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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 male had a 12-year history of aplastic anemia and a 3-year history of paroxysmal nocturnal hemoglobinuria. 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 count and hemoglobin level 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 the cytopenia worsened. Morphological evaluation of the marrow smears revealed increased cellularity with an increased percentage of erythroid progenitors without evident dysplasia. Cluster of differentiation 55 and 59 expression were 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, acanthocytes and target cells. Discontinuation of GC treatment resulted in rapidly increased platelet counts and steady increases in hemoglobin levels. The patient’s platelet count and hemoglobin level returned to the levels prior to GC treatment 4 wk 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 (Plts) 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 (vWF) secretion, activate innate immune cells, exacerbate complement dysregulation, accelerate coagulation cascade, promote Plt activation and drive Plt 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, Plts, coagulation factors, complement components and immune cells synergistically facilitate Plt aggregation and microthrombogenesis[4-8]. Endothelial injury and subsequent ultralarge 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 B12 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 Plts in a dose-independent manner, whereas nonimmune-mediated TMA is caused by drugs that directly compromise the vascular endothelium, activate Plts 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, Plt 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 this 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 (Hb) and Plt levels for 3 mo.

***History of present illness***

**Past treatment for blood diseases:** Twelve years prior, a 51-year-old Chinese male was diagnosed with acquired aplastic anemia in several blood disease centers due to gradually aggravated fatigue. He was prescribed cyclosporine and stanozolol, achieving significant hematological improvement.

Three years prior, 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, and anti-Plt drugs became his main treatment. During the 3 years of PNH history, his complete blood count (CBC) results fluctuated within the following range: white blood cell (WBC) count, 5.50–7.50 × 109/L; red blood cell (RBC) count, 2.90-3.30 × 1012/L; Hb level, 80-100 g/L; and Plt count, 170-230 × 109/L.

Three months prior to admission, 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 Hb and Plt levels following GC treatment:** Before methylprednisolone treatment, the patient’s CBC showed the following results: WBC count, 6.73 × 109/L; RBC count, 3.15 × 1012/L; Hb level, 85 g/L; Plt count, 195 × 109/L; and absolute reticulocyte (Ret) count, 290.2 × 109/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 × 109/L; RBC count, 2.73 × 1012/L; Hb level, 70 g/L; Plt count, 106 ×109/L; and Ret count, 283.3 × 109/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 aplastic anemia.

***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 × 109/L; RBC count, 1.72 × 1012/L; Hb level, 65 g/L; Plt count, 98 × 109/L; and Ret count, 274.90 × 109/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 (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 B12 were within the normal limits. Anti-erythrocyte and anti-Plt 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 speed 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 d of hospitalization, his Hb level decreased to 61 g/L, and his Plt level decreased to 7 × 109/L. The patient was transfused with 10 U of Plt concentrate and demonstrated Plt transfusion refractoriness. Observation of Plt transfusion refractoriness suggested that the patient was probably complicated with the development of TMA due to GC treatment because the transfused Plt 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 levels and Plt counts occurred after discontinuation of GC treatment***

After discontinuation of GC treatment, the patient’s Plt 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 Plt counts of 28 × 109/L. The patient was then discharged from our center.

***Hematological changes following initiation and discontinuation of GC treatment***

After the patient was discharged from our center, repeated CBC monitoring revealed that his Plt 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 hydroxybutyric dehydrogenase and LDH levels, and the Plt count in CBC monitoring severely decreased, resulting in the requirement for Plt transfusion. Observation of Plt 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 Plts 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[18-22]. 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 mo of GC treatment due to the intravenous hemolysis of PNH itself and the lack of awareness of GC-induced TMA.

The promotion of TMA onset 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 Plt 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 CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis) complement regulatory proteins on blood cells. Thrombotic propensity due to complement-mediated Plt 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]. Reduced serum levels of complement C3, increased serum levels of LHD 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 Plt 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 Plt 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 Plt 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 Plts occurs promptly after GC discontinuation, the diagnosis of GC-induced TMA can be established.

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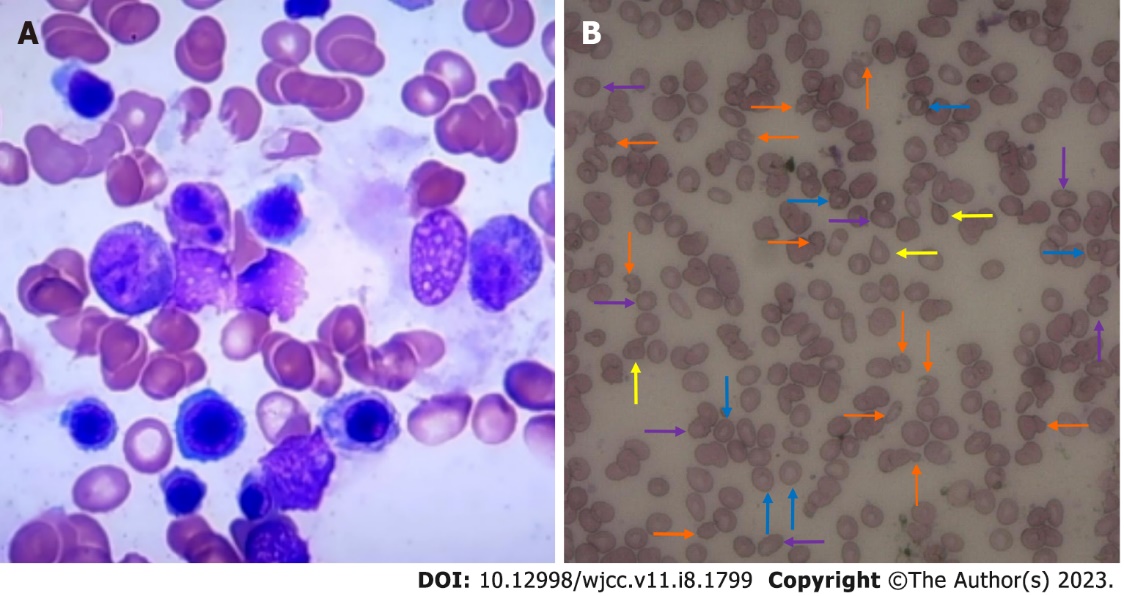
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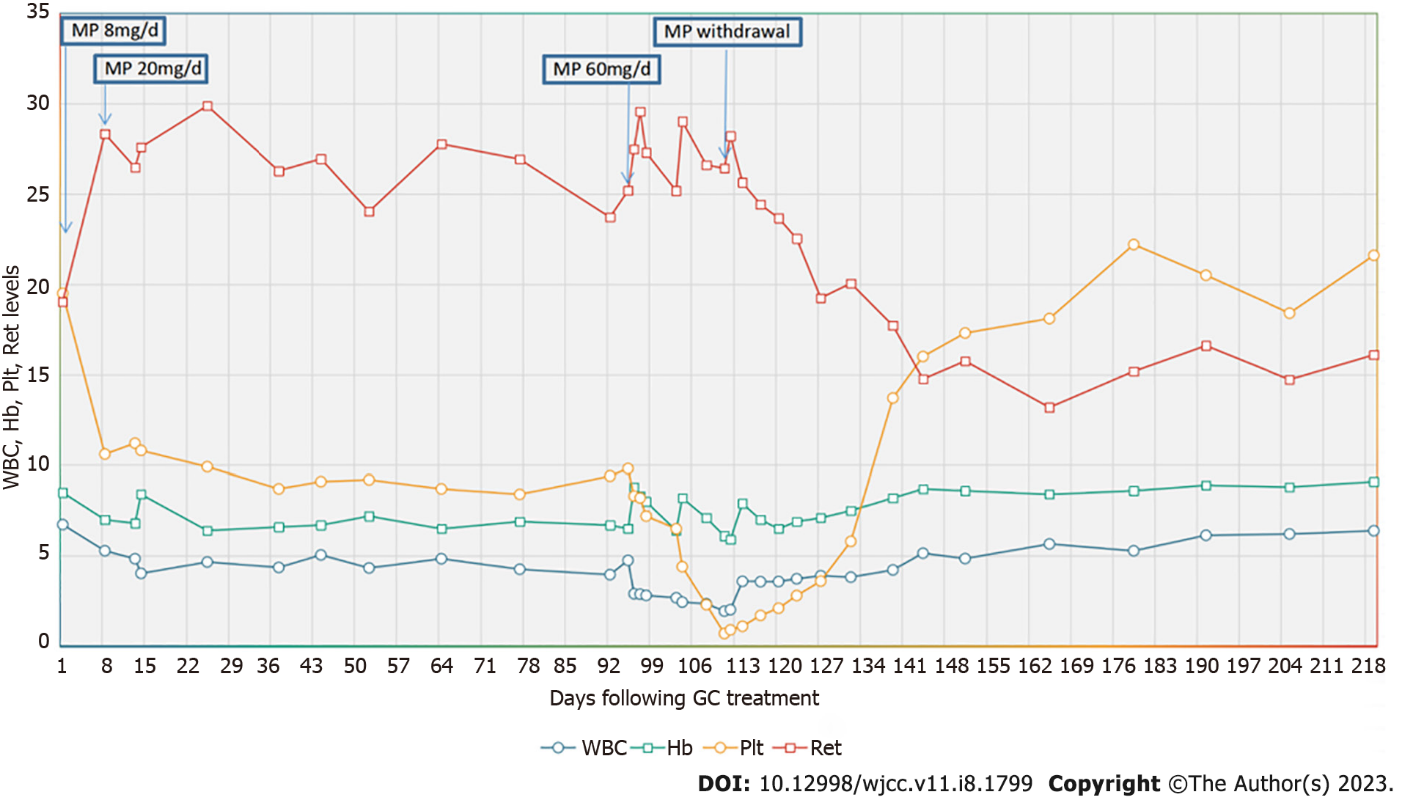
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**Figure Legends**



**Figure 1 Morphological examination of marrow and blood smears.** A: Marrow smears showed significantly increased cellularity with an increased percentage of erythroid progenitors in the absence of evident dysplasia. The number of megakaryocytes was within the normal level without immature and dysplastic features; B: Blood smears revealed the presence of a small number of schistocytes (orange arrows), dacryocytes (yellow arrows), acanthocytes (purple arrows) and target cells (blue arrows), confirming the existence of microangiopathic hemolysis. Platelets were visualized rarely.



**Figure 2 Sequential hematological changes following initiation and discontinuation of glucocorticoid treatment.** Following initiation of methylprednisolone treatment, the hemoglobin levels (Hb; × 10 g/L) and platelet counts (Plt; × 10 × 109/L) rapidly decreased, together with a decrease in white blood cells (WBC; × 109/L) and an increase in absolute reticulocyte count (Ret; × 10 × 109/L). Increasing the methylprednisolone dose after hospitalization resulted in the worsening of platelet consumption and intravenous hemolysis. Discontinuation of methylprednisolone treatment showed significant hematological improvement with restoration of hemoglobin levels and platelet counts similar to those prior to methylprednisolone treatment.



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