 203 × 10^9/L) was observed 4 weeks after the last dose of adalimumab. Therapy for CD was continued with methotrexate combined with mesalazine. There has been no recurrence of the thrombocytopenia during further treatment. His CD remained in clinical remission during treatment with methotrexate. The patient gave informed consent for publication.

3 | DISCUSSION

Anti-TNFα-induced thrombocytopenia has been reported previously in patients with rheumatoid arthritis,[2] psoriasis[3,4] and CD.[5–7] Patients were treated with both **etanercept** and infliximab,[2] infliximab monotherapy[5] or adalimumab monotherapy.[3,4,6,7] Of note, most of these reports have not reported on the presence of specific autoantibodies against platelets. Furthermore, only 2 of the aforementioned reports involved patients with CD who developed thrombocytopenia associated with exposure to adalimumab.[6,7] Salar et al.[7] described a patient with CD who received both infliximab and adalimumab. A thrombocytopenia of 44 × 10^9/L occurred with platelet-associated IgG detected with a (undefined) platelet antibody test. More recently, Casanova et al.[6] reported a patient with CD who developed severe thrombocytopenia of 25 × 10^9/L after rechallenge treatment with adalimumab. Tests for the presence of antibodies were not performed. In accordance with the 2 patients with CD,[6,7] our patient showed an increased number of megakaryocytes in the bone marrow supporting an immune thrombocytopenia (ITP)-related mechanism. Although an ITP-related mechanism has been speculated on in other reports, our report with confirmed GPIIb/IIIa and GV platelet autoantibodies provides conclusive evidence for this notion.

What is already known about this subject

- Anti-tumour necrosis factor-α agents may cause adverse effects including cytopenias. The mechanisms involved in anti-tumour necrosis factor-α agent-induced thrombocytopenia are scarce.

What this study adds

- This study explores the mechanism involved in adalimumab-induced platelet antibodies leading to severe thrombocytopenia which could lead to a better recognition of this potentially fatal phenomenon.

Our patient developed thrombocytopenia after 3 weeks of treatment. In other reports, the time between the first exposure of the anti-TNFα agent varied and extended up to >2 years. Some reports[3,6,7] showed an asymptomatic thrombocytopenia detected by routine blood samples, while other cases presented with bleeding symptoms.[1]

Drug-induced thrombocytopenia can be classified into non-immune and immune-mediated thrombocytopenia. Drug-induced ITP can be categorized into several mechanisms including the formation of drug-specific antibodies or drug-dependent antibodies (e.g. quinine) and production of autoantibodies specific to platelets (e.g. gold).[8]

The exact pathophysiological mechanism of adalimumab-induced ITP is not known. A possible explanation, analogous to Aster et al.,[8] is that adalimumab interacts with the platelets membrane GPIIb/IIIa and GPV through bridging interactions resulting in removal from the immune system. Another possible mechanism is that binding of adalimumab to the platelets membrane can cause a conformational change of the GPIIb/IIIa and GPV resulting in a neo-epitope which stimulates the formation of antibodies against platelets. Finally, previous reports hypothesized that anti-TNFα agents could induce apoptosis of Th1 lymphocytes leading to a relative excess of Th2 lymphocytes that could in turn lead to the production of antibodies.[6,7]

This report adds to a general understanding of drug-induced thrombocytopenia induced by adalimumab, which could lead to a better recognition of this potentially fatal phenomenon. Adalimumab-induced ITP is rare and is reversible upon adalimumab discontinuation. We report antibodies against multiple epitopes including GPIIb/IIIa and GPV without bone marrow suppression. monoclonal antibody-specific immobilization of platelet antigens testing, if available, can be used to determine the platelet glycoprotein target(s). To prevent serious adverse events, we recommend monitoring thrombocyte levels

closely after initiation of anti-TNFα therapy. Although specific studies are lacking for drug-induced ITP, standard ITP treatment with intravenous immunoglobulins and/or steroids may be considered if interventions are clinically warranted.

3.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

COMPETING INTERESTS

All authors state that they have no conflict of interest.

CONTRIBUTORS

HJB and SA collected the data, performed the analysis and wrote the paper. FHJW and PEW revised the manuscript and gave important intellectual content. All authors approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Henk-Jan Boiten https://orcid.org/0000-0002-6381-9908
Sufia Amini https://orcid.org/0000-0001-9414-0044
Frank H. J. Wolfhagen https://orcid.org/0000-0002-5308-1735
Peter E. Westerweel https://orcid.org/0000-0002-0746-7039

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