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Glucocorticoid-induced thrombotic microangiopathy in paroxysmal nocturnal hemoglobinuria: A case report and review of literature

Yang XD *et al*. GC-induced TMA in PNH

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Abstract

BACKGROUND

Thrombotic microangiopathy (TMA) is a group of disorders that converge on excessive platelet aggregation in the microvasculature, leading to consumptive thrombocytopenia, microangiopathic hemolysis and ischemic end-organ dysfunction. In predisposed patients, TMA can be triggered by many environmental factors. Glucocorticoids (GCs) can compromise the vascular endothelium. However, GC-associated TMA has rarely been reported, which may be due to the lack of awareness of clinicians. Given the high frequency of thrombocytopenia during GC treatment, particular attention should be given to this potentially fatal complication.

CASE SUMMARY

An elderly Chinese man had a 12-year history of aplastic anemia (AA) and a 3-year history of paroxysmal nocturnal hemoglobinuria (PNH). Three months earlier, methylprednisolone treatment was initiated at 8 mg/d and increased to 20 mg/d to alleviate complement-mediated hemolysis. Following GC treatment, his platelet counts and hemoglobin levels rapidly decreased. After admission to our hospital, the dose of methylprednisolone was increased to 60 mg/d in an attempt to enhance the

suppressive effect. However, increasing the GC dose did not alleviate hemolysis, and his cytopenia worsened. Morphological evaluation of the marrow smears revealed increased cellularity with an increased percentage of erythroid progenitors without evident dysplasia. Cluster of differentiation (CD)55 and CD59 expression was significantly decreased on erythrocytes and granulocytes. In the following days, platelet transfusion was required due to severe thrombocytopenia. Observation of platelet transfusion refractoriness indicated that the exacerbated cytopenia may have been caused by the development of TMA due to GC treatment because the transfused platelet concentrates had no defects in glycosylphosphatidylinositol-anchored proteins. We examined blood smears and found a small number of schistocytes, dacryocytes and acanthocytes. Discontinuation of GC treatment resulted in rapidly increased platelet counts and steady increases in hemoglobin levels. The patient's platelet counts and hemoglobin levels returned to the levels prior to GC treatment 4 weeks after GC discontinuation.

CONCLUSION

GCs can drive TMA episodes. When thrombocytopenia occurs during GC treatment, TMA should be considered, and GCs should be discontinued.

Key Words: Aplastic anemia; Paroxysmal nocturnal hemoglobinuria; Glucocorticoid; Methylprednisolone; Thrombotic microangiopathy; Platelet transfusion refractoriness; Case report

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Core Tip: Glucocorticoid-associated thrombotic microangiopathy has rarely been reported. Here, we report a patient with paroxysmal nocturnal hemoglobinuria whose

hematological parameters worsened during methylprednisolone treatment, and increasing methylprednisolone doses further exacerbated the cytopenia. Observation of platelet transfusion refractoriness suggested the possibility of thrombotic microangiopathy development. Significant hematological improvement was achieved after discontinuation of methylprednisolone treatment, confirming that methylprednisolone treatment acted as the triggering factor to promote platelet aggregation within the microcirculation. Given the wide use of glucocorticoids in clinical practice and the high incidence of thrombocytopenia during glucocorticoid treatment, particular attention should be given to this potentially fatal complication.

INTRODUCTION

Thrombotic microangiopathy (TMA) is caused by uncontrolled adhesion, activation and aggregation of platelets within the microvasculature, leading to consumptive thrombocytopenia, microangiopathic hemolysis and ischemic end-organ dysfunction. Mutations and polymorphisms in genes of the complement and coagulation systems predispose patients to TMA development[1,2]. The delayed onset and diverse penetrance indicate that the development of symptomatic TMA requires an engagement of environmental factors to trigger acute episodes. A variety of precipitating factors compromise the vascular endothelium, increase the shear stress of blood flow, stimulate ultralarge von Willebrand factor (UL-vWF) secretion, activate innate immune cells, exacerbate complement dysregulation, exacerbate coagulation dysregulation, promote platelet activation and promote platelet aggregation, thereby triggering TMA episodes in genetically susceptible individuals or initiating TMA occurrence by the combined effects of acquired susceptibilities and precipitating factors[1-3]. In TMA development, interactions among the vascular endothelium, vasomotoricity, vWF, platelets, coagulation factors, complement components and immune cells synergistically facilitate platelet aggregation and microthrombogenesis[4-8]. Endothelial injury and subsequent UL-vWF secretion play a pivotal role in this process[8,9], and complement activation, particularly the generation of anaphylotoxins, provokes and exacerbates endothelial

injury[5,7,10,11]. Previously reported environmental factors that can trigger TMA episodes include various infections, malignant hypertension, autoimmune disorders, neoplasms, pregnancy, organ transplantation, critical illness, severe trauma, vitamin B_{12} deficiency and drugs[1-3].

Drug-induced TMA has been reported to involve immune- and nonimmune-mediated mechanisms. Immune-mediated TMA is caused by the generation of autoantibodies that activate endothelial cells and platelets in a dose-independent manner, whereas nonimmune-mediated TMA is caused by drugs that directly compromise the vascular endothelium, activate platelets or disrupt the immune system in a dose-dependent manner. Drug-induced TMA is frequently associated with chemotherapeutic agents, anti-vascular endothelial growth factor (VEGF) antibodies, VEGF receptor inhibitors, heparin, platelet inhibitors, thrombopoietin receptor agonists, immune suppressants, recombinant cytokines and immune checkpoint inhibitors[12-15]. Glucocorticoids (GCs) are widely used drugs, and the occurrence of thrombocytopenia during GC treatment is a common event in clinical practice. GC treatment can trigger TMA episodes[16-20] and exacerbate preexisting TMA[21,22]. However, GC-associated TMA has rarely been reported, which may be due to the lack of awareness of clinicians, the complexity of the underlying conditions and the lack of sufficient evidence for the diagnosis of microangiopathic hemolysis in most circumstances[2,23,24]. In the present case report, we present a patient with paroxysmal nocturnal hemoglobinuria (PNH) who developed TMA following GC treatment.

CASE PRESENTATION

Chief complaints

The patient experienced rapid decreases in hemoglobin and platelet levels for 3 months.

History of present illness

Past treatment for blood diseases: Twelve years earlier, a 51-year-old Chinese man was diagnosed with acquired aplastic anemia (AA) in several blood disease centers due to

gradually aggravated fatigue. He was prescribed cyclosporine and stanozolol, achieving significant hematological improvement.

Three years ago, the patient developed evident hemoglobinuria and was diagnosed with PNH based on increased marrow cellularity and a significant decrease in cluster of differentiation (CD)55 and CD59 expression on erythrocytes and granulocytes. Cyclosporine and stanozolol were tapered off, and antiplatelet drugs became his main treatment. During the three years of PNH history, his complete blood count (CBC) results fluctuated within the following range: white blood cell (WBC) count, 5.50–7.50 × 10^9/L; red blood cell (RBC) count, 2.90-3.30 × 10^{12}/L; hemoglobin (Hb) level, 80-100 g/L; and platelet (Plt) count, 170-230 × 10^9/L.

Three months earlier, the patient's hemoglobinuria worsened, and he initiated oral administration of methylprednisolone at a dose of 8 mg/d and sodium bicarbonate at a dose of 1.0 g three times per day at another hospital to alleviate complement-mediated hemolysis.

Rapid decreases in hemoglobin and platelet levels following GC treatment: Before methylprednisolone treatment, the patient's CBC showed the following results: WBC count, 6.73 × 10^9/L; RBC count, 3.15 × 10^{12}/L; Hb level, 85 g/L; Plt count, 195 × 10^9/L; and absolute reticulocyte (Ret) count, 290.2 × 10^9/L. Following GC treatment, the patient's fatigue worsened, and headache, palpitation and dyspnea symptoms emerged and worsened. Seven days after initiating methylprednisolone treatment, his CBC showed the following results: WBC count, 5.28 × 10^9/L; RBC count, 2.73 × 10^{12}/L; Hb level, 70 g/L; Plt count, 106 ×10^9/L; and Ret count, 283.3 × 10^9/L. From that time, intermittent transfusion of packed RBCs was initiated, and the dose of methylprednisolone was increased to 20 mg/d. Along with the increase in methylprednisolone dose, his Hb level and Plt count further decreased, and the frequency of blood transfusion increased. Four days before presenting at our center, the patient's fatigue was severe with intolerable palpitations and dyspnea.

History of past illness

The patient had no history of diseases in hematological, immunological or other systems before the diagnosis of AA.

Personal and family history

The patient had no family history of inherited, hematological, autoimmune or malignant diseases.

Physical examination

The physical examination results of the patient were as follows: height of 171 cm; body weight of 70 kg; body temperature of 36.1 °C; breathing rate of 19 breaths per minute; heart rate of 90 beats per minute; and blood pressure of 130/90 mmHg. Physical examination revealed the presence of a pale face and conjunctiva in the absence of conspicuous mucocutaneous hemorrhage, jaundice and exanthemata. No significant signs of nervous system, respiratory system, cardiovascular system, gastrointestinal system, urogenital system or skeletal musculature system abnormalities were found.

Laboratory examinations

Routine laboratory examinations: On admission, the patient's CBC showed the following results: WBC count, 4.75 × 10^9/L; RBC count, 1.72 × 10^{12}/L; Hb level, 65 g/L; Plt count, 98 × 10^9/L; and Ret count, 274.90 × 10^9/L. The coagulation profile was within the normal limits with a D-dimer level of 0.77 mg/L. Urine examination revealed occult blood of 3+ and protein of 1+. Biochemical analysis revealed elevated serum levels of conjugated bilirubin (10.4 μmol/L), unconjugated bilirubin (24.4 μmol/L), lactate dehydrogenase (LDH, 3349 U/L) and hydroxybutyric dehydrogenase (HBDH, 2695 U/L) in the absence of abnormalities in hepatic and renal functions. The results for hepatitis A, B, and C viruses as well as human immunodeficiency virus were negative. Various antinuclear antibodies and biomarkers of neoplasms were also negative.

Specific laboratory examinations for blood diseases: Morphological examination of the marrow smears revealed increased cellularity with a significantly increased percentage of erythroid precursors in the absence of evident dysplastic features (Figure 1A). Bone marrow biopsy confirmed the increased cellularity and increased erythropoiesis. Coomb's test was negative. Significantly decreased CD55 and CD59 expression on erythrocytes (11.24% and 7.80%) and granulocytes (40.26% and 37.35%) was identified by flow cytometric analysis. Decreased serum levels of complement C3 but not C4 were detected. Serum levels of ferritin were slightly decreased, and serum levels of folic acid and vitamin B_{12} were within the normal limits. Anti-erythrocyte and anti-platelet antibodies were undetectable. Myeloid neoplasm-associated gene mutations were also undetectable.

Imaging examinations

No evident abnormalities were found in the patient's chest and abdominal computed tomography scans.

FINAL DIAGNOSIS

These laboratory data fulfilled the diagnostic criteria for PNH.

TREATMENT

After hospitalization, the patient was prescribed intravenous administration of methylprednisolone at a dose of 60 mg/d and 5% sodium bicarbonate (100 mL) two times per day. After transfusion of 800 mL of packed RBCs, his Hb level increased to 88 g/L. In the following days, however, his Hb and Plt levels rapidly declined, and the rate of decline in the Hb levels was disproportionate to the expected life of normal blood cells, indicating that hemolysis occurred not only in the PNH clones but also in normal RBCs. On the 16th day of hospitalization, his Hb level decreased to 61 g/L, and his Plt level decreased to 7×10^9/L. The patient was transfused with 10 U of platelet concentrate and demonstrated platelet transfusion refractoriness. Observation of

platelet transfusion refractoriness suggested that the patient was probably complicated with the development of TMA due to GC treatment because the transfused platelet concentrates did not have defects in GPI-anchored proteins. We then examined the blood smears (Figure 1B) and found the presence of a small number of schistocytes, dacryocytes, acanthocytes and target cells, confirming the existence of microangiopathic hemolysis[2,24]. Thereafter, GC treatment was discontinued.

OUTCOME AND FOLLOW-UP

Rapid increase in Hb level and Plt counts occurred after discontinuation of glucocorticoid treatment

After discontinuation of GC treatment, the patient's platelet counts and Hb levels increased without the need for blood transfusions. Eleven days after the discontinuation of GC treatment, CBC monitoring showed an Hb level of 69 g/L and platelet counts of 28×10^9/L. The patient was then discharged from our center.

Hematological changes following initiation and discontinuation of glucocorticoid treatment

After the patient was discharged from our center, repeated CBC monitoring revealed that his platelet counts rapidly increased and his Hb levels steadily increased. The patient's WBC counts, Hb levels, Plt counts and Ret counts in the following CBC monitoring are shown in Figure 2.

DISCUSSION

The patient was treated with methylprednisolone to reduce complement-mediated hemolysis. Initially, he was prescribed methylprednisolone at 8 mg/d, which failed to ameliorate hemoglobinuria and worsened the hematological profile. In the following months, the dose was increased to 20 mg/d. After hospitalization, the morphological, immunological, cytogenetic and molecular biological examinations of the marrow and blood samples met the diagnostic criteria for PNH. The dose was increased to 60 mg/d,

and the hematological profile was rapidly exacerbated. The longevity of transfused RBCs was greatly reduced with further increases in the HBDH and LDH levels, and the Plt counts in CBC monitoring severely decreased, resulting in the requirement for platelet transfusion. Observation of platelet transfusion refractoriness and mental symptoms suggested the development of TMA. Therefore, we examined the blood smears and found a small number of schistocytes, dacryocytes, acanthocytes and target cells. Although the number of schistocytes was no more than 10%, their appearance was sufficient to confirm the existence of microangiopathic hemolysis[2,24]. GC treatment was discontinued. As expected, the platelets rapidly increased and the LDH and BHDH levels rapidly decreased. The hematological improvement after discontinuation of GC treatment suggested that the exacerbated cytopenia was caused by TMA development due to GC treatment[12].

GCs are widely used drugs for treating a variety of conditions, and the development of thrombocytopenia during GC treatment is a common complication in clinical practice. However, GC-induced TMA has rarely been reported[18-23]. The major reason for the rarity of GC-induced TMA reports may be due to the lack of awareness of clinicians, the dilemma for clinicians to make a definitive diagnosis by examining blood smears on which the percentage of fragmented erythrocytes is not enough to meet the diagnostic criteria[2,23,24] and the complexity of underlying conditions for GC treatment. In the present case, TMA development was not considered during the 3 months of GC treatment due to the intravenous hemolysis of PNH itself and the lack of awareness of GC-induced TMA.

The promotion of TMA by GCs may be due to their physiological functions and pharmacologic effects. GCs and catecholamines are the main components of acute and chronic stress responses[25,26]. GCs increase the sensitivity of precapillary arterioles to catecholamine-induced contraction, thus increasing the shear stress of the microcirculation[25-27]. High-dose GCs can induce vasospasm and aggravate preexisting vasoconstriction[28,29]. GCs inhibit VEGF, inflammation, hypoxemia-induced angiogenesis and vascular repair, which damages vascular endothelial integrity[30-32].

GCs inhibit the biosynthesis of prostacyclin[33,34], nitric oxide[35] and hydrogen sulfide[36], which increases the shear stress of the microcirculation[37,38], promotes the adherent activity of vWF[39] and activates platelet aggregation[40,41]. All of these effects of GCs are precipitating factors for TMA development[1-3].

In PNH pathogenesis, deranged activation of the alternative complement pathway is caused by extremely low levels of the CD55 (decay accelerating factor, ADF) and CD59 (membrane inhibitor of reactive lysis, MIRL) complement regulatory proteins on blood cells. Thrombotic propensity due to complement-mediated platelet activation and intravenous hemolysis is an intrinsic property of PNH[42,43]. In the present case, GC treatment likely acted as a precipitating factor, breaking down the vulnerable balance between prothrombotic and antithrombotic factors in the context of defects in the complement regulatory components, thereby provoking vascular endothelial injury and promoting C3 deposition to the vascular endothelium.

When thrombocytopenia develops during GC treatment, GC-induced TMA should be considered because the predisposing factors are unknown in most cases[44,45]. In the present case, reduced serum levels of complement C3, increased serum levels of LHD, increased serum levels of HBDH and increased Ret counts in CBC monitoring were useful parameters to suggest the occurrence of TMA. The presence of schistocytes on blood smears, although no more than 10%, facilitated the diagnosis of TMA[2,24]. However, the absence of schistocytes cannot exclude the diagnosis of TMA[23]. If TMA is suspected, GC treatment should be discontinued, and drugs that inhibit platelet aggregation and complement activation should be considered[1,2]. Drugs that increase the biosynthesis of endogenous prostacyclin are beneficial for the reduction of GC-mediated vascular injury[40,46,47].

The present study had limitations. The diagnosis of GC-induced TMA was mainly based on exacerbated cytopenia after GC treatment and hematological improvement after discontinuation of GC treatment. The fragmented erythrocytes on blood smears were no more than 10% of the total RBCs. Although the presence of hyaline thrombi in

biopsied tissue is direct evidence of platelet aggregation in the microvasculature, a biopsy was not performed in the present case.

CONCLUSION

GC treatment can cause TMA in predisposed patients, and GC-induced TMA has been underestimated. Because GCs are widely used in treating various diseases and TMA is a potentially fatal condition, GC-induced TMA should be promptly diagnosed. In the case of a significant decrease in platelet counts during GC treatment, GC-induced TMA should be taken into consideration. In this situation, blood smears should be carefully examined, and GC treatment should be discontinued. If an increase in platelets occurs promptly after GC discontinuation, the diagnosis of GC-induced TMA can be established.

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