Anti-Glomerular Basement Membrane Glomerulonephritis Complicated by Thrombocytopenia

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Abstract

Rapidly progressive glomerulonephritis (RPGN) is characterized by the rapid deterioration of the renal function associated with crescent formation on renal biopsies. This report describes a case of RPGN caused by anti-glomerular basement membrane (GBM) glomerulonephritis in an elderly man with severe thrombocytopenia and a platelet count of $1.4 \times 10^4/\muL$. Thrombotic microangiopathy (TMA) and heparin-induced thrombocytopenia (HIT) were implicated in the severe decrease in platelets. This report also discusses the pathological background and clinical management of TMA and HIT among patients with anti-GBM glomerulonephritis.

Key words: Anti-GBM glomerulonephritis, crescent, heparin-induced thrombocytopenia, thrombotic microangiopathy, plasma exchange

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Introduction

Rapidly progressive glomerulonephritis (RPGN) is characterized by the rapid deterioration of the renal function and the observation of crescent formation on renal biopsy specimens (1). Crescentic glomerular injury is recognized to occur in various types of glomerular disease, including anti-glomerular basement membrane (GBM) glomerulonephritis, immune complex-mediated glomerulonephritis and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (1, 2). The initial pathogenic steps may be distinct; however, they eventually merge to a substantial degree forming a final common process of injury that results in glomerular inflammation, necrosis, leakage of fibrin-fibrinogen into the urinary space and crescent formation (3). This report describes a case of RPGN caused by anti-GBM glomerulonephritis in an elderly man with thrombocytopenia. Thrombotic microangiopathy (TMA) and heparin-induced thrombocytopenia (HIT) were implicated in the severe decrease in platelets.

Case Report

A 68-year-old man was admitted in September 2010 due to rapid deterioration of his renal function and general fatigue. Although he had no past medical history of renal disease, his serum creatinine (sCr) level was 1.02 mg/dL at the end of August 2010 and further increased to 2.65 mg/dL at the beginning of September 2010. Fifteen years prior to admission, the patient was found to have mild hypertension, for which he had received no medical care. He had smoked for more than forty years and denied the use of any drugs.

A physical examination performed at the time of admission revealed the patient to be alert and afebrile with edema in the lower extremities. The patient’s blood pressure was 169/103 mm Hg, his pulse was 89 beats/min and his respiratory rate was 12 breaths/min. Although the patient’s oxygen saturation was 97% while he breathed ambient air, a chest X-ray film demonstrated an accumulation of fluid in the left thorax. There were no rashes or lymphadenopathy, and no petechiae were found. The patient’s heart sounds were normal. Renal sonography revealed that the size of both kidneys and the renal cortex echogenicity were slightly

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Figure 1. A photomicrograph of the renal biopsy specimen. (A) Three sections of the same glomerulus showing collapse of a small amount of remaining glomerular tufts associated with segmental fibrinoid necrosis and cellular crescent formation. Note that the Bowman’s capsule appears to be almost totally destroyed. (Upper panel, Hematoxylin and Eosin (HE) staining; Middle panel, Periodic acid-Schiff (PAS) stain; Lower panel, Periodic acid-methenamine-silver (PAM) stain). (B) Three sections of the same glomerulus stained with anti-IgG antibodies (upper panel), anti-IgA antibodies (middle panel) and anti-IgM antibodies (lower panel). (C) Electron microscopy failed to show the presence of deposits along the capillary walls. The scale bars and scale are indicated in each panel.
negative in association with elevations in the levels of both Hb and hematocrit (Hct) immediately after the first PEX session. However, the patient’s platelet count remained around 4 to 6×10^4/μL despite the continuous administration of 30 mg/day of argatroban combined with 100 mg/day of aspirin. Moreover, the patient continued to exhibit decreases in the level of haptoglobin, subsequently requiring the administration of another session of PEX. The hemolytic and thrombocytopenic responses lagged behind for an additional twelve weeks after the platelet count and haptoglobin level normalized (Fig. 2). The patient’s deteriorated renal function persisted, and a periodic HD program was continued.

**Discussion**

The poor prognosis of patients with glomerulonephritis with extensive crescent formation has been documented for several decades, and various regimens of corticosteroids, immunosuppressants, anti-coagulants and anti-inflammatory agents have been administered to ameliorate glomerular damage with varied degrees of success (1). Moreover, the clinical significance of PEX in the treatment of various types of crescentic glomerulonephritis, especially anti-GBM glomerulonephritis, has been evaluated, and improvements in the renal function occurring after the initiation of PEX have been demonstrated in several studies (5-7). However, this regimen has so far never been properly assessed due to the rarity and acuteness of RPGN; therefore, the monotherapeutic significance of PEX in patients with RPGN remains to be elucidated. Indeed, it was difficult to precisely evaluate the clinical impact of PEX in the current case since the therapy was administered as an adjunct treatment to corticosteroids. Nevertheless, the immediate disappearance of anti-GBM and anti-PF4/heparin complex antibodies with a partial but prompt recovery in the levels of Hb and Hct and the platelet count just after the initial session of PEX suggest that the procedure was advantageous, at least in part, in controlling the accompanying disease activities implicated in the development of severe thrombocytopenia.

TMA is a pathological condition characterized by thrombosis of small vessels, intravascular breakdown of red blood cells, elevations in the levels of serum LDH and consumption of platelets. Hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) have received attention as two typical phenotypes of TMA (4, 8-10); however, TMA is also associated with other clinical conditions, such as malignant hypertension, malignancies, post-transplantation and various types of glomerular injuries (10). Not surprisingly, an association between TMA and anti-GBM glomerulonephritis has been demonstrated as well (11-15). There may be an etiological link between an ADAMTS 13-dependent mechanism and the development of TMA in patients with anti-GBM glomerulonephritis (13, 14); however, this was not the case in the current patient since no decreases in the ADAMTS 13 activity were confirmed. Previous reports of TMA occurring in association with varied diseases imply that vascular lesions might be associated with glomerular injuries or other as yet unidentified immune-mediated vascular injuries; however, they are not a specific disease entity. The gradual but transient decreases in LDH observed during each session of PEX might be related to immunomodulative effects on the as-
sumptive immune-based pathogenesis of TMA (1); however, the overall impact of PEX in the current case should be evaluated carefully since the clinical benefits of PEX have been primarily confirmed in TMA patients with decreased ADAMTS 13 activity (10, 13). Indeed, in the present case, schistocytes were still detectable on peripheral blood smears and gradual increases in the serum LDH level resumed, even after the second session of PEX was administered, suggesting that the TMA was persistent and refractory to PEX, although we failed to confirm any significant decreases in the serum level of haptoglobin. Otherwise, the condition may have been associated with the degree of fibrinoid necrosis within the kidneys, which may also have determined the grade of glomerular damage (4, 8). Interestingly, we confirmed severe destruction of GBMs on the renal biopsy, which can result in negative immunostaining for IgG along the glomerular capillary walls (3), as demonstrated in the current patient. Meanwhile, the presence of vasculopathies associated with TMA, such as occluded arterioles with fibrin plugs or schistocytes, was not confirmed in the renal biopsy specimen of the current patient. This is not surprising, however, since clinical phenotypes and pathological findings may not necessarily be confirmed simultaneously (16, 17). Finally, the fact that the titer of anti-GBM antibodies increased, even after the initiation of steroid treatment, led us to consider that there might be further tissue damage associated with the development of TMA, especially in light of the renal biopsy findings. At present, we do not know whether the duration of thrombocytopenia after the second session of PEX in the current case was reasonable, although a similar period before the clinical remission of thrombocytopenia and hemolysis due to TMA may not be exceptional (14).

Although there is no information available regarding the lower limit for platelet counts among patients with TMA, the severe decrease in the platelet count observed in the current case led us to consider that an alternative pathological mechanism was also associated with the development of thrombocytopenia in the present patient. Various agents have been implicated in the development of thrombocytopenia (18); however, we failed to confirm any improvements in several clinical parameters, including the platelet count, the haptoglobin level and the serum LDH level, despite the discontinuation of the suspicious agents. Instead, further serological evaluations revealed the presence of anti-PF4/heparin complex antibodies, suggesting the involvement of HIT in the excessive consumption of platelets (19, 20). The time period between the onset of thrombocytopenia and the administration of heparin varies according to a patient’s remote history of exposure (21). Patients who require HD and/or PEX could be at risk for HIT since anticoagulation therapy with heparin is the standard treatment in these procedures. In the current case, heparin was not used as an anticoagulant for HD; however, daily heparin flushes of dialysis catheters should play a pivotal role in the development of HIT. Indeed, there are several reports of cases of HIT induced by heparin flushes, although the precise frequency with which such conditions lead to HIT remains to be elucidated (22, 23).

The goal of treating HIT is to reduce the risk of thrombosis by reducing platelet activation and thrombin generation. All sources of heparin should be discontinued, and initial treatment requires several types of anticoagulant agents such as argatroban (21). Therapeutic PEX may also have potential benefits for the treatment of HIT, although there is limited information available regarding this issue (24, 25). Treatment with PEX and argatroban seemed to be partially successful in recovering the platelet count in the current case; however, the persistence of thrombocytopenia despite continuous administration of argatroban combined with aspirin suggested that HIT may be less responsible for the development of thrombocytopenia than TMA in the present patient. An association between anti-GBM glomerulonephritis and HIT may not be exceptional (26); however, the lack of data regarding such conditions suggests that the combination of these diseases is exceedingly rare. Nevertheless, the widespread use of heparin as an anticoagulant agent and/or heparin flushes for dialysis catheters in patients with RPGN who are dialyzed or treated with PEX implies that physicians are likely to encounter this problem. Conducting further studies and accumulating additional clinical cases are required to better determine the optimal management of RPGN in patients with TMA and/or HIT.

The authors state that they have no Conflict of Interest (COI).

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