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Letter to Editor

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Natalizumab-induced thrombocytopenia: A case report

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Natalizumab (Tysabri®, Biogen-Idec, Cambridge, MA, USA) is a humanized monoclonal antibody against anti-α4 integrin on leukocytes. By blocking their binding to their endothelial receptors (vascular cell adhesion molecule 1 (VCAM-1), it inhibits adhesion and migration of inflammatory cells to central nervous system (CNS).[1] Since its first approval for relapsing remitting multiple sclerosis (RRMS) in 2004, significant side effects, especially progressive multifocal leukoencephalopathy (PML), have been matters of concern.[1] Although immune-mediated hematologic complications are considered to be rare, they could be life-threatening. Here, we report a case of patient with RRMS who developed severe thrombocytopenia related to natalizumab administration.

A 35-year-old woman was diagnosed with RRMS at the age of 29. Her presenting symptom was left side paresthesia. The diagnosis was confirmed by typical magnetic resonance imaging (MRI) findings, meeting McDonald criteria 2017. Past medical history was negative for other disorders. She was treated with interferon beta-1a (IFNβ-1a) (high dose, high frequency) for four years. In 2018, considering the increased disability [rise in Expanded Disability Status Scale (EDSS) score from 1 to 4] and a clinical relapse (left lower limb weakness), her treatment was switched to rituximab (1 g every 6 months). She was in a relatively good condition until December 2019, when she developed right lower limb paresis. It was one month after an endometriosis surgery. The weakness improved after pulse therapy with intravenous (IV) methylprednisolone (1000 mg for five days). Rituximab was continued. Six months later, the patient developed right lower limb weakness again. We decided to change treatment to natalizumab. Treatment with natalizumab was delayed until CD19 levels became normal. In December 2020, natalizumab (300 mg IV infusion monthly) was initiated.

Before starting natalizumab, routine blood tests came out to be normal. In addition, complete blood count (CBC) and liver function test (LFT) were monitored before each course of medication. Three weeks after receiving the second course of natalizumab, the patient developed pethechia and purpuric skin rashes on her face and extremities.

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There were no other symptoms such as arthritis, weight loss, or fever. She was not taking any drug other than natalizumab. She had no history of recent viral or bacterial infections. Laboratory tests showed severe low platelet count (below 5000). All other blood cells [white blood cells (WBCs) and red blood cells (RBCs)] were in the normal range. Other laboratory tests including serum electrolytes, blood urea nitrogen (BUN), creatinine, coagulation tests [prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)], and LFTs were normal. Hematologic consult was requested. Peripheral blood smear and peripheral blood cytology showed no schistocytes and/or atypical cells. Tests for vasculitis [antinuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid (anti-dsDNA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), anti-Sjögren's-syndrome-related antigen A (anti-SSA), anti-Sjögren's syndrome antigen B (anti SSB), antiphospholipid antibodies, and complement] were negative. She was tested negative for human immunodeficiency virus (HIV) antibody, hepatitis B surface (HBS) antigen, and hepatitis C virus (HCV) antibody. Abdominal sonography was normal. Considering possible immunological etiology for platelet depletion, corticosteroid therapy (dexamethasone) was initiated and platelet count began to rise. Therefore, treatment with natalizumab was discontinued. The patient was discharged with 60 mg oral prednisolone. After one month of corticosteroid treatment, platelet count returned to the normal range (176×10^3 /mm^3); therefore, prednisolone was tapered. Due to thrombocytopenia and normality of other blood tests as well as patient's condition, the final diagnosis of thrombocytopenia induced by natalizumab was made by hematologist. MS drug switched to rituximab and after a six-month follow-up, the patient prognosis was good.

Although hematologic complications are recognized in newborns exposed to natalizumab, they are reported to be rare in adult patients.

In 2011, Stosic et al. described the first case of natalizumab-induced thrombocytopenia in a 25-year-old African American female patient. Three weeks after the first dose, her platelet count dropped. It responded to oral prednisolone. As no previous case of such adverse event was reported, natalizumab was restarted. Thrombocytopenia recurred two weeks after the second dose of the drug. Since no evidence of any other cause was found, they concluded that the most likely etiology for the immune thrombocytopenic purpura (ITP) was natalizumab.[2]

Midaglia et al. reported one case of ITP in a 61-year-old patient with RRMS three weeks after tenth natalizumab infusion. With other possibilities excluded, she was treated with methylprednisolone and IV immunoglobulin (IVIG).[3]

Cachia et al. presented a 52-year-old woman with a ten-year history of RRMS, with previous mild reactive thrombocytopenia after interferon (IFN). She developed thrombocytopenia to a nadir of 43000/mm^3 after third cession of treatment with natalizumab. Ruling out other differential diagnoses, diagnosis of immune-mediated thrombocytopenia was confirmed by antibodies to platelet-specific antigens. She was treated by methylprednisolone.[4]

Rini et al. reported a 40-year-old man with a very severe thrombocytopenia (zero count) three weeks after fifth natalizumab infusion. Not finding any other possible causative agent or pathology, natalizumab-induced thrombocytopenia was diagnosed.[5]

Our case has highlighted a rare complication of natalizumab. Although the pathogenesis of drug-induced thrombocytopenia is not fully clear, immune mechanism is thought to be the cause of platelet degradation. However, discontinuation of the drug and initiation of corticosteroid is a suitable treatment in this regard.

Conflict of Interests

The authors declare no conflict of interest in this study.

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None.

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