Three kidneys, two diseases, one antibody?

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Abstract
Anti-factor H antibody has been recently described as responsible for thrombotic microangiopathies (TMA) as well as membranoproliferative glomerulonephritis (MPGN). We report here, for the first time, the case of a woman with an anti-factor H antibody, who developed MPGN on native kidney, rapid recurrence on first graft, and TMA on second graft despite immunosuppressive therapy and plasma exchanges. This case supports the hypothesis that MPGN and TMA are closely linked by common pathogenic mechanisms and the need for complete exploration of complement pathway including factor H activity and autoantibody in front of any MPGN.

Keywords: anti-factor H antibody; complement alternative pathway; membranoproliferative glomerulonephritis; thrombotic microangiopathies

Background
Anti-factor H antibody has been recently described as being responsible for atypical haemolytic and uraemic syndrome (aHUS) [1, 2] as well as being implicated in the development of membranoproliferative glomerulonephritis (MPGN) [3]. We report the case of a woman with an anti-factor H antibody, who developed MPGN on her native kidney and first graft and aHUS on her second graft.

Case report
A 36-year-old female was hospitalized in December 1998 for acute renal failure (ARF) (creatininaemia 370 l mol/L) with nephrotic syndrome (proteinuria > 3 g/day, albuminaemia 20 g/L) and haematuria in the second month of her third pregnancy. Kidney biopsy showed MPGN with crescent formation on 40% of the glomeruli. Subendothelial deposits of C3 and few C1q and IgG were detected by immunofluorescence. Serum complement (C3, C4, CH50) levels were normal. A bilateral maxillary sinusitis was considered as the cause of MPGN. Despite corticosteroids and cyclophosphamide (after therapeutic pregnancy interruption), she commenced haemodialysis in April 1999.

The first renal transplantation occurred in January 2004. Immunosuppressive therapy consisted of basiliximab, cyclosporine and mycophenolate mofetil (MMF) and no corticosteroids. The creatininaemia at J5 was at 114 μmol/L.

On the 26th day post-transplantation, she presented ARF (creatininaemia 350 l mol/L) and nephritic syndrome (proteinuria 2 g/day and macroscopic haematuria). The C3 fraction of the complement was reduced (430 mg/L normal 660–1250 mg/L), while the C4 fraction was normal (110 mg/L normal 93–380 mg/L) (Table 1). Kidney biopsy showed MPGN though no crescents or acute rejection was observed. Immunofluorescence was not performed. Since this presentation suggested early recurrence of initial disease, immunosuppressive treatment was increased with high dose of corticosteroids, four injections of rituximab 375 mg/m², 12 plasma exchanges and cyclosporine to tacrolimus switch. Following this, creatininaemia decreased to 106 μmol/L and proteinuria decreased to 0.31 g/24 h.

In December 2005, a kidney graft biopsy was performed following creatininaemia increase (130 l mol/L) and nephrotic syndrome (proteinuria 2.83 g/L, albuminaemia 30 g/L and haematuria). She was treated with tacrolimus and azathioprine (in substitution of MMF because of intestinal disorder). Biopsy showed recurrence of MPGN and few lesions resulting from tacrolimus toxicity though no acute rejection. Complement was normal. Irbesartan was started for proteinuria and hypertension. Immunosuppressive regimen was not modified. Proteinuria and microscopic haematuria persisted. Renal function progressively decreased. The final renal biopsy in August 2007 reported lobular MPGN with subendothelial deposits of C3 and C1q, similar to initial glomerulonephritis (Figure 1). Peritubular capillary C4d was negative. She had to resume haemodialysis.

In November 2007, she received a second renal transplantation with thymoglobulins, corticosteroids, sodic mycofenolate. Creatininaemia nadir was 84 μmol/L. In April 2008, she was hospitalized for
increased creatininaemia (159 μmol/L) and proteinuria (1 g/day). Graft biopsy did not indicate any acute rejection but could not exclude early endocapillar nephritis. Peritubular capillary C4d was negative. She was treated by high doses of corticosteroids, cyclophosphamide and 14 plasma exchanges without any benefit. In June 2008, creatininaemia was 258 μmol/L and proteinuria 2 g/day. Hæmoglobin was 12.6 g/dL, without red cell fragmentation, and platelets 295 000/mm³. Graft biopsy showed chronic and acute thrombotic microangiopathies (TMA) and tu- bulointerstitial lesions without any inflammatory infiltrate (Figure 1). Immunofluorescence showed few subendothelial C1q deposits and vascular C3 deposits. Peritubular capillary C4d was negative. Electron microscopy showed glomerular basement membrane damage as well as cell fragments inside the capillaries confirming chronic TMA. She resumed haemodialysis 8 months after the second transplantation.

Confronted with this clinical feature, a complete exploration of complement system proteins was performed on recent and previous sera (Table 1). Retrospectively, we found that, just before the second transplantation, there was an anti-factor H antibody, which disappeared in July 2008, after plasma exchanges. N/A, not applicable. Bold values correspond to abnormal values.

**Discussion**

Factor H deficiency has been reported in several cases of aHUS or MPGN. Anti-factor H antibody has been identified as the culprit for aHUS [1, 2] but implicated in one case of MPGN [3]. Several clinical cases have already described the occurrence of the two diseases in the same patient with factor H deficiency [4] though none involved anti-factor H antibody.

The case described here is exceptional as this patient presented an anti-factor H autoantibody and both diseases on three different kidneys: MPGN on the native kidney, recurring in the same pattern on the first kidney graft, and aHUS on the second graft. We were able to identify anti-factor H antibody on sera prior to and after the second kidney transplantation. Unfortunately, we could not retrospectively assess the antibody levels at the time of initial disease nor at the time of first renal transplantation due to a lack of sera. However, rapid recurrence on the first graft in the absence of immunosuppressive preparation therapy and the initial response to immunosuppressive intensification by plasma exchanges and rituximab are main arguments for antibodies-linked pathogenesis. Usual triggers such as

<table>
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<th>CH50</th>
<th>C3 Ag 600–1250 mg/L</th>
<th>C4 Ag 93–380 mg/L</th>
<th>FB Ag 30–320 mg/L</th>
<th>FH Ag 65–140%</th>
<th>FI Ag 70–130%</th>
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<td>141</td>
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<td>106</td>
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</table>

*aMeasurement of C3 Ag, C4 Ag and CH50 was always normal during the first transplantation, except at Day 26 (02/2004) when the C3 fraction was slightly reduced at 430 mg/L. Retrospectively, we found that, just before the second transplantation, there was an anti-factor H antibody, which disappeared in July 2008, after plasma exchanges. N/A, not applicable. Bold values correspond to abnormal values.

Fig. 1. (a, b, c) Graft biopsy of August 2007 at the end of the first transplantation, just before starting haemodialysis, showing lobular MPGN with subendothelial deposits of C3 and C1q, similar to initial glomerulonephritis (a: Masson trichrome’s ×100; b: Jones silver stain ×200; c: immunofluorescence with anti-C3 antibody ×200)—(d, e): Graft biopsy of June 2008 at the end of the second transplantation, showing chronic and acute lesion of TMA (Masson trichrome’s ×400).
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In the literature, two different autoantibodies have been described, suggesting different pathogenesis: the factor H C-terminal surface-binding region would be the target of aHUS autoantibodies, while ‘miniautoantibodies’ targeting the factor H N-terminal regulatory domain would be involved in MPGN [6]. The first would promote endothelial cell damage by affecting surface regulatory functions of factor H. The second scenario has been described in only one patient [3] in which IgG lambda-chain dimers would affect factor H regulatory function in the fluid phase. Our case, however, suggests that the same autoantibody will disturb factor H activity and according to the environment will result in either MPGN or aHUS.

This case underlines the need for complete exploration of complement pathway, especially in relation to the major regulator protein factor H when confronted with cases of both MPGN and aHUS. In our case, plasma exchanges finally allowed us to suppress anti-factor H antibody though this was performed too late to save the second transplant. However, in theory, plasma exchanges and rituximab therapy [7] or even the use of eculizumab (humanized monoclonal lambda light chain) [8], before and during the second transplantation, might have blocked the development of aHUS on the second renal graft. Finally, this case supports the hypothesis that MPGN and aHUS are closely linked by common pathogenic mechanisms, with a central role for the dysregulation of the complement alternative pathway [6].

Abstract

We report a 41-year-old Chinese female with Fabry disease and diffuse thinning of the glomerular basement membrane (GBM). The patient presented with peripheral edema, mild proteinuria, microscopic hematuria, normal renal function, hypertension and tinnitus. Family screening showed that her daughter had microscopic hematuria, tinnitus and neuropathic pain. Renal biopsy of the proband showed focal segmental glomerulosclerosis with cytoplasmic vacuolization of the glomerular visceral epithelial cells by light microscopy. Laminated myelin inclusions in some of the glomerular podocytes, parietal epithelia, distal tubular epithelial cells and vascular endothelial cells along with diffuse thinning of the GBM (mean thickness of GBM: 216 ± 31 nm) were identified by electron microscopy. Genetic analysis detected a de novo novel GLA mutation, 1208 ins 21 bp, while a new variant of COL4A3 SNP M1209I was carried by mother and daughter as well as the proband’s father (I-1) and one sister (II-4). The coexistence of thinned GBM should be considered in patients with Fabry disease-manifested familial hematuria.

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Conflict of interest statement. None declared.

References


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