Adalimumab-induced immune thrombocytopenia: A case report and literature review.

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Abstract

Background: Adalimumab, an anti-Tumor Necrosis Factor-α (TNFα) agent, is effective in managing Inflammatory Bowel Diseases (IBD) such as Crohn's Disease (CD) and Ulcerative Colitis (UC). While generally well-tolerated, rare complications such as anti-TNFα-induced thrombocytopenia have been reported.

Case presentation: Hereby, we report a case of a 19-year-old female with pancolonic UC treated initially with oral corticosteroids and subsequently escalating to Adalimumab due to persistent disease activity. Unexpectedly, severe immune thrombocytopenia developed after the third injection of Adalimumab, necessitating treatment cessation. Extensive investigations ruled out alternative causes, confirming Adalimumab-induced immune thrombocytopenia. Despite a challenging clinical course with severe thrombocytopenia and transfusion dependence, oral corticosteroid therapy led to a gradual improvement in platelet counts.

Conclusion: The presented case underscores the importance of vigilance for hematological abnormalities during anti-TNFα therapy, and contributes to the limited literature on Adalimumab-associated thrombocytopenia, emphasizing the need for further research to elucidate mechanisms and risk factors for this rare adverse effect.

Keywords: Adalimumab, Anti-TNFα, Ulcerative colitis, Induced immune thrombocytopenia.

Abbreviations:

TNFα: Tumor Necrosis Factor-α; CD: Crohn's Disease; UC: Ulcerative Colitis; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; CMV: Cytomegalovirus; EBV: Epstein-Barr Virus; HSV: Herpes Simplex Virus; VZV: Varicella-Zoster Virus; ANA: Antinuclear Antibodies; DIT: Drug-Induced Thrombocytopenia; ITP: Immune Thrombocytopenia; IVIG: Intravenous Immunoglobulin; RTX: Rituximab; rh-TPO: recombinant human Thrombopoietin; MMF: Mycophenolatemofetil

Introduction

Adalimumab is an anti-Tumor Necrosis Factor-α (TNFα) agent that proved its effectiveness in managing Inflammatory Bowel Diseases (IBD) notably Crohn's Disease (CD) and Ulcerative Colitis (UC). While generally well-tolerated, these agents carry the risk of adverse effects. Anti-TNFα-induced thrombocytopenia is a very rare complication that has only been reported in few individual cases [1]. We hereby present a case of Adalimumab induced thrombocytopenia in a patient with UC. Our ability to demonstrate drug-induced platelet antibodies in this case prompts a discussion on the proposed mechanisms underlying anti-TNFα-induced thrombocytopenia.

Case Presentation

We report the case of a 19-year-old female patient with a history of anemia since 2021, who has been diagnosed with pancolonic Ulcerative Colitis (UC) in October 2022. Her disease was initiated by a moderate flare, treated with oral corticosteroid therapy at a dose of 0.6 mg/kg/day. One month into oral corticosteroid therapy, there was no improvement noted. An ileocolonoscopy revealed persistent endoscopic lesions consistent with a moderately active UC extending to the ascending colon with a normal ileum. Thus, intravenous corticosteroid therapy was initiated, followed by oral therapy on day 7, resulting in clinical and biological remission after one month of oral corticosteroid therapy [2]. Maintenance therapy with Mesalazine was started at the dose of 25 mg/day of oral corticosteroid.

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After 3 months of mesalazine treatment, she continued having non-bloody diarrhea four times a day. Fecal calprotectin was >1000 µg/g. A follow-up colonoscopy revealed mild UC flare with UCEIS score of 2. Consequently, the Mesalazine dose was increased to 4 g/day. Fecal calprotectin persisted at >1000 µg/g 4 months later.

Considering the patient's young age, a decision was made to escalate therapy with a top-down strategy. Monotherapy with Adalimumab was initiated after a negative pre-therapeutic assessment. She received 160 mg subcutaneously at week 0, 80 mg at week 2 and 40 mg at week 4. At the third Adalimumab injection, the blood test showed severe thrombocytopenia at 27 × 10^3/µl, which persisted at the fourth injection. The treatment was then discontinued. Etiological investigation revealed normal abdominal ultrasound, negative serology for Hepatitis B (HBV) and C (HCV), as well as Human Immunodeficiency Virus (HIV). Serology for Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), and Varicella-Zoster Virus (VZV) were indicative of past immunity. Antinuclear Antibodies (ANA) were negative. Sternal puncture revealed a normal bone marrow, suggesting peripheral thrombocytopenia.

The patient's condition worsened, with platelet counts dropping to 6 × 10^3/µl, requiring repeated platelets transfusions despite a 5-week treatment interruption. A collaborative decision with hematologists and pharmacovigilance specialists ruled out the direct toxic mechanism of Adalimumab in causing thrombocytopenia. An autoimmune phenomenon triggered by this medication was suspected [3,4]. Oral corticosteroid therapy at 1 mg/kg/day was initiated and led to a gradual improvement in platelet count, reaching 75 × 10^3/µl on the third day of treatment, normalizing at 195 × 10^3/µl on day 7, and 253 × 10^3/µl on day 12, confirming the diagnosis of Adalimumab-induced immune thrombocytopenia.

Fecal calprotectin measured on day 15 of corticosteroid therapy was 200 µg/g. Corticosteroid tapering was then initiated. As a maintenance treatment, we decided to put the patient on Azathioprine with good clinical and biological tolerance.

Results and Discussion

Drug-Induced Thrombocytopenia (DIT) is a significant adverse reaction linked to the administration of various medications. Studies suggest that around 25% of critically ill patients face an elevated risk of developing DIT, and the global incidence is estimated to reach up to 10 cases per million people annually.

A case report and a literature review by Al-Tkrit et al., declares that severe thrombocytopenia, defined by a platelet count below 50,000/mm^3, is exceptionally linked to the use of anti-TNF-alpha agents, with most available literature being confined to case reports. Comparative analyses indicate that Adalimumab, in contrast to infliximab, is less frequently associated with thrombocytopenia. Clinical trial data collected by the manufacturer revealed an incidence of thrombocytopenia (platelet count<100,000/mm^3) at approximately 0.1% for adalimumab, while the incidence ranged between 0.5% and 1.9% for infliximab [5].

DIT can be categorized into non-immune and immune-mediated thrombocytopenia. In the case of Immune Thrombocytopenia (ITP) induced by drugs, various mechanisms come into play. This includes the development of drug-specific antibodies or drug-dependent antibodies. Additionally, autoantibodies specific to platelets may be produced [6]. The exact mechanism responsible for adalimumab-induced ITP remains unknown. One plausible explanation, Aster et al., suggest that adalimumab may interact with the platelet membrane GPIIb/IIIa and GPV through bridging interactions, leading to their removal from the immune system. Another potential mechanism involves the binding of adalimumab to the platelet membrane, causing a conformational change in GPIIb/IIIa and GPV, resulting in a neo-epitope. This neo-epitope could then stimulate the formation of antibodies against platelets [7]. Lastly, some prior reports have hypothesized that anti-TNFα agents, including adalimumab, might induce apoptosis of Th1 lymphocytes, creating a relative excess of Th2 lymphocytes. This shift in lymphocyte balance could potentially lead to the production of antibodies.

In a review, Liao et al., summarized findings from 13 publications including 20 reported cases of thrombocytopenia induced by anti-TNF-α drugs. The onset of thrombocytopenia occurred within a range of 4 days to 29 months after exposure to the drug, with varying recovery times spanning from 6 days to 32 weeks. Notably, platelet levels normalized in 9 out of the 20 patients upon discontinuation of the implicated drug. Among the remaining 11 patients, alternative treatments were administered, including glucocorticoids in 10 cases, Intravenous Immunoglobulin (IVIG) in 4 cases, double filtration plasmapheresis in 1 case, Rituximab (RTX) in 1 case, and recombinant human Thrombopoietin (rh-TPO) in 1 case. Strikingly, seven patients were re-exposed to anti-TNF-α drugs after their platelet counts returned to normal. However, a second decline in platelet levels was observed in four of them. Immunological assessments were conducted in eight individuals, revealing that six of them tested positive for antinuclear antibodies, and four were positive for antiplatelet antibodies [8]. Furthermore, six patients experienced additional adverse effects, including four cases of granulocytopenia, and one case each of erythema multiforme exudativum and pneumonia. This collective evidence underscores the complexity of the clinical course and diverse manifestations associated with anti-TNF-α drug-induced thrombocytopenia.

Thrombocytopenia can manifest with diverse clinical symptoms, ranging from asymptomatic cases to presentations involving petechial hemorrhages, purpura, ecchymosis, buccal mucosa bleeding, or severe hemorrhaging, with the latter occurring most commonly when platelet counts fall below 20,000/mm^3. Thrombocytopenia induced by anti-TNF-alpha agents exhibits variable onset times, ranging from less than a day up to three years after medication initiation. Clinical improvement often follows drug cessation, with re-exposure linked to relapses.

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Management of DIT depends on severity and symptom occurrence. Mild-to-moderate cases (platelet count>50,000/mm^3) may require only discontinuation of the causative agent with clinical and laboratory monitoring. For platelet counts below 50,000/mm^3, especially with clinical manifestations, additional treatment may be necessary. Corticosteroids are the first-line treatment. Platelet transfusion is generally discouraged due to ongoing immune-mediated platelet destruction in the drug's presence. However, post-drug discontinuation, it might be considered if platelet counts are below 20,000/mm^3 with severe bleeding [9]. In cases requiring rapid platelet increment or unresponsive to corticosteroids, IVIG can be employed, and reports suggest potential use of Rituximab (RTX) and Mycophenolatemofetil (MMF) (Table 1).

Table 1. *Evolution of platelet count following discontinuation of adalimumab and initiation of corticosteroid therapy.*

Time point	Clinical intervention	Platelet count (× 10^3/µL)	Interpretation
Before/around 3rd adalimumab injection	Adalimumab continued	27	Severe thrombocytopenia
After treatment discontinuation	Adalimumab stopped	6	Further platelet decline
Day 3 of corticosteroid therapy	Prednisolone 1 mg/kg/day	75	Early response
Day 7	Continued corticosteroid therapy	195	Platelet normalization
Day 12	Corticosteroid taper initiated	253	Complete hematological recovery

Conclusion

Adalimumab-induced immune thrombocytopenia is an exceedingly rare complication in the treatment of IBD. The presented case underscores the importance of vigilance for hematological side effects during anti-TNFα therapy, particularly in young patients. Diagnosis can be challenging due to variable onset times, necessitating a comprehensive evaluation to exclude alternative etiologies. While discontinuation of Adalimumab typically results in platelet recovery, severe cases may require additional interventions such as steroids, intravenous immunoglobulin, and platelet transfusions. This case contributes to the limited literature on Adalimumab-associated thrombocytopenia, emphasizing the need for further research to elucidate mechanisms and risk factors for this rare adverse effect.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

Availability of Data and Materials

Data and materials are available.

Competing Interests

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Authors' Contributions

HS and MM drafted the manuscript. LC and AA participated in the design of the manuscript. MM and LM performed the bibliographic research. AA and HG conceived the study. NT participated in coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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