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Anti-Glomerular Basement Membrane Disease With Thrombotic Thrombocytopenic Purpura

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ABSTRACT

We report a 25-year-old man who was initially presented with Rapidly Progressive Glomerulonephritis (RPGN) in Shahid Modarress Hospital, Tehran, Iran. His diagnosis was Anti-Glomerular Basement Membrane (Anti-GBM) disease that was confirmed by kidney biopsy, as his serum Anti-GBM antibody was undetectable. Although the patient was on cyclophosphamide and high dose prednisolone, he developed Thrombotic Thrombocytopenic Purpura (TTP). We initiated treatment with a high dose of prednisone and plasmapheresis. Because of his poor response, rituximab was administered. After that, the patient's hematologic criteria and clinical symptoms improved to an acceptable level. Our case is a unique form of negative serum Anti-GBM antibody disease which was complicated with TTP and responded to treatment with rituximab.

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Introduction

Rapidly Progressive Glomerulonephritis (RPGN) refers to clinicopathological features in which renal function deteriorates in a short period of time, accompanied by considerable crescentic formation [1, 2]. Along with other causes of this entity, Anti-Glomerular Basement Membrane (Anti-GBM) antibody disease is an insidious underlying cause of RPGN. In this disease, the intrinsic antigen of the glomerular basement membrane is invaded by circulating antibody resulting in glomerular damage [3-5].

Thrombotic thrombocytopenic purpura (TTP) is a microangiopathic disorder arising from thrombus formation in small vessels and platelet entrapment that finally causes thrombocytopenia, hemolytic anemia, and even organ damage [6]. The novel use of rituximab was a promising treatment in the management of patients with TTP and Anti-GBM antibody disease. Rituximab as the first line of therapy seems advantageous, especially in conditions like our patient with manifestations of both diseases [3, 7-9].

Not only Anti-GBM antibody disease is a rare situation but also limited data are available about the exact pathogenic mechanism, management, and association of this comorbidity [5, 10-13]. This case report presents a patient with the characteristics mentioned above. Then a brief review of literature about some similar cases was done with searching keywords of "Anti-GBM antibody", "TTP", "microangiopathy", and "rituximab".

Case Presentation

A 25-year-old man without any significant past medical history or previous measurement of serum creatinine referred to our clinic in Shahid Modarress Hospital, Tehran, Iran with the complaints of generalized fatigue, nausea, vomiting, headache, and both lower extremity edema within the past week in January 2017. He was admitted for further evaluation. He was a barber with a long standing history of intermittent alcohol consumption and smoking. He denied any drug abuse or notable family history.

At the time of hospitalization, his vital signs were as follows: conspicuous blood pressure 200/100 mm Hg, respiratory rate of 18 breaths /minute, and oral temperature of 37.8°C. His physical examination revealed pallor and bilateral lower extremity pitting edema. The rest of the examination findings were unremarkable. His urinary output was normal. The patient's oxygen saturation with the breathing room air was 97% and chest radiograph findings were unremarkable. Blood gas results were pH: 7.32, pCO_2: 37 mmHg, and HCO_3: 17.9. Hypertension was well-controlled by medications (Amlodipine 5mg/ BD, losartan 50 mg/ BD, Lasix 40 mg/TDS and diltiazem 120 mg/ BD).

An initial laboratory evaluation showed the following results: serum creatinine: 5.6 mg/dL; blood urea nitrogen: 42 mg/dl; potassium: 6 meq/L; hemoglobin: 6.2 mg/dL; platelet count: 241000/mL; LDH: 300 U/L; normal reticulocyte count. There were no significant findings in peripheral blood smear. His urine analysis revealed 3+ proteinuria and 2+ blood. Hyperkalemia was treated.

Renal sonography revealed increased echogenicity in both kidneys and median renal lengths were 12.5 cm on the left side and 12.8 cm on the right side. Despite medical therapy, his renal function progressively deteriorated, and hyperkalemia and anemia persisted. Because of no response to medical therapy, hemodialysis was initiated and the patient was referred to our hospital about one week after his first admission in the hospital.

At the time of admission, he was afebrile, his blood pressure was at 140/80 mm Hg and his oxygen saturation was 95% in room air. With the suspicion of RPGN, the patient underwent renal needle biopsy and received empirical methylprednisolone pulse therapy on three consecutive days.

Further laboratory tests were negative for Anti-Neutrophil Cytoplasmic Antibody (ANCA), Anti-GBM autoantibodies, complement levels, blood cultures, Anti-Aouble-Stranded DNA (Anti dsDNA), viral markers, Antistreptolysin O (ASO) Titer and Anti-Antinuclear Antibody (ANA).

The kidney needle biopsy showed extracapillary proliferative glomerulonephritis suspicious for the Anti-GBM related disease. Seven out of 17 glomeruli showed cellular crescents (Figure 1). The other glomeruli showed fibrocellular to fibrous crescents and IF/TA in 20% of the specimen (Figure 2). The IF microscopy study showed linear IgG and C3 deposition along the GBM. Based on pathological and serological findings, RPGN was caused by serum negative autoantibodies and the Anti-GBM disease was diagnosed. To treat Anti-GBM disease, he was given 750 mg intravenous infusion of cyclophosphamide and 7 sessions of plasma exchange. Then he was scheduled for second cyclophosphamide pulse therapy three weeks later. He was discharged with oral

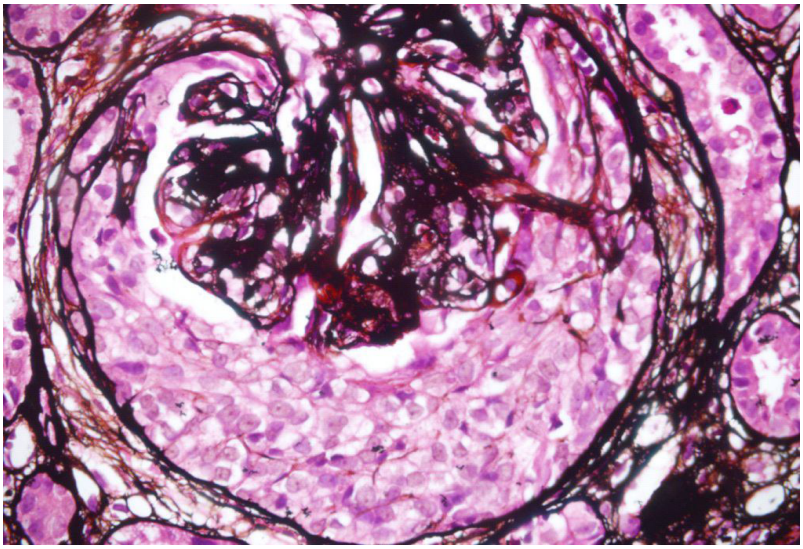

Figure 1. Renal biopsy on light microscope showing cellular and fibrocellular crescents (H&E, 200×)

prednisolone 1 mg/kg and conventional hemodialysis was scheduled (3-4 hour session per week).

After one week of second dose of Cyclophosphamide pulse therapy, he experienced one episode of generalized tonic-clonic seizure fever (oral temperature: 38°C). In general examination, mental status was normal and there was no signs or symptoms of infection or concomitant neurological damage. Laboratory tests showed: platelet counts 44000 per microlitre, LDH elevated to 1100 units/L. More than 5 percent fragmented RBC were presented in peripheral blood smear and no platelet aggregation was seen. Corrected reticulocyte count, PT and PTT were normal. Patient's hemoglobin remained low despite packed cell transfusions. Brain CT-scan was unremarkable.

As TTP was suspected, bone marrow aspiration and biopsy were done to exclude another differential diagnosis which was normal. Before plasmapheresis initiation, blood samples were collected for haptoglobin and ADAMTS13 activity measurement.

He underwent 14 sessions of Plasma Exchange (PEXs) and 500 mg methylprednisolone pulse therapy for 3 days but his platelet counts remained low and schistocyte was still above 5% in a peripheral blood smear. We provided twice a day PEX for 3 days and also 2 sessions of PEX using cryo-poor FFP solution.

ADAMTS13 activity level was 99.1% and haptoglobin level was undetectable. Despite these treatments, platelet counts reached to 80000 per mL, LDH decreased but not to the normal level. We administered

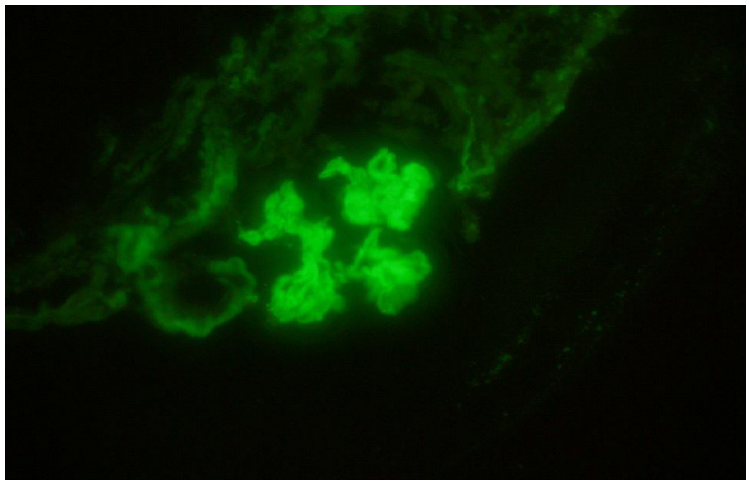

Figure 2. The immunofluorescence microscopy study showing linear IgG and C3 deposition along the GBM

a cycle of two 1000-mg intravenous infusions of rituximab separated by one week, resulting in remission of TTP. His platelet counts and LDH level reached the acceptable value.

After 30 days of hospitalization, the patient discharged with 50 mg oral prednisolone per day while platelet count was about 150 and no fragmented RBC on the blood smear. And he was free of symptoms like headache, nausea, vomiting, and fatigue. The patient is undergoing maintenance hemodialysis and is on the renal transplant waiting list.

Discussion

As mentioned above, RPGN is described by at least 50% crescent disposition of glomeruli histologically and is manifested with progressive renal dysfunction and glomerular injury. The amount of crescent formation, creatinine level, and the necessity of dialysis depend on the severity of the disease [1, 2]. Our patient had some good prognostic factors like negative ANCA antibodies and spared pulmonary involvement, but he required renal replacement therapy at presentation.

The incidence of Anti-GBM antibody disease is 0.5 –1 per million people per year and it is estimated that it consists of less than 20% cases of RPGN disease [3, 4]. Up to 90% mortality is reported in patients with the Anti-GBM disease who have not been managed in a timely fashion, especially with the association of pulmonary involvement [4, 11-15]. Our patient had no pulmonary involvement confirmed by history, physical exam, and imaging.

There is some evidence suggesting that exposure to benzene and other hydrocarbon inhalation like cigarette smoking, cocaine, or infection affect lungs and it might be linked to the onset of the disease [16, 17]. Our patient was a smoker but he did not have contact with any other potential stimulus mentioned above.

Despite the rareness of the disease, the pathogenesis of the disease has been well studied. Moreover, its clinical symptoms, manifestation, and prognosis have been reviewed in the literature; the Anti-GBM autoantibodies are directed against the a3 chain of type IV collagen within the glomeruli and or pulmonary basement membrane, and complement system activation, especially C4 may have a role in this scenario which may be triggered by infection, though the main mechanism is unknown [5, 10].

The diagnosis of Anti-GBM antibody disease is by documenting of Anti-GBM antibody in serum or linear deposition of IgG on renal biopsy, but the accuracy of serology assessment is uncertain [18]. In a few pieces of literature negative Anti-GBM antibodies, the disease has been described as a factor associated with the delay in diagnosis and appropriate medical management that increase mortality and morbidity among patients [19, 20].

The possible explanation lies in different laboratory methods for antibody measurement [18]. We used standard ELISA technique to detect serum Anti-GBM autoantibodies. In these cases, the efficacy of treatment by plasma exchange is variable, but in general it is efficacious; plasmapheresis should be cut off when circulating Anti-GBM antibody is no longer detectable in serum [21]. In these circumstances like our patient, deciding on the length of treatment will be spectacular.

Because of technical limitations of laboratory assays and despite lack of clarity of the effectiveness in these circumstances, we used plasma exchange for the patient, according to successful similar previous studies in serum negative Anti-GBM disease patients [22-24].

All patients in previous reports, like our patient, had increased serum creatinine level at presentation. Current regimens used to eradicate circulating antibody consist of corticosteroid, immunosuppressant drugs, and anti-inflammatory agents [22]. As the first line of therapy, we administered steroid with intravenous cyclophosphamide.

With the justification that PEX removes serum antibodies, it is a beneficial combination therapy in the setting of Anti-GBM disease, but as monotherapy in RPGN, its advantages are not well documented [10].

Some case reports portrayed complete remission by the use of rituximab in Anti-GBM disease. Touzot et al. reviewed 8 patients in a retrospective study who received rituximab for the severe cases of Anti-GBM disease. The results show that this therapy can be used as an alternative therapy in this disease [7]. It is recommended that rituximab is used in some conditions like the failure of immunological response, severe cases of disease, and dependency to plasmapheresis or hemodialysis. Notable amelioration of clinical symptoms was seen in our case with rituximab use. It has been proposed that rituximab can be used as a sparing agent to decelerate side effects of other immunosuppressive drugs and also escalate clearance of Anti-GBM antibodies. It attacks B cells which produce Anti-GBM anti-

bodies, and in our case, it was negative so we could not appraise the rituximab value based on this mechanism [25].

Thrombotic Microangiopathy (TMA) is a specific pathologic lesion of arterioles and capillaries. TTP is a phenotype of TMA, presented by neurologic abnormalities, Lactate Dehydrogenase (LDH) elevation, and thrombocytopenia and schistocyte in PBS [6]. Despite various predisposing risk factors, the main etiology of TTP is inherited or acquired deficiency of ADAMTS13 [6]. ADAMTS13 activity may be low while clinical symptoms are consistent with the disease, or vice versa; antibodies levels during remission are arbitrary [26].

ADAMTS13 activity is low in a preponderance of TTP patients but not all [27]. The current research studies have shown that microangiopathic hemolytic anemia and thrombocytopenia are entailed for a definitive diagnosis of TTP. The results may be affected by various factors [28]. TMA is a spectrum of pathophysiological processes which comprise a group of diseases. Regardless of the intersection of these diseases, all are described as TMA [29].

In our patient, ADAMTS13 activity was reported normal; however, TTP was the most congruous diagnosis based on our patient's clinical features. Based on presumptive diagnosis and previous studies, we initiated PEX. However, we considered other possible causes, but all other evaluations were negative.

At the time of thrombocytopenia presentation, our patient had no infection. His stool exam was negative for organisms and toxins, and his blood pressure was under control with no signs and symptoms of vasculitis. Our patient presented with thrombocytopenia, elevated serum LDH, more than 5% red cell fragments on PBS and one episode of seizure.

Anti-GBM antibody disease comorbid with TMA is uncommon [3, 8, 9, 24]. There are some theories that explain TMA in association with Anti-GBM. It was suggested that TMA is triggered by endothelial injury in the context of necrotizing glomeruli affected by crescentic GN. Some theories suggest that the release of ADAMTS13 mediates this mechanism [5, 30].

In some studies, methylprednisolone, cyclophosphamide, and other cytotoxic agents are blamed as the cause of TMA in the setting of bone marrow transplant [3, 31, 32]. Inflammation and autoimmunity may be associated with TTP and Interleukin (IL)-12 elevation enact in the pathogenesis of both TTP and Anti-GBM disease [33]. IL-12 and gamma interferon contribute to the crescent formation as well [34].

Stave GM in 1984 and Li et al. (2004) described TMA as a complication of Anti-GBM GN but they merely explained their cases without mentioning any theory for pathology and the treatment [3, 8]. One study explained an unknown common genetic pathway, based on a report of a daughter with TMA whose mother had Anti-GBM antibody disease [35].

Plasma exchange with steroids is the acceptable treatment in the setting of TTP. Plasma exchange in some cases have been effective and in some cases did not yield desired results [5, 36-41]. In the failure of treatment with intensified glucocorticoid and PEX regimen, immunosuppressive agents such as vincristine and cyclophosphamide can be tried.

Addition of rituximab to standard therapy is a novel treatment for TTP. Though studies are limited in this regard, in general, rituximab is recommended for patients with TTP and it shows even as the first-line therapy with lower relapse. There are no reports of a case similar to our patient with negative Anti-GBM autoantibodies, acute renal failure, anemia and Anti-GBM deposits on renal biopsy with TMA features simultaneously.

According to previous related studies and comorbidity of Anti-GBM antibody disease and TTP in our case, we finally prescribed rituximab as the best choice. In conclusion, according to other studies that we reviewed here, using rituximab as an alternative therapy in combination with other main treatments for this disease, may be effective for both Anti-GBM disease and TTP. Finally, the study of these rare cases helps us to better understand this autoimmune disease. Further clinical studies are necessary for the evaluation of the effectiveness of this treatment.

Ethical Considerations

Compliance with ethical guidelines

Informed consent was obtained from individual participant involved in the study.

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Conflict of interest

The authors declared no conflict of interest.

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