Pereira et al. Int J Blood Res Disord 2016, 3:020
Volume 3 | Issue 1
ISSN: 2469-5696

International Journal of
Blood Research and Disorders

Case Report: Open Access

Chronic Use of Adalimumab as Potential Cause of Severe Thrombocytopenia in Psoriatic Arthritis Patient: The Need for Regular Monitoring of Cytopenias

*Viviane Chaves Pereira, Karoline Honorato Costa and Leonardo Rodrigues de Oliveira**

Internal Medicine Department, Triangulo Mineiro Federal University, Uberaba, MG, Brazil

***Corresponding author:** *Leonardo Rodrigues de Oliveira, Internal Medicine Department, Triangulo Mineiro Federal University, Getúlio Guarita, snº 38025-440 Uberaba, MG, Brazil, Tel: +55-34-33185158, E-mail: leonardorodoli@hotmail.com*

Abstract

Anti-tumor necrosis factor alpha (anti-TNFα) agents are used to treat inflammatory diseases with recognized safety and efficacy. Although they are rare, severe hematologic adverse effects are described and may be fatal. The current study describes the case of a patient presenting psoriatic arthritis, and under prolonged treatment with adalimumab. His condition worsened due to severe acute thrombocytopenia and severe hemorrhagic manifestations. Adalimumab was considered to be the probable cause of the thrombocytopenia and, therefore, its use was discontinued. The treatment consisted of corticosteroids, human immunoglobulin, rituximab and transfusion support. The regular monitoring of cytopenias in patients using anti-TNFα agents may be a safe measure for the early detection of severe hematologic adverse events. It is worth conducting additional studies to better characterize the interaction between anti-TNFα agents and the hematopoietic and immune systems.

Keywords

Thrombocytopenia, Adalimumab, Arthritis, Psoriatic, Tumor necrosis factor-alpha

Introduction

Anti-tumor necrosis factor alpha (anti-TNFα) agents are increasingly used to treat intestinal, skin and rheumatic inflammatory diseases with proven efficacy and safety [1]. Hematologic adverse events are described as potentially fatal when they are severe or belatedly detected [1].

The current study presents the evolution of a patient presenting acute and severe thrombocytopenia, which was probably induced by adalimumab using criteria for drug-induced thrombocytopenia described by George *et al.* [2]. The medication use was discontinued and after the patient was treated with corticosteroids, human intravenous immunoglobulin (IVIG) and rituximab he presented platelet count recovery.

Case Report

The current study reports the case of a 58-year-old male patient with psoriatic arthritis (mutilating form) for ten years and subjected to prior treatment with corticosteroids and anti-inflammatory medication. After a short period using infliximab (5 mg/Kg, intravenously administered on weeks 0, 2 and 6; interruption after third dose due to dyspnea and urticarial skin rash), he was subjected to treatment with prolonged use of adalimumab (40 mg, subcutaneously administered, every two weeks), and presented satisfactory rheumatologic control. Comorbidities included hypertension, type 2 diabetes mellitus and morbid obesity (120 Kg; 1.73 m; body mass index 40.1 Kg/m^2), which were treated with regular use of losartan (50 mg twice a day), hydrochlorothiazide (25 mg once a day), amlodipine (10 mg once a day), glibenclamide (5 mg twice a day) and metformin (850 mg twice a day).

After 24 months of regular adalimumab use, the patient sought assistance for a recent hematochezia onset. Diffusely distributed petechiae as well as chronic deformities in the joints of the hands and feet were observed during the physical examination. Vital signs were stable: body temperature of 36.8ºC, blood pressure of 132/78 mmHg, and pulse rate of 92 bpm. Chest examination revealed no crepitations. No lymphadenopathy or visceromegaly was detected. At the time the patient was admitted, severe thrombocytopenia (1 × 109/L - normal: 150-400 × 109/L) was confirmed, and it was associated with mild anemia (Hb 12 g/dL - normal: 13-17 g/dL) and normal white blood-cell count (8.9 × 109/L, 78% neutrophils and 16% lymphocytes - normal white blood-cell count 4-12 × 109/L). No cytopenia had been found in the blood count performed eight weeks prior to the patient's admission.

Laboratory evaluation was conducted on the assumption of immune thrombocytopenia (ITP). The results showed normal thyroid function and antinuclear antibodies (ANA), rheumatoid factor and serologies non-reactive (HIV, hepatitis B and C, cytomegalovirus). Ferritin, vitamin B12 and folate serum levels were normal and the direct antiglobulin test came out negative. Epstein-Barr virus research and anti-platelet antibodies tests did not performed. Abdominal ultrasound was normal. Megakaryocytic hyperplasia in the hypercellular bone marrow caused by erythroid and granulocytic hyperplasia was documented in the bone marrow aspiration analysis (absence of cancer cells or infectious agents).

ClinMed International Library

Citation: Pereira VC, Costa KH, de Oliveira LR (2016) Chronic Use of Adalimumab as Potential Cause of Severe Thrombocytopenia in Psoriatic Arthritis Patient: The Need for Regular Monitoring of Cytopenias. Int J Blood Res Disord 3:020

Received: March 24, 2016: **Accepted:** May 25, 2016: **Published:** May 28, 2016

After extensive laboratory evaluation, adalimumab was considered to be the potential cause of thrombocytopenia and, therefore, the medication use was discontinued and the other chronic use medications were kept. Treatment consisted of intravenous corticotherapy (methylprednisolone - 1 g/day for three days) followed by oral prednisone (1 mg/kg/day) and platelet transfusion. However, the treatment result showed unfavorable platelet increase, persistent digestive bleeding and hemoglobin decrease (> 2 g/dL). IGIV therapy (1 g/kg on D1 and D3) was then applied and it resulted in satisfactory platelet increment (39 × 109/L) and bleeding control. After four days of IGIV and corticosteroid therapy, the patient showed new platelet count decrease (12 × 109/L). Thus, it was made the option for using intravenous rituximab (100 mg every seven days for four weeks). Platelet transfusions were administered for control of bleeding when platelet count was lower than 10 × 109/L. The patient's condition improved with sustained normalization of platelet count 18 days after the onset of symptoms and eight days after the beginning of the treatment with rituximab, without the reintroduction of adalimumab.

Discussion

Anti-TNFα agents are used in a myriad of inflammatory diseases, especially in rheumatoid arthritis, psoriasis/psoriatic arthritis and crohn's disease [1,3]. Although they are safe and show limited hematological toxicity, several unusual hematologic adverse events were reported in association with these medications, especially thrombocytopenia, neutropenia, pancytopenia, hypercoagulability and aplastic anemia [1,4-8]. Most guidelines about the use of anti-TNFα agents do not recommend the regular monitoring of cytopenias [1].

Thrombocytopenia associated with anti-TNFα agents is considered to be rare, with actual unknown occurrence and it is apparently less frequent in patients treated with adalimumab in comparison to those treated with other anti-TNFα agents [1,6,7]. Brunasso et al. found 5.97% occurrence of platelet counts below 50 × 109/L whereas Chen *et al.* did not report such finding [4,7]. Despite the known role of TNFα in the control of hematopoiesis in association with other cytokines, the exact mechanism of this association remains unknown, fact that leads to some assumptions:

- The production of medication-associated antibodies that bind to platelet glycoproteins and induce platelet destruction; [6,7]
- The formation of immune complexes that bind to the platelet surface with consequent destruction by the activation of the complement system; [6]
- The Th1 lymphocyte apoptosis induction by the relatively increasing Th2 lymphocytes and by stimulating the production of platelet antibodies; [6,7]
- Blocking stem cell differentiation [5,7,9].

Platelet recovery after the discontinuation of these medications and the recurrence of thrombocytopenia upon the re-exposure to them indicate the causal relationship between anti-TNFα agents and thrombocytopenia [2,4]. The mean time between the beginning of the medication use and thrombocytopenia considerably varies and it may extend up to three years [4,10]. Thrombocytopenia intensity may be discreet (with no clinical consequences) or severe (with or without hemorrhagic manifestations). However, thrombocytopenia has been pointed out as an idiosyncratic reaction rather than an event related to the class of anti-TNFα agents [5,7,11].

The management of thrombocytopenia is defined according to its intensity and to the occurrence of hemorrhagic manifestations. Mild-moderate thrombocytopenia (> 50 × 109/L) may be managed by simply discontinuing the medication use and by clinical and laboratory follow-up. On the other hand, the most serious cases of severe thrombocytopenia (< 30-50 × 109/L) may require specific treatment in addition to medication use discontinuity, especially when these cases are associated with bleeding events.

The pharmacological management of adalimumab-related thrombocytopenia resembles ITP treatment, since they are conditions in which the immune mechanism is implicated in the pathophysiology [4]. The first-line treatment consists of using corticosteroids. Severe cases requiring rapid platelet increment or non-responsive corticotherapy cases may be treated with IVIG. There are few case reports describing the use of other medications such as mycophenolate mofetil and rituximab [4].

The probable causal relationship between thrombocytopenia and adalimumab in the current case is supported by the fact that thrombocytopenia was detected after the patient was exposed to adalimumab and that he showed sustained platelet count recovery after the discontinuation of the anti-TNFα agent. In addition, the other medications used by the patient were excluded as cause of thrombocytopenia since their continuity did not affect platelet recovery. Other possible causes of thrombocytopenia were also excluded. In this case, there is no definitive evidence supporting the effective role rituximab plays in the platelet count recovery due to the concomitant use of other medications (corticosteroids and IVIG) and to the short time interval (eight days) from the beginning of rituximab use to platelet recovery.

In conclusion, despite the established safety of the anti-TNFα agents, it is suggested that the regular monitoring of cytopenias should be taken into consideration in patients taking this type of medication. Additional studies should be conducted to allow better understanding the interaction mechanisms between these agents and the hematopoietic and immune systems.

References

1. Bessissow T, Renard M, Hoffman I, Vermeire S, Rutgeerts P, et al. (2012) Review article: non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. Aliment Pharmacol Ther 36: 312-323.
2. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, et al. (1998) Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 129: 886-890.
3. Salar A, Bessa X, Muñiz E, Monfort D, Besses C, et al. (2007) Infliximab and adalimumab-induced thrombocytopenia in a woman with colonic Crohn's disease. Gut 56: 1169-1170.
4. Brunasso AM, Massone C (2009) Thrombocytopenia associated with the use of anti-tumor necrosis factor-alpha agents for psoriasis. J Am Acad Dermatol 60: 781-785.
5. Pathare SK, Heycock C, Hamilton J (2006) TNFalpha blocker-induced thrombocytopenia. Rheumatology (Oxford) 45: 1313-1314.
6. Casanova MJ, Chaparro M, Martínez S, Vicuña I, Gisbert JP (2012) Severe adalimumab-induced thrombocytopenia in a patient with Crohn's disease. J Crohns Colitis 6: 1034-1037.
7. Chen M, Holland MJ, Mir MR, Wong MG, Kelley BP, et al. (2011) Frequency of thrombocytopenia in psoriasis patients treated with tumor necrosis factor-a inhibitors. J Drugs Dermatol 10: 280-284.
8. Kuruvilla J, Leitch HA, Vickars LM, Galbraith PF, Li CH, et al. (2003) Aplastic anemia following administration of a tumor necrosis factor-alpha inhibitor. Eur J Haematol 71: 396-398.
9. Vidal F, Fontova R, Richart C (2003) Severe neutropenia and thrombocytopenia associated with infliximab. Ann Intern Med 139: W-W63.
10. Warkentin TE, Kwon P (2005) Immune thrombocytopenia associated with efalizumab therapy for psoriasis. Ann Intern Med 143: 761-763.
11. Stinco G, Piccirillo F, Patrone P (2008) Transient and slight thrombocytopaenia induced by etanercept during treatment of psoriatic arthritis. Acta Derm Venereol 88: 281-282.