

Case and Review

Etanercept-Induced Anti-Glomerular Basement Membrane Disease

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Keywords

Tumour necrosis factor-alpha/antagonists and inhibitors · Etanercept · Anti-glomerular basement membrane disease

Abstract

Anti-glomerular basement membrane (anti-GBM) disease is a rare form of small-vessel vasculitis that typically causes rapidly progressive glomerulonephritis with or without alveolar haemorrhage. Previously, there has only been one reported case of tumour necrosis factor- α (TNF- α) antagonist-induced anti-GBM disease. Here, we describe the first reported case of etanercept-induced anti-GBM disease. A 55-year-old Caucasian man was referred to our tertiary specialist renal centre with a history of painless macroscopic haematuria. The patient has been receiving weekly etanercept injections over the past 12 months for psoriatic arthropathy. The serum immunology panel results highlighted a significantly raised anti-GBM titre (370.1 U). Etanercept was stopped, and the patient was empirically commenced on pulsed methylprednisolone, cyclophosphamide, and plasma exchange. A renal biopsy showed crescentic glomerulonephritis. Few days after admission, he tested positive for coronavirus disease 2019 (COVID-19), and a decision was made to withhold cyclophosphamide. There was further decline in renal function with hyperkalaemia for which he received 2 sessions of haemodialysis. He was restarted on cyclophosphamide upon discharge. The patient was switched to rituximab treatment afterwards as he developed leucopenia 2 weeks following the commencement of cyclophosphamide. The serum creatinine level continued to improve and remained dialysis-independent. In conclusion, with the increased use of etanercept and other TNF- α antagonists, the prescribing clinician must be aware of the rare but life-threatening drug-induced vasculitis. We recommend careful monitoring of renal indices with the use of this class of medications.

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Introduction

Anti-glomerular basement membrane (anti-GBM) disease is a rare form of small-vessel vasculitis that typically causes rapidly progressive glomerulonephritis with or without alveolar haemorrhage. The exact cause of its immune trigger is not well understood. It has been hypothesized that environmental factors can cause clusters of anti-GBM disease in genetically susceptible individuals [1].

Tumour necrosis factor- α (TNF- α) antagonists such as adalimumab, infliximab, and etanercept are commonly used to treat inflammatory diseases such as psoriasis, rheumatoid arthritis, and inflammatory bowel disease. Previously, there has only been one reported case of TNF- α antagonist-induced anti-GBM disease, where the patient received adalimumab for over 4 years to manage his rheumatoid arthritis [2]. We describe the first reported case of etanercept-induced anti-GBM disease.

Case Presentation

A 55-year-old Caucasian man was referred to the local district general hospital by his general practitioner with a 3-week history of sudden-onset painless macroscopic haematuria. The patient has been receiving weekly etanercept injections over the past 12 months for psoriatic arthropathy, which was diagnosed in 2017 when he initially presented with oligoarthritis in his left knee and elbow. Etanercept injections were effective in managing his psoriatic arthritis symptoms in remission. The patient received methotrexate treatment prior to initiation of etanercept. Other than psoriatic arthropathy, there was no history of renal disease or other significant past medical history. The patient is a non-smoker and denied previous use of anabolic steroids or other synthetic bodybuilding supplements.

In view of the severity of his renal function derangement upon admission (serum creatinine 4.7 mg/dL), the patient was transferred to our tertiary specialist renal centre. Upon our review, he denied clinical symptoms such as haemoptysis, epistaxis, or appearances of skin rash manifestations. No features of active arthritis were detected on physical examination. Though there was mild pitting oedema on both ankles, clear chest sounds were noted on auscultation. Urinalysis showed haematoproteinuria (blood 3+, protein 1+). Chest X-ray did not identify abnormal radiological signs with clear lung fields and normal mediastinal and cardiac shadows. A further contrast computed tomography scan showed normal-sized kidneys without evidence of obstructive disease. The serum immunology panel results highlighted a significantly raised anti-GBM titre (370.1 U). Etanercept was stopped, and the patient was empirically commenced on 3 doses of pulsed intravenous (IV) methylprednisolone (250 mg each), oral cyclophosphamide (2 mg/kg/day), and plasma exchange via an intravascular catheter. A renal biopsy was performed which on pathological examination showed cellular crescents in 14 out of 28 glomeruli with the presence of moderate interstitial inflammation (shown in Fig. 1). Falling anti-GBM titres were observed in the initial days following treatment initiation, though serum creatinine levels continued to rise (shown in Fig. 2).

The patient tested positive for coronavirus disease 2019 (COVID-19) on day 5 following admission on a routine surveillance throat swab polymerase chain reaction, which was performed as he was in close contact with another patient who tested positive. After the positive COVID-19 results, the decision was made to withhold cyclophosphamide following discussion with the patient on the risks of immunosuppressive treatment with a positive COVID-19 diagnosis. Treatment with 30 mg/day oral prednisolone and plasma exchange continued with monitoring of respiratory symptoms. During the next 11 days of inpatient

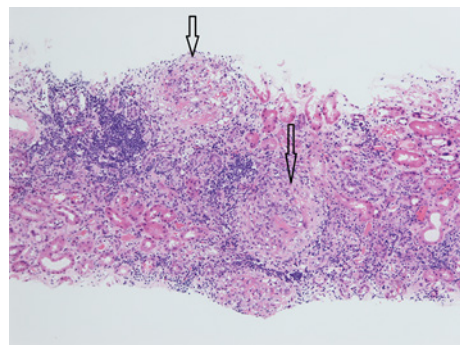


Fig. 1. Cellular crescent with interstitial inflammatory changes in light microscopy. (Arrows show crescents of similar age.)

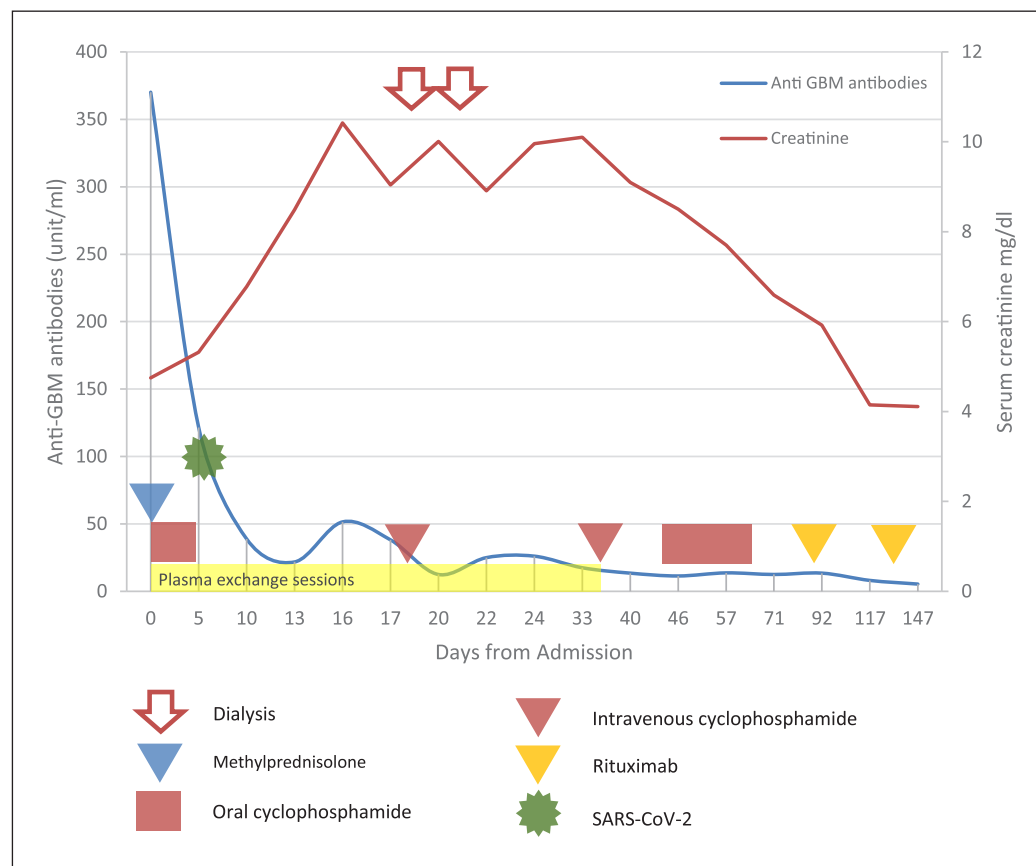


Fig. 2. Progression of anti-GBM titre and serum creatinine levels from day 0 to day 147 following initial hospital admission. GBM, glomerular basement membrane.

admission, there was further decline in renal function with hyperkalaemia, for which he received 2 sessions of in-centre haemodialysis.

On day 16 following admission, the patient recovered clinically, and he received 1 g IV cyclophosphamide prior to home discharge the same day. He received another 1 g IV cyclophosphamide in the community under supervision before switching to an oral preparation of cyclophosphamide. The patient was switched to rituximab treatment afterwards and received 2 doses (1 g per dose). This was due to the development of leucopenia 2 weeks following the commencement of oral cyclophosphamide. By that point, full tissue typing results were

available, which showed the patient having the HLA-DRB1-15 allele, conferring a high susceptibility of him developing anti-GBM disease [3].

The patient's serum creatinine levels decreased by almost two-thirds from peak admission levels at 5 months following hospital discharge, and he is under close follow-up review from the renal unit. Currently, there is no further immunosuppression planned as his anti-GBM antibody titres remain negative. The patient did not require further dialysis, and his psoriatic arthritis remained in remission without further requirements for etanercept or another form of disease-modifying anti-rheumatic therapy.

Discussion

TNF- α , released into human circulation in its functional 17-kDa soluble form, is a cytokine primarily involved in homeostasis of the body's immune cells [4]. TNF- α is chiefly produced by activated macrophages, although T-helper cells and natural killer cells amongst other cell types contribute towards its production. As an acute phase reactant, excess TNF- α production promotes systemic inflammation [5]. Collectively, TNF receptor (TNFR) 1 and TNFR2 are markers of the TNF pathway [6]. TNFR1 is detected in most cell types and could be activated by both the membrane-bound and trimeric soluble forms of TNF- α [7]. TNFR2 is selectively located in cells of the immune system – oligodendrocytes, astrocytes, T cells, endothelial cells, human mesenchymal stem cells, myocytes, and thymocytes. It will usually only respond towards homotrimeric, membrane-bound forms of TNF- α [8–14]. TNF- α either exists as a free protein or is bound to these circulating receptors in plasma [6].

There is dysregulation of TNF- α in the pathophysiology of various autoimmune disorders, namely, rheumatoid arthritis, ankylosing spondylitis, and psoriasis-associated conditions. Excess TNF- α also plays a key role in renal inflammation. In healthy individuals, TNFR1 could be detected within the normal glomerular endothelial structure, situated usually at the Golgi apparatus, whilst TNF- α and TNFR2 are not expected to be found [15]. During an inflammatory response, TNF- α , TNFR1, and TNFR2 would be expressed and disseminated across the glomerular and tubular cellular structures [16]. Animal studies have demonstrated TNF- α recruitment within the intrinsic renal structure prior to its direct effects of promoting kidney injury [17]. TNF- α is a pleotropic cytokine and its immunomodulatory and anti-inflammatory activities through immune cell apoptosis should be recognized [18]. TNF- α antagonists have been the conventional pharmacological treatment for autoimmune and immune-mediated diseases where a high level of TNF- α is present, where it is a good target for inflammatory suppression. Anti-TNF- α therapy is either a monoclonal antibody or, in the case patient's scenario, a circulating receptor fusion protein such as etanercept. Monoclonal antibodies to TNF- α , such as infliximab and adalimumab, could bind to both soluble and transmembrane TNF- α , using this mechanism to downregulate TNF- α -inflammatory activity including adhesion molecule expression, cytokine production, neutrophil activity, dendritic cell production, matrix metalloproteinase production, and osteoclast differentiation. Most monoclonal antibodies to TNF- α can lyse cells which express TNF- α in the presence of complement [19]. Etanercept has a much longer half-life in the circulation as opposed to the simple soluble TNF receptor. As a fusion protein, etanercept functions as a decoy receptor which binds to TNF- α , thereby deactivating TNF- α and blunting its effects of inducing an inflammatory response [20].

The associations between etanercept and intrinsic renal disease are complex. Historically, there have been multiple findings of glomerulonephritis presentations related to etanercept use (Table 1). Previously reported cases include necrotizing crescentic glomerulonephritis, membranous nephropathy, ANCA-positive glomerulonephritis, minimal change disease, lupus nephritis, Henoch-Schonlein purpura with glomerulonephritis, extracapillary glomerulonephritis,

Table 1. Reported cases of glomerulonephritis in patients on etanercept treatment

Author	Age, yr, sex	Duration of etanercept	Discontinuation of etanercept	Treatment received	Outcome
<i>Necrotizing crescentic glomerulonephritis</i>					
Ammar et al. [21]	56, F	3 years	Yes	Oral prednisolone Mycophenolate mofetil	Discharged with outpatient follow-up
Kaneko et al. [22]	35, F	28 months	Yes	Supportive	Discharged with outpatient follow-up
Kaneko et al. [22]	65, F	18 months	Yes	IV pulsed methylprednisolone	Discharged with outpatient follow-up
Doulton et al. [23]	34, F	8 months	Yes	Oral prednisolone Cyclophosphamide	Discharged with outpatient follow-up
Stokes et al. [24]	55, M	4 months	No	IV cyclophosphamide	Died
Kemp et al. [25]	65, F	11 months	Yes	Not described	Discharged with outpatient follow-up
<i>Membranous glomerulonephritis</i>					
Kaushik et al. [26]	60, F	2 months	Yes	Supportive	Discharged
Stokes et al. [24]	53, F	6 months	Yes	Oral prednisolone Cyclophosphamide	Discharged with outpatient follow-up
<i>ANCA-positive glomerulonephritis</i>					
Alkhunaizi and Dawamneh [27]	30, F	2 months	Yes	Oral prednisolone Cyclophosphamide	Discharged following recovery
Nazarro et al. [28]	64, M	“Few months”	In Italian	IV methylprednisolone	Discharged with outpatient follow-up
Saint Marcoux and De Bandt [29]	21 patients – age and gender not individually described	Mean duration 11.2 months	Not individually described	Not individually described	Not individually described
<i>Minimal change disease</i>					
Piga et al. [30]	75, F	8 months	Yes	IV methylprednisolone Oral prednisolone	Discharged with outpatient follow-up
Koya et al. [31]	43, M	3 months	Yes	Supportive	Discharged with outpatient follow-up

Table 1 (continued)

Author	Age, yr, sex	Duration of etanercept	Discontinuation of etanercept	Treatment received	Outcome
<i>Lupus nephritis</i>					
Yahya et al. [32]	57, F	8 months	Yes	Supportive	Discharged with near resolution. Outpatient follow-up
Haake et al. [33]	70, M	21 months	Yes	Oral prednisolone IV cyclophosphamide	Discharged
Stokes et al. [24]	30, F	30 months	Yes	Oral prednisolone Mycophenolate mofetil	Discharged with outpatient follow-up
<i>Henoch-Schönlein purpura (IgA vasculitis) with glomerulonephritis</i>					
Rolle et al. [34]	61, M	5 months	Yes	IV pulsed methylprednisolone Oral prednisolone	Discharged with outpatient follow-up
Asahina et al. [35]	61, F	6 months	Yes	Oral prednisolone	Discharged with outpatient follow-up
Rolle et al. [34]	61, M	5 months	Yes	IV pulsed methylprednisolone Oral prednisolone	Discharged with outpatient follow-up
Asahina et al. [35]	61, F	6 months	Yes	Oral prednisolone	Discharged with outpatient follow-up
Lee et al. [36]	57, M	11 months	Yes	IV methylprednisolone Oral prednisolone	Discharged with outpatient follow-up
Duffy et al. [37]	60, F	3 months	Yes	IV methylprednisolone IV cyclophosphamide	Discharged with outpatient follow-up
<i>Extracapillary glomerulonephritis</i>					
Menè et al. [38]	15, F	5 months	Yes	IV methylprednisolone Oral prednisolone	Discharged with outpatient follow-up
<i>IgA nephropathy</i>					
Kemp et al. [25]	Not described	11 months	Not described	Not described	Not described
Kemp et al. [25]	Not described	1 month	Not described	Not described	Not described

IV, intravenous.

and IgA nephropathy [21–38]. The pathophysiology of how etanercept leads to crescentic glomerulonephritis remains unclear, but the plausible mechanisms would include a genetic predisposition, epigenetic dysregulation, and drug biotransformation. COVID-19-associated anti-GBM disease has been reported recently, but the negative COVID-19 polymerase chain reaction test and antibody serological test on the day of admission ruled out this possibility [39].

Cases describing manifestations of anti-GBM disease in patients receiving etanercept have not been published previously. Although the manifestation of anti-GBM disease is associated with various factors, reported cases of autoimmune glomerular injury following etanercept treatment >12 months suggest the possibility of a temporal relationship between etanercept treatment and anti-GBM disease [21, 22, 24, 33]. In our case, a renal biopsy was done even before we received the anti-GBM titre result, and hence, an immunofluorescence on the biopsy was not routinely performed. We acknowledge that this may limit the diagnosis of anti-GBM disease. However, the following points strongly supported the diagnosis of anti-GBM disease: (1) the crescents in the haematoxylin and eosin stain of the biopsy were all in similar age, (2) the high specificity of the anti-GBM antibody assay used in this case (specifically directed to type IV collagen alpha 3), (3) a genetic predisposition of our patient for anti-GBM disease by carrying the HLA-DRB1-15 allele, (4) absence of a history or clinical features of Alport's syndrome, and (5) a particularly good response to treatment (decline in anti-GBM titres and renal function recovery).

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Statement of Ethics

Written informed consent from the patient has been obtained for publication including images. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study is exempt from ethical committee approval as it is not required for a single case report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.A.-C. and A.P. obtained the history, performed the physical examinations, and obtained investigation reports. S.A.-C. and H.H.L.W. wrote the initial draft. R.C. and A.P. reviewed the paper and revised it critically. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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