Thrombocytopenia with Refractory Idiopathic Thrombocytopenic Purpura with Extensive Thrombosis in an Obesity Patient: Internal Correlations

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Abstract

The combination of thrombocytopenia with extensive thrombosis is indeed very rare. We hereby report the case of a 42-year-old obese female patient with characteristic Idiopathic Thrombocytopenic Purpura (ITP) bone marrow presentation, who initially responded to corticosteroid treatment but eventually showed continuous low platelet count after corticosteroid reduction. What is more, she developed thrombosis rapidly and extensively in half a month during the period of thrombocytopenia, we presume that the extensive thrombosis could be complexity. Upon further investigation; the level of multiple hormones was low. Using the Enzyme Linked Immune Sorbent Assay (ELISA) detection method, the level of peripheral APA was found higher than that of the normal control (P<0.05). it was found that the patient might be an atypical Sheehan Syndrome (SS). Therefore, we proposed a following pathogeny for the complex symptoms in present report: Hypopituitarism → hypothyroidism → obesity → Multiple thrombosis → consumptive thrombocytopenia → iatrogenic Cushing syndromes. She was stopped on corticosteroid and replacement thyroxine. After 24 months follow-up, the patient's condition improved significantly.

Keywords: Obesity; ITP; Thrombosis; Internal correlations

Case Presentation

A 42 year-old female patient, visited the local hospital for chest tightness and unprecedented fatigue in October 2016. Blood routine revealed a white Blood Cell Count (WBC) of 5.3 × 10⁹/L, Hemoglobin count (HB) of 110g/L and a Platelet Count (PLT) of 5 × 10⁹/L. Bone Marrow (BM) smear showed megakaryocyte maturation disorder. At onset, corticosteroid therapy was effective but after corticosteroid reduction, the platelet count started to decrease. Even after the addition of Danazol and Rituximab, the platelet count fluctuated around 20-44 × 10⁹/L for the following 8 months, On August 16, 2017, the patient presented with right lower extremity edema and Doppler ultrasound revealed thrombosis in the popliteal and saphenous veins. The patient underwent angiography followed by inferior vena cava filter placement on the 15th of August.

She was referred to our hospital on the 19th of August due to thrombocytopenia for more than ten months, right lower limb swelling for three days. Chest CT showed signs of lung infection Physical examination showed an ECOG score of 3, patient's height was 165 cm, weight was 107 Kg, Body Surface Area (BSA) was 2.3 m², The patient was sane and presented with full moon face, "Cushing" characteristic appearance, And then the results of the various tests and examinations run on the patients upon admission are listed.

Corticosteroid treatment was continued with simultaneous anti-infection treatment, Fibrinogen (Fg) supplement, plasma transfusion and fondaparinux sodium anticoagulation therapy, but The patient developed thrombosis rapidly and extensively and platelet count dropped to 21 × 10⁹/L, full double lower extremity swelling (Figure 1A). Since thrombocytopenia is an absolute contraindication of anticoagulant therapy and the use of Thrombopoietin (TPO) was to be with caution with thrombosis, and the following treatment options were contradictory. But considering anticoagulation, Low Molecular Weight Heparin (LMWH) also inhibits the synthesis of Platelet Factor 4 (PF4) and Transforming Growth Factor (TGF-β), hence enhanced megakaryocyte proliferation [1]. So on September 2nd, the patient was started on a continuous daily administration of LMWH (4000U q12h) for 4 months. By October 4th, PLT count had increased to 220 × 10⁹/L. After that, the thrombosis and swelling showed significant amelioration and so far, the platelets remained stable (Figure 1B).

Discussion and Analysis

The pathogenesis of the thrombocytopenia

Primary immune thrombocytopenia, or Idiopathic Thrombocytopenic Purpura (ITP), is an autoimmune disorder characterized by isolated thrombocytopenia. The main pathogenesis is to produce its own anti-platelet antibody, which increases the destruction of platelets [1], This patient was a young woman with...
primary thrombocytopenia, whereby corticosteroid treatment was initially effective, but after the dose reduction, PLT count dropped significantly and continued dropping after intervention with second-line drugs, henceforth the case was classified as refractory thrombocytopenia after excluding factors of secondary thrombocytopenia such as autoimmunity, tumor or drug use. Nevertheless, the patient presented with extensive thrombosis, first confirmed in the right popliteal and great saphenous veins, followed by thrombosis in the pulmonary artery, and then in the basal vein system. The possibility of Thrombotic Thrombocytopenic Purpura (TTP) was ruled out since the patient presented with mild to moderate normochromic without obnubilation, fever, renal malfunction, or nervous system involvement; the peripheral incidence of broken RBC was 7/500, the plasma ADAMTS13 inhibitor was tested negative, thus not conforming to the diagnosis of TTP [2]. After the use of anticoagulants (Fondaparinux), PLT count showed a further dropping trend while lead to speculations about the possibility of Heparin Induced Thrombocytopenia (HIT) [3]. In addition to anticoagulation, Low Molecular Weight Heparin (LMWH) also inhibits the synthesis of PF-4 and TGF-β, hence promoting platelet production [4].

The major factors contributing to the extensive thrombosis

Obesity: The patient delivered a macrosomic baby boy at the age of 20 and after the delivery, her body weight increased year by year: she weighed 65 kg before the delivery and after the delivery, her weight 75 kg and reached a maximum of 107 Kg with a BMI of 39.1 kg/m², which according to the 2017 diagnostic criteria of obesity in the United States indicated severe obesity (class 2). Obesity is a chronic metabolic disease caused by multiple factors. It is an independent disease and is a risk factor for many diseases. Obesity has been cited as one of the ten major risk factors for disease burden by the World Health Organization (WHO). The patient weighed 107 Kg with a Body Mass Index (BMI) of 39.1 kg/m², which according to the 2017 diagnostic criteria of obesity in the United States indicated severe obesity (class 2). A retrospective cohort study was carried out with 622 patients with Deep Venous Thrombosis (DVT) [5]. Cox regression model adjusted age, sex, pulmonary embolism and warfarin treatment time, and found that obesity (BMI >40) was significantly correlated with DVT (P = 0.013). In that report, genome-wide association studies identified 5 BMI SNPs that were associated with VTE (P<0.05), and therefore proved that there was a cause-and-effect relationship between high BMI and VTE risk.

About the hypothetical underlying mechanism, basic research points out that adipose tissue of obese people can generate many tissue factors such as tumor necrosis factor-α (TNF-α), IL-6 and Tissue Factor (TF) plasminogen activator inhibitor (PAI)-1 that promote thrombosis. By accelerating the expression and secretion of lipoproteins and fat factors and hence stimulating the preinflammatory state and pre-thrombotic state, obesity might be the main mechanism of thromboembolism [6,7].

Long-term use of corticosteroid

Corticosteroid treatment was initiated in October 2016, mostly maintained by oral dosages of 30 mg to 60 mg, followed by gradual dosage decrease till termination. Corticosteroid was the main drug used for the treatment of ITP and was initiated in October 2016, mostly prescribed as oral dosages of 30 mg to 60 mg, followed by gradual dosage reduction till termination, over a total treatment duration of almost a year. In reports by Rowland K, it was shown that after three years of oral corticosteroid (<20 mg/day), the probability of adverse events increased gradually with time (P<0.001). The risk VTE also gradually increased. Although the overall treatment time was only about a year, but the early advent of thrombosis and the use of corticosteroid were nevertheless related [8].

Infection

The patients presented with significant lower extremities swelling with more than 10 blisters which eventually ruptured and got infected (Figure 1A). Upon hospitalization in August, the patient complained of cough with mucopurulent sputum: Chest Computed Tomography (CT) showed signs of severe pneumonia and blood gas analysis revealed type I respiratory failure. It has been reported that after infection of Gram Negative (G-) bacteria, vascular endothelial cells are damaged stimulating the activation of the endogenous coagulation system. Thus further aggravating thrombosis in this patient [9].

Hypopituitarism

In half a month, thrombosis developed from the right lower extremities to the double extremities, to the waist and buttock, and eventually in the pulmonary (Figure 1C) and the vertebral arterial systems (Figure 1D). Simultaneously, the levels of several adenohypophysis secreted tropic hormones (FT3 and TT4, TSH, FSH, LH and ACTH) were found to be lower while enhanced head CT suggested non-uniform density of the pituitary, the radiological findings conformed to the characteristics of hypopituitarism and also consistent with the diagnosis of hypothyroidism. According to a national survey in Japan, hypopituitarism is an important cause of obesity [10]. As for the possible underlying mechanism behind how hypothyroidism combined with obesity could be associated to extensive thrombosis

Atypical sheehan syndrome

Upon careful investigation of the patient’s medical history, it was noted that the patient’s body weight gradually increased after the birth of a giant baby at the age of 20. The patient had a weight of 107 kg when hospitalized. The patient had no postpartum hemorrhage and had normal postpartum milk secretion during prenatal period. Since there were no significant clinical symptoms, no further investigation was carried out at that time; hence the case is not consistent with the diagnosis of the classic Sheehan syndrome. In recent years, it has been reported that there are still about 1/2 of Sheehan syndrome patients where at the onset of the disease [11], the pituitary only has small necrotic lesions while with time, several years postpartum or several decades, there is the emergence of significant pituitary dysfunction manifested by various symptoms. The clinical manifestation is mild and is easily ignore. It has been reported that the production level of the Anti Pituitary Autoantibody (APA) is closely related to the degree of pituitary ischemia and in this case, using the Enzyme Linked Immune Sorbent Assay (ELISA) detection method [12], the level of peripheral APA was found higher than that of the normal control (P<0.05), suggesting that the auto-immune antibody was related to the micro-ischemic pituitary lesions and associated immune factors.

It has been reported that the level of APA is closely related to the degree of cerebral ischemia the peripheral blood APA of this patient was higher than normal range, suggesting the possibility of the chronic hypopituitarism due to micro-thrombosis in the pituitary cannot be completely ruled out [13]. After treatment with thyroxin tablets, 4 of the adenohypophysis hormones had recovered to the normal range by February 2018. All the thrombus disappeared in the body (Figure 1E and F),and the pituitary function was restored. During the whole process from thrombus formation to progression to extensive
systemic thrombosis, the levels of various adenohypophysis-secreted tropic hormones were found to be lower (TSH, FSH, LH and ACTH). Finally, after supplementing thyroxine tablets, pulmonary thrombosis is recanalization and pituitary hormones returned to normal. After 24 months follow-up, the patient’s condition improved significantly.

Conclusion

In conclusion, ITP with extensive thrombosis is rare, but for an obese woman who has been subjected to long-term corticosteroid treatment, physicians need to be highly vigilant of the risk of thrombosis and timely withdrawal corticosteroid. The levels of various hormones need to be monitored and cautious with an atypical Sheehan Syndrome (SS). We proposed a following pathogeny for the complex symptoms in present report: Hypopituitarism → hypothyroidism → obesity → Multiple thrombosis → consumptive thrombocytopenia → iatrogenic Cushing syndromes. This report underscores that, for patients with thrombocytopenia combined with thrombosis, the key to treatment is to start anticoagulation therapy at the beginning and administer alternative therapy as soon as possible.

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Ethical approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 2008 (5).

References


