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Fingolimod-Associated Immune - Thrombocytopenia after Long-Term Usage

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Abstract

Introduction: Drug-Induced Immune Thrombocytopenia (DITP) is a type of secondary immune thrombocytopenic purpura caused by low platelet count due to drug-mediated-antibody-platelet destruction. Quinidine, trimethoprim-sulfamethoxazole, and GPIIb/IIIa inhibitors are one of the most reported drugs with higher rates of DITP. Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator and is one of the Disease-Modifying Therapies (DMT) in multiple sclerosis (MS). With this case we aim to describe a patient with MS diagnosing drug-induced-immune-thrombocytopenia (DITP) due to fingolimod treatment.

Case Report: 40-year-old male patient with MS had taken fingolimod treatment since 2015. The patient did not experience any adverse effects for six years until he presents to our clinic with spontaneous ecchymoses after not coming to his regular follow-ups for 1.5 years due to stable medical condition. His thrombocyte count was found to be 12 K/uL (150-400 K/uL). There was no additional drug usage for thrombocytopenia. Probable DITP was suspected, fingolimod was discontinued and 3 days after starting oral steroid treatment his platelet count rose to 300 K/uL. His platelet count dropped to 21 K/uL after re-initiating the fingolimod treatment, and a definite DITP diagnosis related with fingolimod usage was established. No mortal bleeding was experienced under fingolimod during this time and the patient was switched to dimethyl fumarate treatment as his disease-modifying therapy in MS.

Conclusion: We report a rare case of definite DITP related to fingolimod treatment in an MS patient, which was thought to be induced by S1P receptors on thrombocytes after 6 years of usage. The clinicians should keep this in mind and monitor for thrombocytopenia during the follow-up period, which may occur years after starting treatment.

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Introduction

Drug-induced Immune Thrombocytopenia (DITP) is a type of secondary immune thrombocytopenic purpura caused by low platelet count due to drug-mediated-antibody-platelet destruction. Quinidine, trimethoprim-sulfamethoxazole, and GPIIb/IIIa inhibitors are one of the most reported drugs with higher rates of DITP [1]. The overall risk of DIPT with the initiation of any new drug is rare, approximately about 10 per million [2].

Fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator and is one of the Disease-Modifying Therapies (DMT) in Multiple Sclerosis (MS). It prevents activated T lymphocytes from leaving secondary lymphoid organs, thus inhibiting the transmigration of autoreactive lymphocytes into the central nervous system [3]. Adverse effects such as bradyarrhythmia, atrioventricular block, macular edema, liver injury, opportunistic infections, and development of skin cancer are documented on fingolimod therapy [4]. Here we present a rare case of fingolimod-associated DITP.

Case presentation

A 40-year-old male patient who had his first attack as optic neuritis was diagnosed with relapsing-remitting MS in 2008. His past medical history was insignificant except for hemorrhoid and lumbar herniation surgeries. Neurological examination revealed a vision of 20/32 bilaterally, decreased sense of vibration bilaterally, paresthesia at right T6-T8 dermatomal regions, and mild left-sided dysdiadochokinesia. His Expanded Disability Status Scale (EDSS) score was calculated to be 1.5. He was started on oral fingolimod in 2015, after continuing to have frequent attacks and disability progression on interferon beta-1a treatment subcutaneously for 8 years. Before and during this treatment, he was regularly evaluated by cardiology, dermatology, and ophthalmology departments with blood tests and others for possible adverse effects; at that time there were no adverse effects, and the patient was radiologically (Figure 1) and clinically stable.

After a 1.5-year period of not coming to his regular follow-ups due to the pandemic and stable medical condition, the patient presented with spontaneous progressive bruises on his thighs and hands in 2023. His platelet count was found to be 12 K/uL (150-400 K/uL) without a prior history of thrombocytopenia. He was evaluated by the hematology department, with presumed Immune-Thrombocytopenic Purpura (ITP). His complete blood count, biochemistry, collagenosis markers and infectious panel were unremarkable except for his low platelet count. He had no antecedent infections, and the physical examination was normal except for ecchymoses. Fingolimod and gabapentin treatment was halted for "probable" DITP, the patient was started on oral methylprednisolone 16mg/day for 5 days and on the 3rd day of the treatment his platelet count rose to 317 K/uL (150-400 K/uL). After the treatment, the patient was re-started on fingolimod treatment and on the 7th day the platelet count was revealed to be 21 K/uL (150-400 K/uL) again. His blood smear revealed low levels of thrombocytes with no schistocytes. With the definite diagnosis of DITP, the fingolimod treatment was discontinued and he was started on oral methylprednisolone 16 mg/day with a tapering regimen of 9 weeks. In the first week of treatment, the platelet count rose to 343K/uL (150-400 K/uL). No other bleeding was experienced. Thrombocyte levels returned to normal with treatment discontinuation and steroid treatment. We summaries the changes in thrombocyte counts with the treatment changes on table 1. The last neurological examination of the patient was found to be normal. Then, the fingolimod therapy was switched to dimethyl fumarate.

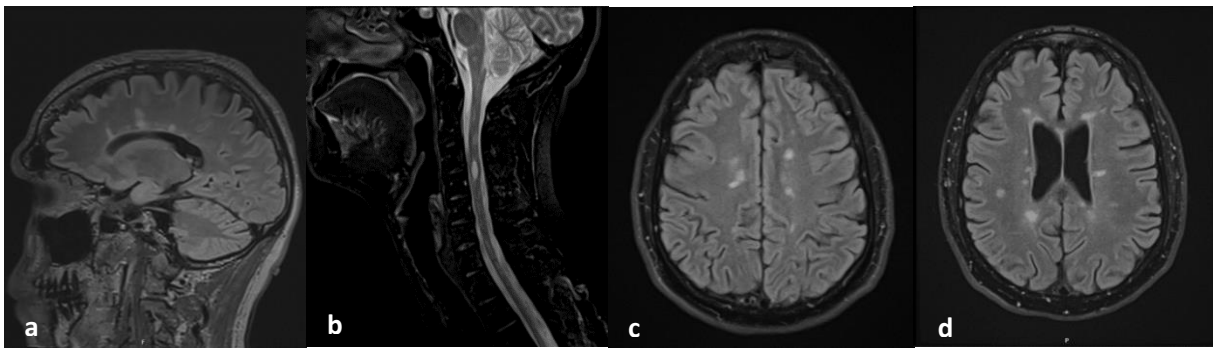

Figure 1: (a) Hyperintense demyelinating lesions seen in sagittal cranial T2A-FLAIR weighted images, perpendicular to the lateral ventricles, located bilaterally in periventricular white matter at the level of centrum semiovale, corpus callosum and pericallosal regions. **(b)** Multiple short segment hyperintense demyelinating lesions seen in T2A-FLAIR weighted images (shown with arrows), located at cervical spinal cord, at the level of C1-C2-C3, accompanied by a focal syringomyelia at C3-C4 level. **(c,d)** Multiple periventricular hyperintense demyelinating lesions seen in axial cranial T2A-FLAIR weighted images.

Table 1: Changes in thrombocyte counts with the changes in treatments.

	First thrombocytopenia detection under fingolimod+gabapentin treatment	3 days after discontinuing fingolimod + gabapentin and starting oral steroid	1 week after re-starting fingolimod	1 week after discontinuing fingolimod and starting oral steroid
Thrombocyte count (150-400 x 10^3 K/uL)	12	317	21	343
Lymphocyte count (1.2-5.8 x 10^3 K/uL)	0.85	1.27	1.26	1.00
Neutrophil count (1.51-7.07 x 10^3 K/uL)	1.89	6.06	2.01	8.90

Discussion

This is one of the few rare cases of fingolimod-related ITP [5,6] in a patient with MS while being the first case with the confirmation of the diagnosis of DITP after a long time of usage of fingolimod treatment [7]. Other etiologies of thrombocytopenia were excluded with laboratory tests including a blood smear, and the patient responded dramatically to the discontinuation of fingolimod, which was seen twice consecutively, confirming the definite diagnosis of DITP.

Fingolimod is an S1P receptor modulator, which functions by allowing the transmigration of autoreactive lymphocytes from lymph nodes into circulation. As fingolimod down-regulates receptor's expression of the S1P type, it prevents the lymphocytes from entering the central nervous system [4,8]. While the mechanisms regarding the pathogenesis of DITP remain unclear, it's known that lacking S1P receptor 1 lead to thrombocytopenia in mice by extravasation of proplatelets and destruction of intravascular proplatelets [9]. It's also been found that S1P may decrease megakaryopoiesis and suppress thrombopoiesis [10].

In conclusion, we report a rare case of definite DITP related to fingolimod treatment in an MS patient. With this case, we aimed to emphasize that regular follow-up of patients using fingolimod therapy is important and that hematological side effects may occur even years later.

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