Adalimumab-induced platelet antibodies resulting in severe thrombocytopenia

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Abstract

Anti-tumor necrosis factor alpha (TNFα) agents are effective in diseases including Crohn's disease (CD) but may cause cytopenias. The mechanisms involved in anti-TNFα agents 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 24x10*9/L) after which adalimumab was discontinued. Bleeding symptoms included cutaneous hematomas and mild epistaxis. Direct monoclonal antibody-specific immobilization of platelet antigens (MAIPA assay) revealed autoantibodies specific to glycoprotein IIb/IIIa (GPIIb/IIIa) and glycoprotein V (GPV) 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 potential fatal phenomenon.

Introduction

Anti-tumor necrosis factor alpha (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.

Methods

Adalimumab, a human anti-TNF monoclonal antibody, is effective for inducing and maintaining remission in patients with Crohn disease who are naive to infliximab (8–10).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 one 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 (ANA) and anti-double-stranded DNA (anti-dsDNA), 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 160mg subcutaneously at week 0, followed by 80mg at week 1 and was then maintained on 40mg every 2 weeks. His polyarthralgia and myalgia resolved and his weight stabilized. After three injections of adalimumab, routine laboratory tests revealed a deep thrombocytopenia (thrombocytes $24x10^9$/l) after which adalimumab was discontinued. His other medication at this time was

mesalazine only. Bleeding symptoms included cutaneous hematomas**hematomas hematomas** 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 anemia (hemoglobin 13.05 g/dL [normal 13.5-17.5] with unremarkable leukocyte 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 (MAIPA assay) revealed autoantibodies specific to glycoprotein IIb/IIIa (GPIIb/IIIa) and glycoprotein V (GPV) platelet receptors. The thrombopoietin level was normal (10 E/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 two 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.

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 two of the aforementioned reports involved patients with CD who developed thrombocytopenia associated with exposure to adalimumab (6,7). Salar et al. (7) describe 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 two patients with CD (6,7) our patient showed an increased number of megakaryocytes in the bone marrow supporting an 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.

Our patient developed thrombocytopenia after three 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 nonimmune and immune-mediated thrombocytopenia. Drug-induced immune-thrombocytopenia (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 potential fatal phenomenon. Adalimumab-induced immune-thrombocytopenia is a rare cause of thrombocytopenia reversible upon adalimumab discontinuation. We report antibodies against multiple epitopes including GPIIb/IIIa and GPV without bone marrow suppression. MAIPA assay testing, if available, can be used to determine the platelet glycoprotein target(s). In order to prevent serious adverse events we recommend to monitor 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.

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