CASE REPORT

Drug-induced thrombocytopenia secondary to natalizumab treatment

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SUMMARY

A 52-year-old woman with a 10-year history of relapsing-remitting multiple sclerosis (RRMS) was started on natalizumab after she developed side effects for interferon β -1a and glatiramer acetate. The patient presented with acute severe infusion reaction after the third treatment with natalizumab, developing whole-body purpura. Laboratory testing revealed progressive worsening thrombocytopenia up to 3 weeks following natalizumab discontinuation. Platelet antibodies to platelet-specific antigen as well as antibodies against natalizumab were positive. Bone marrow biopsy was negative. The patient was diagnosed with drug-induced immune thrombocytopenia (DITP) as a rare case of natalizumab side effect which was treated with intravenous methylprednisolone followed by rituximab with successful resolution of thrombocytopenia. The patient had a stable course of RRMS with no relapses and no brain MRI changes at 2 years after initiation of rituximab.

BACKGROUND

Natalizumab is a humanised monoclonal antibody directed against α -4 β 1-integrin expressed by leucocytes. Although it is an effective therapy for multiple sclerosis (MS), the serious adverse effect of natalizumab has until now resulted in a total of 398 progressive multifocal leukoencephalopathy (PML) cases. As on 5 November 2013, the overall risk of PML was 3.40/1000 patients.

A few postmarketing severe adverse effects (such as PML, liver failure and melanoma) have been reported with the use of natalizumab. There was a low incidence (<1%) of serious systemic hypersensitivity reactions described as anaphylactoid or anaphylactic, and they appeared to be effectively managed by post-treatment observation and by timely and appropriate medical treatment.¹ Haematological changes are commonly reported in clinical trials of interferon β , although its most common adverse effects are hepatic dysfunction, bone marrow suppression and thyroid dysfunction. The incidence of thrombocytopenia secondary to interferon β -1a from postmarketing surveillance is around 12%.²

We describe a rare case of drug-induced immune thrombocytopenia (DITP) after treatment with natalizumab.

CASE PRESENTATION

A 52-year-old woman with a 10-year history of relapsing-remitting multiple sclerosis (RRMS), supported by typical MRI findings (figures 1 and 2),

was started on natalizumab after she developed side effects to interferon β -1a and glatiramer acetate. Interestingly, the patient had a history of mild thrombocytopenia during treatment with weekly interferon β -1a. Her platelet count had decreased to 109 000/ μ L during treatment with interferon and normalised after discontinuation of intramuscular injection of interferon β -1a. She presented with an acute severe infusion reaction after the third treatment with natalizumab, developing whole-body purpura.

INVESTIGATIONS

Laboratory testing revealed that her platelet count had dropped from pretreatment levels of 119 000–63 000/ mm^3 after treatment day 92. Platelet counts continued to decrease in the 3 weeks following natalizumab discontinuation to a nadir of 43 000/ mm^3 . Her red blood cell count, haemoglobin and haematocrit values remained stable (13.8/40.8–14.2/42.5). No haemorrhagic complications were present. Peripheral blood smear as well as renal function was monitored which showed no signs of schistocytes or renal failure suggestive of thrombotic thrombocytopenic purpura. Immunosuppressive state was evaluated with CD4 count within normal

Figure 1 MRI of the brain, axial view of T2/fluid-attenuated inversion recovery sequence showing hyperintense lesions scattered throughout the subcortical white matter of both cerebral hemispheres.

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Figure 2 MRI of the brain, sagittal view of T2/fluid-attenuated inversion recovery sequence showing hyperintense lesions scattered throughout the deep and periventricular white matter.

range. Peripheral blood cytology showed no aberrant immunophenotypic expression suggestive of lymphoma. Inflammatory workup was obtained with negative erythrocyte sedimentation rate, anti-Sjögren's syndrome B, anti-Sjögren's syndrome antigen, anti-ribonucleoprotein, DNA double-stranded antibody (Ab), rheumatoid factor (RF) as well as complement. The patient showed no signs of rashes, arthritis, renal injury, lung or cardiac involvement suggestive of lupus erythematosus.

Platelet antibodies to platelet-specific antigens were positive during her hospitalisation. Antibodies against natalizumab (measured using an ELISA method) were persistently positive up to 6 months after the last infusion. Bone marrow aspirate was normal. She was at this point diagnosed with DITP.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses include: thrombotic thrombocytopenic purpura, HIV infection, lymphoma, systemic lupus erythematosus or myelodysplasia.

TREATMENT

The patient was initially treated with intravenous methylprednisolone 1 g/day for 5 days followed by prednisone 1 mg/kg/day for 2 weeks, resulting in a transient improvement of the thrombocytopenia. Owing to persistent thrombocytopenia and worsening of the MS activity the patient was started on rituximab to address ITP and RRMS. She received rituximab 1 g intravenous every 2 weeks with this regime repeated every 6 months. Her platelet count returned to normal 30 days after initiation of rituximab with resolution of her skin rash. She had a stable course of RRMS with no relapses and no brain MRI changes at 2 years after initiation of rituximab.

OUTCOME AND FOLLOW-UP

The patient had a stable course of RRMS with no relapses and no brain MRI changes at 2 years after initiation of rituximab.

DISCUSSION

In this report, we describe a rare complication of natalizumab treatment. Although registry data reveals the possibility of interferon-induced thrombocytopenia (especially with interferon α), which is also reported as a possible side effect for alemtuzumab, only one other case report in the literature discusses immune-mediated thrombocytopenia secondary to natalizumab use.³

DITP can occur as an adverse drug reaction by the following six mechanisms⁴:

1. Immune-complex formation
2. Hapten formation
3. Autoantibody formation
4. Drug-specific antibody formation
5. Fibrin-type drug mechanism
6. Quinine-type drug mechanism.

Thrombocytopenia is the result of increased destruction of antibody-coated platelets by the reticuloendothelial system in the spleen. There is increasing evidence suggesting a significantly increased rate of apoptosis of megakaryocytes, which correlates with a reduction in platelet production capacity. This has been shown in vitro with megakaryocytes treated with autoantibodies from patients with DITP and in vivo by showing decreased number of megakaryocytes in the bone marrow of patients with ITP. Recently, it was shown that anti-GPIb/IX DITP antibodies might be involved in targeting megakaryocytes. However, the pathogenesis leading to thrombocytopenia secondary to natalizumab is still unclear. Given the immediate onset of thrombocytopenia with the initiation of natalizumab, the presence of antibodies against natalizumab and platelets, complete resolution of symptoms with stopping exposure to natalizumab and treatment with rituximab, it appears that drug-induced immune-mediated thrombocytopenia is the most likely cause of the patient's symptoms. We raise the hypothesis that patients with positive natalizumab antibodies are more susceptible to other immune-mediated drug-induced complications such as ITP.

Management of patients with refractory ITP is difficult. Recent data have shown that rituximab, a chimeric anti-CD20 monoclonal antibody that induces B-cell depletion, is useful in the treatment of these patients, with overall response rates of about 50%.⁵ Clinical response in patients with refractory ITP occurs with little toxicity and should be considered as an early therapeutic option in this setting.⁶ There is also increasing evidence that B lymphocytes are involved in the pathogenesis of MS. There are recent studies showing decreased inflammatory gadolinium-enhancing lesions detected on MRI of the brain and reduction of clinical relapses for 48 weeks after a single dose of rituximab in treating relapsing-remitting MS.⁷

Learning points

- ▶ This case highlights drug-induced immune thrombocytopenic purpura as a rare side effect of natalizumab.
- ▶ We advise caution when using natalizumab in patients with a prior history of immune thrombocytopenic purpura (ITP) or other causes of thrombocytopenia and there is need for constant haematological monitoring in patients on this medication.
- ▶ The outcome of this case also suggests rituximab as a possible early therapeutic option for refractory ITP.

On the basis of the data above, we decided to treat our patient with rituximab with excellent response of DITP and RRMS. The patient was never rechallenged with natalizumab or interferon β -1a. Agents that directly stimulate the thrombopoietin receptor, increasing platelet production, were recently approved for treatment of chronic ITP and immunodeficiency.^{8,9} Clinical experience will ultimately determine the appropriate indications of these new treatments for ITP.

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Competing interests None.

Patient consent Obtained.

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