Clinical Case Reports

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CASE REPORT

Goodpasture's disease following extracorporeal shock wave lithotripsy: a case report & literature review

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Funding Information
No funding information provided.

Received: 26 June 2014; Revised: 1 October 2014; Accepted: 25 October 2014

***Clinical Case Reports* 2015; 3(3): 160–164**

doi: 10.1002/ccr3.190

Key Clinical Message

Shock wave lithotripsy may unmask epitopes within the glomerular basement membrane, leading to the formation of anti-glomerular basement membrane (GBM) antibodies and clinical disease in susceptible individuals. Although rare, our case highlights the need for vigilant monitoring of renal function following extracorporeal shock wave lithotripsy. This may allow for early recognition, treatment and improved outcome of anti-GBM disease.

Keywords

Anti-gbm, extracorporeal shock wave lithotripsy, goodpasture's, lithotripsy.

Introduction

Anti-glomerular basement membrane disease (anti-GBM) is a rare autoimmune disease causing a pattern of glomerulonephritis and pulmonary hemorrhage. The disease is defined by the presence of autoantibodies directed at specific antigenic targets within the glomerular and/or pulmonary basement membrane [1]. First described in 1918, and named after the physician who initially reported it, the term Goodpasture's disease is now often reserved for those exhibiting both glomerular and pulmonary involvement.

Whilst the pathogenesis of anti-GBM disease is still unclear, it is an area that has been intensely studied as it provides an excellent model of human autoimmune disease. It has become apparent that certain genetic traits predispose to the development of the condition. However, factors that cause disease initiation remain unclear. Numerous case reports have implicated various environmental insults as triggers to the disease. It is proposed that these insults may initiate cell-mediated responses leading to the production of anti-GBM antibodies and thus clinical disease. Here, we describe the case of Goodpasture's disease developing following extracorporeal shock wave lithotripsy (ESWL).

Case Report

The patient is a 67-year-old female who was due to undergo three sessions of ESWL for two symptomatic renal calculi in the right kidney. She was otherwise in good health with hypertension her only significant medical history, for which she took Candesartan. Her baseline creatinine measured before initiation of therapy was 47 μmol/L. She received two treatments with ESWL 4 weeks apart, each session consisting of 3200 shocks on 75 kPa energy.

Five weeks after the first session of lithotripsy the patient was admitted to hospital feeling generally unwell with difficulty passing urine, abdominal pain, and feverish paroxysms. Initial biochemistry revealed an acute kidney failure with a creatinine of 1179 μmol/L, K^+ of 6.92 mmol/L and pH 7.30. Ultrasound revealed no abnormalities other than the presence of a single renal calculus in the right kidney (Fig. 1).The patient became anuric on the wards and dialysis was commenced on the second day of her stay. Further investigations found immunoglobulin and complement levels were all within normal limits. She was negative for ANA and ANCA. However, Anti-GBM titer was positive with a value of 643 AU/mL (laboratory reference value 0–7 AU/mL), a level diagnostic of

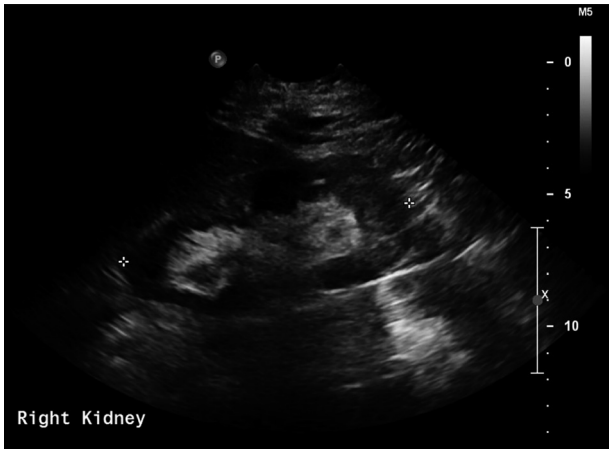

Figure 1. Ultrasound image demonstrating the presence of a solitary renal calculus in the right kidney with no other significant pathology.

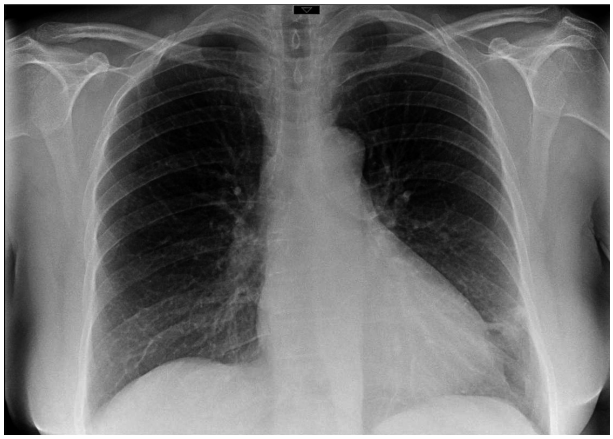

Figure 2. Chest X-ray performed at admission demonstrating clear lung fields.

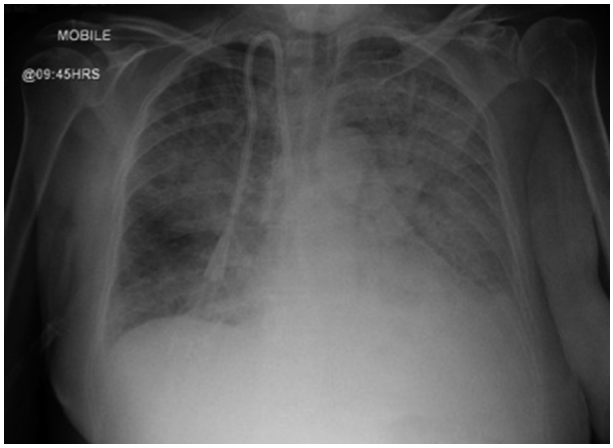

Figure 3. Chest X-ray performed during period of hypoxia demonstrating bilateral fluffy infiltrates compatible with pulmonary haemorrhage.

anti-GBM disease. Circulating levels of anti-GBM antibodies were quantified using enzyme-linked immunosorbent assay (ELISA).

Anti-GBM disease is regarded as a one hit disease [2]. The chance of renal recovery is low if the creatinine reaches a level >504 μmol/L [3, 4] and thus Kidney Disease: Improving Global Outcomes (KIDGO) Guidelines suggest that in those patients who are dialysis dependent from presentation, and in the absence of pulmonary involvement, there is no role for immunosuppressive therapy or plasma exchange [5]. There was deemed to be no benefit, either diagnostically or prognostically in performing a renal biopsy.

The patient was further managed on the outpatient dialysis unit for the next 3 weeks. However, findings of low hemoglobin 7.0 and reports of melaena forced an admission for emergency esophago-gastro duodenoscopy. Prior to endoscopy the patient was transfused two units of packed red cells. This was performed during a session of hemodialysis and a neutral fluids balance was maintained throughout. A routine chest X-ray performed at this point demonstrated clear lung fields (Fig. 2). Endoscopy performed the following day identified a duodenal ulcer was, which was treated with a heat probe resulting in successful cessation of bleeding.

Postprocedure, the patient became hypoxic, with saturations of 80% on air. Clinical examination elicited bilateral crepitations throughout the lungs, with no other evidence of fluid overload. A Chest X-ray at this point revealed bilateral fluffy infiltrates compatible with pulmonary hemorrhage (Fig. 3). Increased gas transfer was demonstrated, with a K_{CO} 2.14 mmol/min kPa/L (145% of predicted value), confirming the diagnosis of pulmonary hemorrhage. This was further supported by evidence of a 3.2 g/L decrease in hemoglobin levels over the next 3 days, as well as persistently elevated anti-GBM titer. A bedside ECHO confirmed normal left ventricular size with good systolic function and normal pulmonary vascular pressures. Given the degree of respiratory failure and the confidence of diagnosis it was felt that bronchoscopy would be of little benefit and would put the patient at undue risk of decompensation. The patient's respiratory failure was managed with high-flow oxygen. Positive pressure ventilation was not required.

At this stage it was decided to start the patient on a treatment regimen including pulsed methylprednisolone, cyclophosphamide, and plasma exchange, which was commenced that day. She underwent 17 sessions of plasma exchange over the following 3 weeks which successfully reduced her circulating levels of anti-GBM antibodies to within acceptable levels. Human Leukocyte Antigen

(HLA) class I and II typing was performed by PCR SSP. The patient was found to express serotype HLA DR4 and DQ6.

Discussion

The glomerular basement membrane is located between the glomerular endothelial and visceral epithelial cells. Fenestrations within the endothelium allow exposure of the basement membrane to blood. The membrane itself is formed of interwoven mesh of type IV collagen with fibronectin, laminins, nidogen, and sulphated proteoglycans [6]. Type IV collagen – which is also a significant component of the pulmonary basement membrane – is formed of five subclasses of α chain [7]. It is the noncollagen domain 1 of the α3 chain (α3 (IV)NC1) that has been identified as the main target for Anti-GBM antibodies [8]. Interestingly, collagen eluted from the glomerular basement membrane does not present the Goodpasture antigen. Glomerular basement membrane has traditionally been separated from the Bowman's capsule in vitro using ultrasonification. However, further proteolysis is required in order to expose the Goodpasture antigen, usually in the form of enzyme therapy [9].

Antibodies against this specific target within the glomerular basement membrane are shown to be pathogenic. In a classic transfer experiment by Lerner et al. [10], it was demonstrated that antibodies eluted from the kidneys of patients with anti-GBM disease could elicit a similar pattern of disease when injected into squirrel monkeys in vivo. Evidence of the pathogenic nature of anti-GBM antibodies is also supported by the observation that the clinical and histological severity of anti-GBM disease is positively correlated with the circulating levels of antibodies [7]. Recent research has highlighted the involvement of cell-mediated mechanisms in the initiation of anti-GBM antibody production. T cells play an important role in response to exposure to the Goodpasture antigen, generating signals that enable B-cell proliferation and production of anti-GBM antibody [1]. This is evidenced by the isolation of T cells from patients with anti-GBM disease that react with auto-antigens known to be recognized by anti-GBM antibodies [11].

As with many autoimmune diseases, initiation of anti-GBM disease is believed to be through environmental stimuli in individuals with a particular genetic susceptibility. The genetics of the disease have therefore been widely investigated with a particular focus on genes related to the coding for the HLA, which forms part of the Major Histocompatability Complex (MHC). HLA class II molecules including DR, DP, and DQ are involved in the presentation of antigen-derived peptides to T cells, thus initiating immune responses, including antibody production [1]. Several studies, including a Meta-analysis of more than 130 patients with anti-GBM disease, have found both positive and negative correlations with particular of the HLA class II molecules [12, 13]. The highest disease susceptibility is seen in those with HLA-DR15 (a split specificity for the formally used DR2) and HLA DR4 phenotypes, which are expressed in more than 90% of patients with anti-GBM disease [14]. Further analysis has shown a six amino-acid motif, in the antigen-binding groove, which is common to the DRβ chains both DR15 & DR4.

Despite this positive association, genetic traits alone are not sufficient in explaining the occurrence of anti-GBM disease. As Pusey speculates [15] there is good reason to believe that environmental factors are required for disease expression, as 25% of the population possess the DR2 phenotype, yet the annual incidence of anti-GBM disease is only one case per 2 million of the population [16]. Reports of anti-GBM disease associated with environmental stimuli are now widespread throughout the literature. As discussed previously, we report the fourth case of anti-GBM glomerulonephritis following ESWL. This is, however, the first case where the full spectrum of Goodpasture's disease has manifested, with both pulmonary hemorrhage and glomerulonephritis occurring. Previous cases have all exhibited highly susceptible HLA class II molecules *(*Table 1*),* and this again is the case in our reported patient who was found to have the HLA DR4 phenotype.

In addition to ESWL there are numerous reports of other environmental stimuli appearing to initiate anti-GBM glomerulonephritis. One recognized association seems to be a preexisting glomerulonephritis, in particular

Table 1. Summary of reported cases of anti-GBM disease following ESWL

Author	Patient demographics	Human leukocyte antigen phenotype	Time elapsed after extracorporeal shock wave lithotripsy (ESWL)	Antiglomerular-basement-membrane antibodies present prior to ESWL
Guerin et al. [17]	67 M	DR2 (now split to DR15 & DR16)	7 months	Negative
Iwamoto et al. [18]	37 F	DR2 (now split to DR15 & DR16)	3 months	Negative
Xenocostas et al. [19]	72 M	DR15	3–7 months	Not measured
Cranfield et al.	67 F	DR4	1 month	Not measured

ANCA-positive vasculitis [20], with up to 38% of patients with anti-GBM disease having detectable ANCA in the serum [21]. Anti-GBM glomerulonephritis has also been described shortly after the occurrence of ureteric obstruction[21]. Similar associations can also be observed between environmental lung insults and the onset of pulmonary hemorrhage in anti-GBM disease.

We propose that ESWL can cause exposure of a previously cryptic epitope within the basement membrane, which in genetically susceptible individual may result in the initiation of clinical anti-GBM disease. As Guerin suggests [18], insult and injury to the basement membrane may cause alterations to its structure, perhaps through local inflammation, with infiltrating leukocytes-releasing granular enzymes and free radicals. This could favor the exposure of the globular domain NC1 of collagen, which contains the cryptic Goodpasture antigen, triggering an autoimmune response. ESWL is certainly capable of producing morphological changes within renal tissue; effects that have been well documented since it was first introduced. Complications described following ESWL include intraparenchymal and subcapsular bleeding, which have been linked to irreversible acute renal failure [22–24]. Histopathological examination after ESWL has revealed alterations in the endothelium and glomerular epithelium [25], with damaged renal corpuscles typically demonstrating breaks in the Bowman's capsule and damage to podocytes and mesangial cells. We suggest that ESWL provides a degree of proteolysis that exposes the Goodpasture antigen in vivo. Our idea of disease pathogenesis is further supported by recent findings indicating that a single T-cell epitope of the antigen is sufficient to initiate glomerulonephritis with the full clinical spectrum of anti-GBM disease [26]. Our hypothesis is yet to be proven in vivo. Westman et al. [27] investigated the occurrence of autoantibodies following ESWL, with no patients demonstrating new formation of anti-GBM antibodies. However, the number of patients studied was small and tissue typing was not performed. Therefore, it is uncertain whether the patients investigated presented disease susceptible HLA class II molecules that may predispose to antibody formation.

It is difficult to draw any conclusions from this single case alone. Whilst patients expressing HLA DR 4 & DR15 may be at increased risk of developing anti-GBM disease it would be clinically inappropriate to suggest that HLA class I and II typing is performed on all patients undergoing ESWL. However, our case highlights the need for vigilant monitoring of renal function following ESWL. It also further supports the recommendation that anti-GBM antibodies should be determined in a patient who develops acute renal failure, allowing for earlier diagnosis and treatment leading to potentially improved outcomes in these cases.

Conflict of Interest

None declared.

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