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SHORT REPORT

Severe adalimumab-induced thrombocytopenia in a patient with Crohn's disease

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Abstract

Crohn's disease is a chronic transmural inflammatory disorder characterized by inflammation of the intestine. Anti-TNF-α drugs are used for induction and maintenance of remission in patients with this condition. Thrombocytopenia is an uncommon side effect of treatment with anti-TNF-α drugs. We report the case of a 71-year-old woman diagnosed with Crohn's disease who developed severe adalimumab-induced thrombocytopenia and who did not respond to standard therapy for thrombocytopenia.

1. Introduction

The pathogenesis of Crohn's disease (CD) is not totally understood. The bowel damage is induced by uncontrolled activation of the innate and adaptive immune systems due to an inappropriate response to luminal antigens that leads to an imbalance between pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), and anti-inflammatory mediators, which maintain chronic tissue damage. TNF-α, which is produced by macrophages and activated T cells, plays a key role in inducing further stimulation and recruitment of other inflammatory cells.[1]

Anti-TNF-α drugs are used for induction and maintenance of remission in patients with CD. Immune thrombocytopenic purpura is a rare extraintestinal manifestation of CD that is characterized by platelet destruction due to the presence of antiplatelet autoantibodies.[2,3] The literature contains very few reports of what might be considered a paradoxical effect of treatment with anti-TNF-α agents, namely, thrombocytopenia in patients with inflammatory bowel disease.[4,5] Furthermore, little is known about the pathogenesis of thrombocytopenia or its treatment and outcome.

2. Case report

We report the case of a 71-year-old woman diagnosed with CD in 1978 who developed severe thrombocytopenia while

Abbreviations CD, Crohn's disease; TNF-α, tumor necrosis factor alpha; IBD, inflammatory bowel disease; IVIG, intravenous immunoglobulin G.

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receiving adalimumab. The patient had undergone several operations for bowel stricture, post-operative recurrence, and refractory perianal disease. She was referred to the inflammatory bowel disease unit of our hospital in 2008. At that time, she was receiving azathioprine at 50 mg/day and had active disease. Her dose was increased to 2.5 mg/kg/day, and ileocolonoscopy revealed a new post-operative recurrence two months later (Rutgeerts score, i2). In October 2010 the patient was prescribed adalimumab (160 mg at baseline, 80 mg two weeks later, and then 40 mg every two weeks). In January 2011, her clinical condition had improved, although a routine analysis showed that the platelet count had fallen to 44,000/mm^3. Thrombocytopenia persisted when the analysis was repeated one week later. Abdominal ultrasound was performed to rule out hypersplenic thrombocytopenia resulting from azathioprine-induced nodular regenerative hyperplasia.

The patient was referred to the hematology service. A bone marrow aspirate revealed normal cellular distribution with normal differentiation of all three hematopoietic lineages. Erythrocytes and granulocytes were mature, with no dysplasia. The lymphoid population had a normal appearance, and megakaryocytes were preserved. The immunophenotype showed no abnormalities suggestive of myelodysplastic syndrome. These findings enabled us to rule out central thrombocytopenia (i.e. azathioprine-induced myelotoxicity). Other causes of peripheral thrombocytopenia, such as Evans syndrome or autoimmune disorder, were also ruled out.

A few days later, the patient was admitted to hospital for severe pneumonia and was eventually transferred to the intensive care unit. During admission, treatment with azathioprine and adalimumab was discontinued, and the platelet count recovered to 113.000/mm^3. At discharge, treatment with adalimumab was restarted but we decided to stop azathioprine to avoid the risks associated with double immunosuppression.

Three months after the discharge from the intensive care unit, a routine analysis revealed the platelet count to be 25,000/mm^3, and adalimumab was once again stopped. The patient was diagnosed with adalimumab-induced thrombocytopenia, and intravenous immunoglobulin G (IVIG) was started. She responded to the first IVIG cycle, but her platelet count fell again. Corticosteroids were started with no clear response, and the platelet count remained at 33,000/mm^3. As the patient continued to have active disease after discontinuation of adalimumab, ustekinumab (an interleukin 12/23 inhibitor) was prescribed for compassionate use. CD is currently in remission, the platelet count is 89,000/mm^3, periodic blood tests are performed, and the patient is not receiving any other treatment for thrombocytopenia.

3. Discussion

Thrombocytopenia is an uncommon side effect of anti-TNF-α drugs.[4] We present the case of a woman with CD receiving azathioprine and adalimumab who developed severe thrombocytopenia. Potential causes in this setting include hypersplenism secondary to nodular regenerative hyperplasia, azathioprine-induced myelotoxicity, toxic agents, or drug side effects.

Despite our initial suspicion, abdominal ultrasound allowed us to rule out hypersplenism secondary to nodular regenerative hyperplasia. A bone marrow biopsy service performed in the hematology service ruled out other causes of thrombocytopenia such as azathioprine-induced myelotoxicity. A clear temporal relationship between exposure to adalimumab and onset of thrombocytopenia was established. In addition, the platelet count recovered when the drug was discontinued and fell again after rechallenge. Additional causes of thrombocytopenia were ruled out.

The mechanism by which anti-TNF-α induces thrombocytopenia is unclear. One hypothesis involves induction of apoptosis, especially of Th1 lymphocytes, by anti-TNF-α drugs. This mechanism could leave a relative excess of Th2 lymphocytes that could in turn stimulate antiplatelet antibody production, thus leading to platelet destruction and thrombocytopenia.[6,7] Another hypothesis is that anti-TNF-α drugs lead to formation of immune complexes, which in turn bind to the surface of platelets, thus activating the complement cascade and subsequent platelet destruction.[4] Some authors suggest that thrombocytopenia is an idiosyncratic reaction in genetically predisposed patients, and others propose the contribution of unknown autoimmune mechanisms associated with autoantibodies produced during apoptosis.[5]

Adalimumab-induced thrombocytopenia could be produced by an immune-mediated mechanism characterized by the presence of antibodies associated with the drug which bind to glycoproteins on the cell membrane of the platelets and cause their destruction in the presence of the provocative drug. However, it is likely that more than one mechanism has contributed to the destruction of platelets in our patient, including an idiosyncratic reaction. Although adalimumab and specially infliximab have been known to cause development of antinuclear antibodies and anti-DNA antibodies, the onset of autoimmune diseases during anti-TNFα therapy is rare.[8]

The literature contains only two case reports of patients with CD who developed thrombocytopenia while under treatment with anti-TNF-α drugs (Table 1). The first case[5] involved a 42-year-old woman with CD and a perianal fistula who had been treated with infliximab. After three infusions, she presented a platelet count of 44,000/mm^3. Infliximab was discontinued, and the platelet count recovered. She was then rechallenged with adalimumab and her platelet count fell again. The other case[4] involved a 15-year-old boy with CD who was treated with infliximab. Six days after starting treatment he presented a platelet count of 30,000/mm^3. He responded to corticosteroids and IVIG, and his platelet count recovered. No rechallenge was performed.

Although our patient initially responded to IVIG, her platelet count fell again and she did not respond to corticosteroids. In one of the two reported cases of thrombocytopenia secondary to anti-TNF-α in patients with CD, the platelet count recovered after anti-TNF-α drugs were discontinued, without the need for corticosteroids or IVIG.[5] In the other case, IVIG and high doses of corticosteroids were necessary to normalize the platelet count.[4]

The autoantibodies induced during the exposure to a medication are usually transient. However, these

Table 1 Case reports of thrombocytopenia secondary to anti-TNF-α drugs.

Author	Year	N° of cases	Disease	Gender/years	Anti-TNFα	Lowest platelet count	Treatment of thrombocytopenia	Responded to treatment	Recurrence of thrombocytopenia with same/other anti-TNFα
Vidal et al.[12]	2003	1	RA	F/60	IFX	<20.000 /mm^3	Stop IFX	Yes	No attempt to rechallenge
Selby et al.[4]	2004	1	CD	M/15	IFX	4.000 /mm^3	Stop IFX + steroids + IVIG	Yes	No attempt to rechallenge
Hamaguchi et al.[13]	2006	1	Scleroderma overlap/AR	F/47	IFX	120.000/mm^3	Stop IFX + steroids	Yes	No attempt to rechallenge
Pathare et al.[10]	2006	2	RA	F/44	Etanercept	38.000 /mm^3	Stop etanercept	Yes	Commenced on ADA and maintained normal platelet count
			RA	F/56	IFX	26.000 /mm^3	Stop IFX	Yes	Commenced on etanercept and maintained normal platelet count
Salar et al.[5]	2007	1	CD	F/42	IFX/ADA	44.000 mm3	Stop IFX/ADA + steroids	Yes	Platelet count improved after stopping IFX. Commenced of ADA and platelet count fell again
Brunasso et al.[14]	2008	4	Psoriasis	M/53	Etanercept	22.000 /mm^3	Stop etanercept	Yes	Rechallenge with etanercept and platelet count fell again
			Psoriasis	F/67	IFX	1.000 /mm3	Stop IFX + steroids	Yes	Rechallenge with etanercept and platelet count fell again
			Psoriasis	M/55	IFX	18.000 /mm^3	Stop IFX + steroids + IVIG + mycophenolate	No	No attempt to rechallenge
			Psoriasis	F/41	IFX	42.000 /mm^3	Stop IFX	Yes	No attempt to rechallenge
Stinco et al.[11]	2008	1	Psoriatic arthritis	M/61	Etanercept	99.000 /mm^3	None	Spontaneous recovery of platelet count	Stop etanercept because of improvement of psoriatic arthritis
Chen M et al.[7]	2011	2	Psoriasis	No data	ADA	65.00/mm^3	Stop ADA	Yes	No attempt to rechallenge
			Psoriasis	No data	Efalizumab	75.00/mm^3	None.	Spontaneous recovery of platelet count	After one year efalizumab was switched to ADA. Platelet count does not fell again
Azevedo et al.[15]	2011	2	RA	F/54	Etanercept	60.000/mm^3	Stop Etanercept	Yes	No attempt to rechallenge
			Psoriasis	M/61	Etanercept	87.000/mm^3	Stop Etanercept	Yes	No attempt to rechallenge
Casanova et al.*	2012	1	CD	F/71	ADA	25.000/mm^3	Stop ADA + IVIG + steroids	No	Slightly improvement of platelet count after stop ADA. Commenced on ustekinumab. Platelet count does not fell again

RA, rheumatoid arthritis; IFX, infliximab; CD, Crohn's disease; ADA, adalimumab; IVIG, intravenous immunoglobulin G.
*Present case report.

autoantibodies can persist for a long period of time leading to a chronic autoimmune thrombocytopenic purpura. This could explain why our patient did not normalize her platelet count after the second discontinuation of adalimumab. The underlying mechanism of this immune-response is unknown. While the patient is under treatment, the drug might alter the glycoproteins that are present in the surface of the platelets. In consequence, these "new" peptides that are not usually shown by the platelets could be presented to T cells in the context of class II HLA. In this context, the T cells could be activated not only by these "new" peptides, but also by the conventional ones, triggering the immune response.[9]

Patients with rheumatic diseases can develop thrombocytopenia after treatment with anti-TNF-α agents. In some cases, administration of another anti-TNF-α drug when the platelet count returned to normal led to no further decline.[10] However, in other cases, as in ours, the platelet count fell again once the same treatment was reintroduced.[11]

We decided not to change from adalimumab to infliximab because of the severity and refractoriness of the effect and the high risk of worsening the patient's thrombocytopenia; both drugs are monoclonal anti-TNF-α antibodies that share the same Fc domain and bind to the same region of TNF-α. Anti-TNF-α drugs are potent biologic agents that can cause complex changes in the immune system, leading to platelet destruction. As the exact mechanism by which anti-TNF-α drugs induce thrombocytopenia is unknown, the use of another anti-TNF-α agent should be discouraged for the foreseeable future.

In conclusion, we stress that thrombocytopenia can be a side effect of anti-TNF-α drugs; therefore, patients should be regularly monitored. The mechanism by which anti-TNF-α drugs induce thrombocytopenia remains unclear. The platelet count could recover after withdrawal of anti-TNF-α drugs, although treatment with corticosteroids and/or IVIG may be necessary. Even with these treatments, the platelet count may not recover. In a patient who develops severe thrombocytopenia secondary to one anti-TNF-α drug, the use of another anti-TNF-α drug should be discouraged.

Conflict of interest statement

M. Chaparro has served as a speaker and has received research funding from MSD and Abbott. J. P. Gisbert has served as a speaker, a consultant and an advisory board member, and has received research funding from MSD and Abbott.

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