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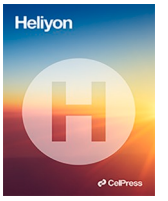

Case report

Protein A immunoadsorption for anti-glomerular basement membrane nephritis

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ABSTRACT

Anti-glomerular basement membrane (GBM) nephritis is a rare autoimmune disorder characterized by acute and rapidly progressive glomerulonephritis. In this report, we present the case of a 52-year-old woman with anti-GBM nephritis who was treated with Staphylococcus Protein A immunoadsorption in combination with glucocorticoids and cyclophosphamide. After 8 cycles of immunoadsorption, the patient's anti-GBM antibodies decreased from 363 AU/mL to less than 20 AU/mL, accompanied by a dropped immunoglobin G level, although renal impairment persisted. We reviewed the therapeutic options for anti-GBM nephritis and compared plasma exchange, double filtration plasmapheresis, and immunoadsorption with regard to plasma consumption, allergic events, and plasma components loss. Protein A immunoadsorption appears to be a promising treatment modality for anti-GBM nephritis.

1. Introduction

Anti-glomerular basement membrane (GBM) nephritis is a rare autoimmune disorder characterized by the rapidly progressive glomerulonephritis (RPGN) and possible pulmonary hemorrhage (PH). Diagnosis is based on the presence of serum anti-GBM antibodies, and linear immunoglobulin G (IgG) deposition along the GBM with crescentic glomeruli with/without alveolar basement membrane involvement. These antibodies target the non-collagenous (NC1) domain shared by the α3, α4, and α5 chains of type IV collagen. Despite its low incidence, anti-GBM nephritis accounts for approximately 20 % of RPGN cases [1]. The main goal in managing this condition is to eliminate circulating anti-GBM antibodies. Currently, the established standard approach for treating anti-GBM nephritis involves a combination of plasma exchange (PE), corticosteroids, and cyclophosphamide (CTX). Immunoadsorption using Staphylococcus protein A (PAIA), is an innovative blood purification therapy that selectively removes IgG antibodies. Unlike PE, it specifically targets IgG and immune complexes, preserving coagulation factors and other plasma constituents. Extensive research has demonstrated its effectiveness in various applications, including sensitized allograft recipients and patients with autoimmune disorders such as systemic lupus erythematosus (SLE) and polyangiitis. In this report, we present a case of an anti-GBM nephritis patient treated with PAIA in combination with immunosuppressive therapy. Therapeutic options for anti-GBM nephritis were discussed.

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2. Case presentation

A 52-year-old female patient who complained of persistent symmetrical lower extremity edema and intermittently coughing up white sputum mixed with bright red blood for the past two weeks was admitted to our hospital. She was first admitted to a local hospital where she received temporary hemodialysis due to elevated serum creatinine (Scr) at 1292 μmol/L with an estimated glomerular filtration rate (e-GFR) of 4.6 ml/min/1.73 m^2. After the detection of elevated anti-GBM antibodies (226.41 AU/mL), she was transferred to our center. At the time of admission, she had been suspended from hemodialysis for 7 days with a daily urine output of nearly 1000 mL. This patient reported no significant past medical history. She recalled in a routine annual medical examination last year, her Scr was within normal range.

The patient's physical examination revealed a body temperature of 36.4 °C, pulse rate of 71 beats/min, blood pressure of 178/103 mmHg, and respiratory rate of 20/min with moderate bilateral lower extremity edema. The anti-GBM antibody level was 363 AU/mL (Table 1), while anti-neutrophil cytoplasmic antibodies (ANCAs) and dsDNA were negative. Chest computed tomography (CT) revealed the presence of inflammatory nodules but not overt PH despite a history of suspected hemoptysis before admission. Due to the patient refusal in the beginning, the kidney biopsy was postponed.

In consideration of her high anti-GBM antibody level and suspected hemoptysis, we initiated immunosuppressive treatment in combination with PAIA, along with supportive care. The immunosuppressive regimen included methylprednisolone at an initial dose of 40 mg/day for 5 days, followed by pulse therapy at 500 mg/day for 3 days, which was subsequently transitioned to an oral dose of 40 mg/day. On the 13th day, the patient was infused with CTX at a dose of 200 mg. During hospitalization, she underwent 8 cycles of PAIA (on days 2, 3, 5, 8, 12, 18, 22, and 25). Most sessions processed a plasma volume of 4800 mL, except on days 5, 8, and 12, when 6000 mL was treated. During hospitalization, the sputum culture results revealed coinfection involving *P. aeruginosa*, Escherichia, and the *Aspergillus fumigatus* complex with elevation in procalcitonin (PCT) level. We supplemented the treatment regimen with cefoxitin (1 g for 19 days) and voriconazole (0.2 g for 6 days and 0.25 g for 7 days). Following this treatment, the PCT level decreased to 0.44 ng/mL, and the second CT scan showed a noticeable reduction in inflammatory foci.

The anti-GBM antibody concentration decreased from 363 AU/mL to 132 AU/mL after the first PAIA session, indicating a significant response to PAIA therapy. Although there were slight rebounds in the levels of circulating anti-GBM antibodies and IgG, they decreased markedly after 8 PAIA sessions, accompanied by the administration of immunosuppressants (Fig. 1). Renal pathology was available two weeks after admission, which revealed crescentic glomerulonephritis. The biopsy specimen contained 19–21 glomeruli, with 1–2 showing spherical sclerosis. There were 18 crescents, consisting of 1–2 cellular crescents, 12–13 fibro-cellular crescents, and 5 fibrous crescents (Fig. 2). Immunofluorescence staining showed liner deposition of IgG antibodies along the glomerular GBM. Electron microscopy confirmed the presence of a sclerosed glomerulus and moderate chronic damage to the tubulointerstitial tissue. During the current hospitalization, no hemoptysis was recorded, but unfortunately, her renal function didn't recover and hemodialysis was resumed. After 31 days in hospital, the patient was successfully discharged. At the recent follow-up at the ninth month, the patient was on maintenance hemodialysis and negative in anti-GBM antibodies, without any extra-renal symptoms.

3. Discussion

Anti-GBM nephritis is a rare small vessel vasculitis that affects the glomerular and pulmonary capillaries. It has a low incidence rate of 1.64 per million population per year, as reported in an Irish study [2]. The GBM is composed of type IV collagen molecules, which consist of triple-helical protomers of the α3, α4, and α5 chains. The autoimmune response in anti-GBM nephritis mainly targets the E(A) and E(B) epitopes of the NC1 domain of α3 or the E(A) region of the α5 chain [3]. These antibodies primarily affect capillaries in the glomeruli, lungs, and occasionally the retina, choroid plexus, and cochlea, leading to autoimmune reactions [4,5]. Anti-GBM nephritis is considered an autoimmune "conformeropathy", whose symptoms can vary depending on the autoantibody profile [3]. Additionally,

Table 1
Laboratory examinations at admission and discharge.

Laboratory test	admission	discharge
CBC		
Hemoglobin (115–150 g/L)	81	92
White blood cell (3.5–9.5*10^9/L)	6.19	8.35
Platelet (100–300*10^9/L)	270	80
Biochemistry		
Protein (65.0–85.0 g/L)	63.9	44.4
Albumin (40.0–55.0 g/L)	33	32.1
Urea (3.1-8.8 mmol/L)	6.6	10.4
Creatinine (48–79 μmol/L)	520	336
Uric acid (155-357 μmol/Lmol/L)	181	185
Potassium (3.5–5.3 mmol/L)	3.59	3.19
e-GFR (ml/min/1.73m^2)	7.62	12.92
Anti-GBM antibodies (<20 AU/mL)	363	16.4
PCT (<0.046 ng/mL)	0.56	0.44

Abbreviations: CBC, complete blood count; e-GFR, estimated-glomerular filtration rate; anti-GBM antibodies, anti-glomerular basement membrane antibodies; PCT, procalcitonin.

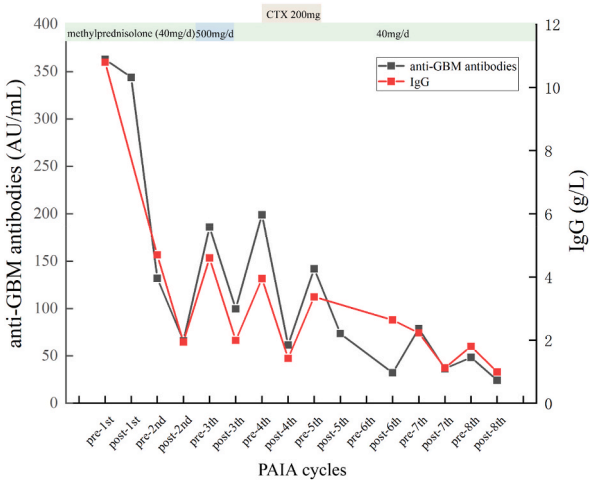

Fig. 1. Changes of anti-GBM antibodies and IgG pre- and post-PAIA cycles Abbreviations: Anti-GBM antibodies, anti-glomerular basement membrane antibodies; IgG immunoglobin G; PAIA, Protein A immunoadsorption; CTX, cyclophosphamide.

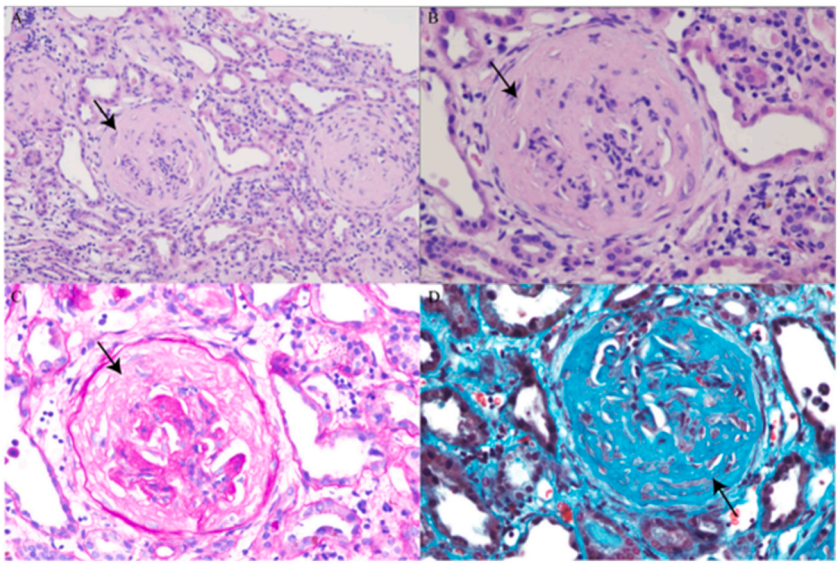

Fig. 2. Glomerular crescents under microscope of renal biopsy tissue
Panel A: Hematoxylin eosin stain (200 ×); Panel B: Hematoxylin eosin stain (400 ×); Panel C: Periodic acid-schiff stain (400 ×); Panel D: Masson staining (400 ×). Arrow: crescent formation.

a recent study identified laminin-521 as a novel target for autoantibodies, which is closely linked to PH, hemoptysis, and smoking. Patients with laminin-521 antibodies have a higher risk of progressing to end-stage kidney disease and mortality compared to those without the antibodies (87.9 % vs. 67.6 %) [6]. Beyond humoral immunity, T cells are capable of striking glomeruli in rat models [7]. Glomerular T lymphocytes have also been observed in kidney biopsy specimens from patients [8,9]. However, more conclusive evidence and a clear understanding of the pathophysiology of T cells and anti-GBM nephritis remains to be clarified.

For RPGN patients, it is essential to differentiate between anti-GBM nephritis and ANCA-associated vasculitis (AAV) and other circulating autoimmune complex-induced kidney impairment such as lupus nephritis. Clinically, AVV and SLE impair multiple systems, while anti-GBM nephritis mainly involve kidneys and lungs. Moreover, renal biopsy results are distinct among the three diseases. Although all of them present with crescentic glomeruli, AAV shows capillary vasculitis and necrotizing tubulointerstitial inflammation with pauci-immune complex, whereas in SLE, renal biopsy shows full-house nephropathy (IgG, IgA, IgM, C3, C1q), while anti-GBM nephritis is characterized by linear IgG deposition. In this case, our patient suffered from kidney damage and suspected lung injury. Serum antibodies against GBM were detected, while ANCAs and dsDNA antibodies were negative. Renal biopsy also revealed crescent formation and IgG deposition without other antibodies or complements. Therefore, the diagnosis of anti-GBM nephritis was made. Timely renal biopsy is essential in assessing renal fibrosis and guiding treatment. The development of noninvasive biomarkers of

the degree of fibrosis is also warranted. Patients who test double-positive for both anti-GBM antibodies and ANCAs constitute approximately 21%–47 % of individuals diagnosed with anti-GBM nephritis [10]. Clinically, they are commonly characterized by concurrent AAV and anti-GBM nephritis. Intriguingly, these "double-positive" patients demonstrate a heightened propensity to rebound from dialysis dependency following standard treatment, displaying superior long-term renal survival compared to that of their single-positive counterparts [11]. However, the patient we reported here was only positive for anti-GBM antibodies.

Regarding therapies, there are three main principles. Firstly, it is crucial to remove the existing anti-GBM antibodies to alleviate PH and promote the recovery of kidney function. Therefore, traditional PE, double filtration plasmapheresis (DFPP), or PAIA are considered the fundamental treatment approaches for eliminating IgG effectively. Secondly, it is essential to halt the progression of inflammation by glucocorticoids, which have been used for over 50 years to treat Goodpasture syndrome [12]. Finally, our ultimate goal is to prevent the formation of new anti-GBM autoantibodies, which is often accomplished by employing cytotoxic agents such as cyclophosphamide or rituximab targeting B-cell depletion. The exploration of optimized therapeutic strategies for anti-GBM nephritis has undergone several stages. Initially, treatments focused on using glucocorticoids and cyclophosphamide to target inflammation and excessive immune responses. However, the prognosis remains unsatisfactory, with over 80 % of patients either succumbing to the disease or requiring long-term dialysis [13]. Encouraged by promising outcomes in a few patients treated with traditional PE, researchers conducted a randomized clinical trial to compare patients receiving immunosuppressive agents with or without PE. The study demonstrated better clearance of anti-GBM antibodies and improved kidney function in the PE group [14]. However, traditional PE indiscriminately removes essential components in plasma, such as albumin, and consumes a large volume of plasma. It is also associated with the risk of anaphylactic events, hemolysis, and transfusion-transmitted infections [15]. To address these concerns, DFPP, which has efficacy comparable to that of traditional PE, was introduced to selectively remove high-molecular-weight immunoglobulins, minimize protein loss, reduce the need for plasma volume, decrease severe complications, and ensure hemodynamic stability [16]. More recently, selective removal of immunoglobin by immunoadsorption (IA) has emerged as a preferred method for more precise elimination of pathogenic antibodies and to minimize adverse events associated with plasma infusion. A retrospective analysis involving 10 patients with anti-GBM nephritis highlighted the robust safety, noninferiority, and comparability of IA to PE in terms of severe complications, renal function, and patient survival [17]. The differences among PE, DFPP, and IA are outlined in Table 2.

Protein A is a component of the cellular wall of Staphylococcus aureus and can bind to the Fc segment of immunoglobulin, especially IgG. PAIA has been used in a variety of diseases such as autoimmune encephalitis, Hashimoto's thyroiditis, and Guillain-Barré Syndrome [18,19], while there have been few reports on its application in anti-GBM nephritis [20]. Interestingly, PAIA seemed to achieve better patient and renal survival than PE in AAV patients [21], but comparisons between PAIA and PE in anti-GBM nephritis are lacking. In this case, PAIA effectively decreased the anti-GBM antibody level which might improve patient outcome and prevent hemoptysis, but her kidney function didn't recover due to the high proportion of fibrotic crescents. The therapeutic effects of PAIA on renal prognosis of anti-GBM nephritis need to be validated in more patients in the future.

4. Conclusion

In conclusion, we present the case of a 52-year-old female diagnosed with anti-GBM nephritis who was treated with methylprednisolone, CTX, and PAIA. Over 8 sessions of PAIA, the anti-GBM antibodies decreased to normal range without overt PH, while her renal function unfortunately didn't recover due to an advanced degree of fibrosis by renal biopsy. PAIA holds promise as a potential treatment option for patients with a significant increase in anti-GBM antibodies, and its therapeutic effects for PRGN need to be further validated in clinical practice.

Ethics statement

Institutional Review Board approval was not required as this was a case report.

Informed consent statement

Informed consent to report the case was obtained from the patient.

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Conflict of interest disclosure

The authors declared that there was no conflict of interest.

Data availability statement

Data will be made available on request. The research data presented in the study are included in the article. Further inquiries can be

Table 2
Comparisons of PE, DFPP, and IA.

Therapy approaches		Advantages	Disadvantages
PE	i) 1–1.5 times plasma volume (maximum 4000 ml); 60 ml/kg body weight; ii) daily (until the level of anti-GBM antibodies are normal)	effectively eliminates wide-spectrum pathogenic autoantibodies and immune complexes	i) a reduction of IgG approximately 65%–70 % per session; ii) loss of albumin, fibrinogen, clotting factors; iii) risk of allergic reactions, sepsis, hemolysis; iv) consume a significant volume of plasma.
DFPP	1–1.5 times plasma volume	i) less consumption in plasma volume ii) semi-selective for pathogenic antibodies compared with traditional PE	less effective in the removal of specific antibodies compared with IA
IA	2.5–3 times plasma volume	i) selective removal of immunoglobulins ii) a reduction of IgG approximately 75%–80 % per session iii) low risk of allergy reactions and bloodborne diseases	i) relatively more expensive ii) less supporting evidence

Abbreviations: PE, plasma exchange; DFPP, double filtration plasmapheresis; IA, immunoadsorption.

directed to the corresponding author.

CRediT authorship contribution statement

Caihong Liu: Writing – original draft. **Xu Li:** Data curation. **Yingying Yang:** Conceptualization. **Yuliang Zhao:** Conceptualization. **Ling Zhang:** Supervision.

Declaration of competing interest

The authors declared that there was no competing interest.

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