CASE REPORT

Recurrent postinfectious glomerulonephritis: an unusual evolution compatible with C3 glomerulopathy

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SUMMARY

Acute endocapillary glomerulonephritis, as its name suggests, is a one-time process, which usually resolves within weeks. However, in a small percentage of patients, the disease becomes chronic. In these cases, a deregulation in the alternative complement pathway, which can be caused by mutations or autoantibodies, has been proposed as a pathophysiological mechanism. As a result, the alternative complement pathway remains active after resolution of infection. We report a patient with two episodes of acute renal failure, both times diagnosed by renal biopsy of acute endocapillary glomerulonephritis, with slow recovery after two episodes of low-serum complement C3, haematuria and proteinuria.

BACKGROUND

Complement system alterations influence the development of different systemic diseases, including several with renal involvement. The complement system is part of the innate immunity, and as its name suggests, ‘complements’ the activity of antibodies by helping to eliminate different pathogens. It is constituted by more than 60 plasma and membrane proteins. These proteins form three different activation pathways, which converge at a common terminal cascade and whose function is to lyse damaged cells or pathogens. Another part of the complement system is a large number of regulatory proteins, whose function is the control of the complement activation so as to help prevent damage to healthy cells.

The three complement activation pathways are called the classical pathway, the lectin pathway and the alternative pathway.^{1–3} Each is activated in a different way, but all converge at a common point, the C3 protein. The classical pathway is activated by IgM or IgG antibodies bound to antigens. The lectin pathway is initiated by the binding of the lectin protein with pathogen carbohydrates, leading to the subsequent activation of the classical complement pathway. Phylogenetically, the alternative pathway is considered the most primitive. It does not require the presence of antibodies or lectins to be activated. This pathway undergoes constant low-level activation in the circulation but is regulated by a set of proteins that keep this activation under control. If C3 is deposited in healthy tissue,

it is rapidly inactivated by regulatory proteins. If C3 binds to a pathogen or a damaged cell, the response of the alternative complement pathway is amplified. Recently, a group of diseases associated with the alternative complement pathway deregulation, which includes paroxysmal nocturnal haemoglobinuria, atypical haemolytic uraemic syndrome and a new entity called C3 glomerulopathy, has been more precisely defined.⁴

C3 glomerulopathy is characterised by C3 accumulation with absent or scanty immunoglobulin deposition in the glomerulus.⁵ This entity includes a heterogeneous group of kidney diseases, among which postinfectious glomerulonephritis (GN) with atypical evolution is found. This atypical evolution consists of a not complete recovery of renal function within a few days to weeks, with persistent or recurrent evidence of kidney disease.

CASE PRESENTATION

A 68-year-old man with a history of hypertension who, after a week of fever and cough, was admitted with acute renal failure, haematuria and proteinuria in nephrotic range. Renal function continued to deteriorate with the following results: creatinine 9 mg/dL, urea 322 mg/dL, proteinuria 13 g/24 hours, sediment over 100 red cells per field. The patient's condition worsened with progression to anuria, so that the start of haemodialysis was necessary. Complementary studies were performed with C3 13 (82–158) mg/dL and C4 2.4 (12–40) mg/dL, with negative antinuclear antibodies and antineutrophil cytoplasmic antibodies. A monoclonal gammopathy IgG-kappa, with a monoclonal peak of 0.19 g/dL, was observed in the electrophoretic serum spectrum. In the electrophoretic urinary spectrum, no monoclonal components were observed. In cultures and serological studies, only *Klebsiella pneumoniae* was detected, >100 000 CFU/mL in urine.

Renal biopsy was performed, which showed seven glomeruli with dilated capillaries and an extensive exudative phenomena with polymorphonuclear cells, mild interstitial oedema and no tubular alterations. Immunofluorescence showed diffuse mesangial granular C3 deposit, being negative for the other antigens (C4, IgA, IgG, IgM, fibrinogen, albumin and kappa and lambda chains). There was not enough tissue for electron

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A

B

Figure 1 Evolution of proteinuria, creatinine and serum complement proteins. (A) Proteinuria (closed diamonds) and serum creatinine (closed squares) levels were registered during the whole follow-up period after the first and second admission. (B) Complement proteins, C3 (closed circles) and C4 (closed squares), were measured to follow their evolution during the whole follow-up period after the first and second admission. Continuous line indicates the lower limit of C4 protein normal serum levels, and discontinuous line indicates the lower limit of C3 protein normal serum levels.

microscopy. The diagnosis of diffuse endocapillary proliferative GN was issued.

TREATMENT

Having pain and inflammation in his knee, the patient received empirical treatment with imipenem, linezolid and steroids. After this treatment was instituted, urine output began to increase, which was interrupted by removing steroids. Given this finding, steroids were restarted with quick recovery of renal function and slow improvement of C3 complement and proteinuria.

OUTCOME AND FOLLOW-UP

A year later, the patient had creatinine 1.28 mg/dL, proteinuria 600 mg/24 hours (figure 1A), microhaematuria 1–5 red cells per field, C3 90 mg/dL and C4 28 mg/dL (figure 1B). Eighteen months after the first episode of acute renal failure, his renal function again deteriorated with nephrotic range proteinuria and haematuria (figure 1A), in the context of fever, without a clear infectious focus. It was also necessary to start haemodialysis for anuria. The patient presented C3 19 mg/dL, C4 6.2 mg/dL (figure 1B) and factor H 11.2 (12–56) mg/dL.

A new renal biopsy was done, and the diagnosis of exudative endocapillary proliferative GN with extracapillary proliferation (21% crescents) was obtained again (figure 2). In direct immunofluorescence, C3 deposit was observed in the subepithelial zone of capillary walls and in mesangium (figure 3), and mild

IgG deposit was observed in mesangial and capillaries walls. C4d staining was negative. In addition, a direct immunofluorescence study was performed on paraffin-embedded material for the detection of light chains, and no deposits were identified. There

Figure 2 Renal biopsy. Diffuse proliferative glomerulonephritis with substantial endocapillary hypercellularity including neutrophils. Masson trichrome stain. Original magnification $\times 40$.

Figure 3 Renal biopsy. C3 deposit in the subepithelial zone of capillary walls and in mesangium. Direct immunofluorescence. Original magnification $\times 40$.

was not enough tissue for electron microscopy in the second biopsy.

An exhaustive study was done to try to identify the infectious agent that could have triggered the disease. Blood cultures, urine culture, antistreptolysin O and PCR of parvovirus B19 in blood were negative, with PCR of parvovirus B19 positive in bone marrow.

Before knowing this result, we started empirical treatment with imipenem, linezolid and steroids with improvement of kidney function.

Subsequently, an immune and genetic study was conducted, detecting complement factor H (CHF) levels in the normal range. In the CHF gene, the patient carried in homozygosis a polymorphism that has been described as a risk haplotype for developing a dense deposit disease. A change in the promoter region of the gene membrane cofactor protein (MCP) was also found of uncertain significance. In the latest revision, the patient maintained a small monoclonal component IgG-kappa of 0.08 g/dL.

DISCUSSION

The case presented is a patient with two episodes of acute renal failure, with haematuria and proteinuria, precipitated by an infectious process. In both episodes, decreased C3 and C4 complement protein was detected. This suggests, at least initially, an activation of the classical complement pathway, because C4 protein belongs to this pathway. In both episodes of acute renal failure, a kidney biopsy is done, yielding a result that correlates with the pathological diagnosis of acute endocapillary GN.

However, what is not fully consistent with this diagnosis is the clinical course of the disease. Acute endocapillary GN is a one-time process that is resolved in weeks. In this case, proteinuria and haematuria recovered slowly, with a new episode of acute renal failure after 18 months. C4 complement recovered quickly after the acute process, whereas complement C3 also took months to normalise. Although this evolution is exceptional, in the literature we can find similar cases.⁶ A recent report documents 11 cases of patients diagnosed by renal biopsy of postinfectious GN, but with an atypical clinical course, with persistent haematuria and proteinuria. In all cases, the histological study revealed proliferative GN on light microscopy, bright C3 staining with or without immunoglobulins on

immunofluorescence microscopy and subepithelial deposits or ‘humps’ on electron microscopy. In all patients, some underlying alteration was detected in the alternative complement pathway, either mutations or autoantibodies. It is considered that in these cases an infection may trigger the disorder, but after recovery from the infection, kidney damage persists due to the continuous activation of the alternative pathway.

In this regard, the traditional classification of GN, mainly based on morphological findings, is being redefined at present, based on pathophysiological mechanisms.⁷ Recently, the term C3 glomerulopathy has been coined, which encompasses a spectrum of glomerular diseases in which the primary pathogenic process is a deregulation of the alternative complement pathway, causing a predominant C3 deposit in glomeruli. We can detect this deposit by immunofluorescence techniques and also by the finding of electron-dense deposits on electron microscopy.^{4,8}

This entity may have different histological presentations, so that various morphological patterns could be considered within C3 glomerulopathy: membranoproliferative glomerulonephritis (MPGN) type II or dense deposit disease, some types of MPGN types I and III and endocapillary proliferative GN.

Although the exact influence of the patient's genetic profile in the pathogenesis of the diseases with an alternative complement pathway deregulation is not completely understood, and more data are required to inform genotype–phenotype correlations in C3 glomerulopathy; it seems that in many cases it could have a great relevance.⁹

There are genetic variants, which are classified as benign, likely benign, variant of uncertain significance, likely pathogenic or pathogenic following international guidelines.¹⁰ Our patient had a change in the promoter region of the gene MCP of uncertain significance and a genetic combination in CHF considered likely pathogenic for developing a dense deposit disease.

Cook proposes that it is possible that immune complexes, which activate the classical pathway of complement, may trigger clinical disease in some patients who have abnormal control of the alternative pathway and C3 glomerulopathy. In these patients, bright C4d staining may provide evidence of classical pathway activation at the time of exacerbation.¹¹ Sethi *et al*¹² examined 13 biopsies of postinfectious glomerulonephritis and found seven positive for C4d, but they do not present follow-up data for these cases and we do not know if C4d deposit could be useful to distinguish cases with different clinical course. In most cases, C4d staining appeared to mirror the IgG staining. This paper shows that C4d could be a useful tool to describe cases of proliferative GN better in the future.

In our patient, although C4 decreased in serum in the two episodes of acute renal failure, C4d staining was negative in the biopsy, with only a C3 deposit, suggestive of C3 glomerulopathy. This is compatible with an infectious process that could have activated the classical pathway in serum and could have triggered a more persistent activation of the alternative pathway with a renal damage.

It is worth noting that other patients with C3 glomerulopathy with a serum monoclonal protein have been published. It is believed that the monoclonal protein may have pathogenic significance. In some cases, the protein acts as a monoclonal antibody to proteins of the alternative pathway.^{13–15} Indeed, recent articles report a high frequency of monoclonal gammopathy of undetermined significance associated with C3 glomerulopathy, reaching up to 31% of cases in some series, mainly in the older population.¹⁶

The existence of possible triggers, such as a monoclonal protein or the infections associated, could have caused in our

patient with this genetic risk profile the development of the disease.

Currently, we have little information about possible therapeutic options used to treat C3 glomerulopathy. Until 2012, an immunosuppressant was used usually against T or B cells, such as cyclophosphamide, mycophenolate or rituximab, sometimes associated with plasmapheresis. The results are inconclusive, and there is little evidence at present to recommend these treatments. Steroid treatment has not proven effective in dense deposit disease, and its effectiveness in other forms of MPGN is variable.^{8 17} In this regard, we must highlight the very favourable response from the patient after receiving steroid treatment. It is possible that the presence of extracapillary proliferation could be related to this response, although this histological finding was obtained only in the second biopsy.

In the future, it is possible that eculizumab, a monoclonal antibody that binds to C5 and prevents the generation of membrane attack complex, can be successfully used at least in some patients who have the disease. So far, there are very few studies, but cases have been reported in which its use has been beneficial.¹⁸

Learning points

- ▶ Postinfectious glomerulonephritis (GN) is usually a one-shot illness with good recovery of kidney function. Occasional patients present an atypical evolution with recurrent episodes of acute kidney injury or persistent abnormal urinalysis.
- ▶ Patients with atypical postinfectious GN may have C3 glomerulopathy and an abnormal alternative pathway of complement. This may be associated with a low-serum C3 and a normal C4.
- ▶ Postinfectious exacerbations may be associated with activation of the classical complement pathway indicated by low-serum C3 and C4.
- ▶ Postinfectious exacerbations may benefit from corticosteroids.

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