Pegylated interferon-alpha induced thrombotic thrombocytopenic purpura: A Case Report

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Abstract

Common hematologic side effects of Pegylated interferon alpha–2a include neutropenia, anemia and thrombocytopenia but thrombotic thrombocytopenic purpura (TTP) was rare. We report a case of 69 years old female patient with type 2 diabetes mellitus, end-stage renal disease on hemodialysis, chronic hepatitis C and hypertensive cardiovascular disease, who presented with chills, fever, drowsiness, thrombocytopenia and microangiopathic hemolytic anemia after treatment with 10 doses of Pegylated interferon alpha–2a for chronic hepatitis C. The patient was treated with plasma exchange. Thrombotic thrombocytopenic purpura was recovered after plasma exchange.

Key Words: Thrombotic thrombocytopenic purpura, Pegylated interferon, Plasma exchange.

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Introduction

TTP was first described by Moschowitz in 1925 as a new disease characterized by unique pathological findings of hyaline thrombi in many organs (1). Amorosi and Ultmann reviewed all 271 published cases up to 1964 and defined the classic pentad of clinical features(2): thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms and signs, renal function abnormalities and fever. Possible etiologies of TTP include ADAMTS13 deficiency, drug toxicity and autoimmune diseases but interferon induced TTP was very rare.

Case Report

A 69 years old female patient with type 2 diabetes mellitus, end-stage renal disease on hemodialysis, chronic hepatitis C and hypertensive cardiovascular disease, was treated at our hospital OPD with Pegylated interferon monotherapy for chronic hepatitis C. She was precribed 10 doses of weekly PEGASYS (Peginterferon alpha–2a) 180mcg intramuscularly. Then, she was found to have chills, fever, drowsiness, and BP 220/100mmHg during hemodialysis. Platelet count reduced to 29,000/cmm and hemoglobin reduced to 9.0g/dL. Blood smear showed fragmented RBCs. Direct and indirect Coomb's tests were negative. Total and indirect bilirubin, AST and LDH were abnormally elevated. TTP was suspected as following: thrombocytopenia, fragmented RBCs, conscious change and fever. The plasma exchange was performed and interferon was discontinued. As a consequence, Platelet count elevated to 122,000/cmm with recovery of conscious disturbance and RBC morphology. So, TTP was diagnosed and considered to be a side effect of Pegylated interferon monotherapy.

Discussion

Possible etiologies of TTP include ADAMTS13 deficiency, drug toxicity with mitomycin C, bleomycin, cisplatin, gemcitabine, cyclosporine, tacrolimus, quinine and ticlopidine; and autoimmune diseases such as antiphospholipid antibody syndrome, systemic lupus erythematosus and scleroderma. A deficiency of or an autoantibody directed against a specific von Willebrand factor-cleaving protease (ADAMTS-13) is responsible for some cases of TTP, leading to the accumulation of unusually large von Willebrand factor multimers and platelet aggregation (3-5).

Pegylated interferon (PEG-IFN) and ribavirin combination was standard treatment for chronic hepatitis C. Pegylation allows for weekly dosing with improved therapeutic effect. PEG-IFN alpha-2a (180μg SC/week) and PEG-IFN alpha-2b (1.5μg/kg SC/week) are similar in efficacy. Sustained response (defined as normalization of serum ALT and clearance of HCV RNA from serum 6 months after completion of treatment) is observed in approximately 55% of all patients. Selected patients may receive PEG-IFN monotherapy with a 20–30% sustained response rate.

During interferon-alpha treatment, thrombocytopenia is a common side effect. Interferon induced TTP was very rare but should be suspected especially when associated with hemolytic anemia, fever, and transient neurological symptoms and signs.

According to papers, we found it was reported only in one study. In this study, a 62-year-old male with chronic hepatitis C developed TTP one month after long-term pegylated-interferon (PEG-IFN) treatment. Serial determination of ADAMTS13 activity and its inhibitor may provide useful information for the diagnosis and treatment of IFN-associated TTP, as well as its pathogenesis (6). The observed low level of activity of plasma ADAMTS13 following PEG-IFN treatment was shown to gradually increase with the improvement of TTP, while the titer of an inhibitory anti- ADAMTS13 IgG antibody decreased concomitantly.

If untreated, TTP in adults typically follows a progressive course in which irreversible renal failure, progressive neurologic deterioration, and death are common outcomes (3.4). The mortality rate prior to the use of plasma exchange was approximately 90 percent(7-9), and is currently as low as 12 to 14 percent in patients treated with plasma exchange (9,10). Moake, JL. and George, JN. suggested that plasma exchange should be initiated even if there is some uncertainty about the diagnosis of TTP and it is considered that the potential risks of TTP exceed the risks of plasma exchange treatment(11,12). If an alternative diagnosis is subsequently discovered (eg, disseminated infection, malignancy), plasma exchange should then be stopped.

George, JN. suggested plasma exchange should be initially performed daily until the platelet count has normalized and hemolysis largely ceased, as evidenced by a return of the serum lactate dehydrogenase (LDH) concentration to normal(12,13). On average, 7 to 16 daily exchanges are required to induce remission, but the variability is large and unpredictable, ranging from 3 to 145

required exchanges. The recommended volume to be exchanged at each procedure is one estimated plasma volume(14).

Serial observations indicate that neurologic symptoms and the serum concentration of lactate dehydrogenase (LDH) tend to improve first (one to three days) and the platelet count starts to rise after several days(15). Improvement in renal function is unpredictable and often incomplete. Even patients who require dialysis during the acute episode (16 percent in one report) generally recover sufficient function to be able to discontinue dialysis(16). However, many patients have a residual impairment in renal function and/or persistent hypertension (16-21). These abnormalities are often not indicative of active disease or the need for continued plasma exchange.

Plasma exchange reverses the platelet consumption that is responsible for the thrombus formation and symptoms that are characteristic of this disorder([3, 22-28). In such patients, plasma infusion presumably supplies the missing enzyme, while plasma exchange can remove some of the acquired autoantibody and the very high molecular weight von Willebrand factor (VWF) multimers. Adjunctive treatments (eg, steroids, rituximab) may reduce the production of autoantibodies. Similarly, in patients whose platelet counts do not increase within several days of treatment with plasma exchange, or those in whom thrombocytopenia recurs when plasma exchange treatments are diminished or discontinued, addition of glucocorticoids is appropriate (29).

George, JN. and Tsai, HM, Raoufi, M, Zhou, W, et al found that ADAMTS13 measurements appear to be of greatest clinical value for estimating the

prognosis for relapse after recovery from an acute episode, and for initial treatment of a patient who has an acute, recurrent episode(29,30). According to Zheng, XL, Kaufman, RM, Goodnough, LT, Sadler, JE.and Coppo, P, Wolf, M, Veyradier, A, et al's reports, the presence of severely reduced ADAMTS13 activity, along with an inhibitor to ADAMTS13, may be associated with a worse overall clinical outcome, including delayed platelet count recovery, a need for more intensive treatment, as well as a higher risk for relapsing disease and death(31,32).

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長效型干擾素引發之血栓性血小板減少性紫斑症
－病例報告－

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摘　要

　　長效型干擾素 α-2a最常見的血液學副作用包括中性白血球減少，貧血，及血小板減少，而血栓性血小板減少性紫斑症是少見的。我們報告一位69歲女性病患，其患慢性C型肝炎，糖尿病，高血壓性心臟病及尿毒症，以長效型干擾素 α-2a每週180mcg治療慢性C型肝炎共10劑量後發生血栓性血小板減少性紫斑症經血漿置換術完全恢復。

關鍵字：血栓性血小板減少性紫斑症，長效型干擾素，血漿置換術