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Atypical haemolytic uraemic syndrome with underlying glomerulopathies. A case series and a review of the literature

Lucio Manenti[1],
Elisa Gnappi[1],
Augusto Vaglio[1],
Landino Allegri[1],
Marina Noris[2],
Elena Bresin[2],
Francesco Paolo Pilato[3],
Elisabetta Valoti[2],
Sonia Pasquali[4]
and Carlo Buzio[1]

[1]Nephrology Unit, University Hospital of Parma, Parma, Italy, [2]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Ranica, Bergamo, Italy, [3]Pathology Department, University Hospital of Parma, Parma, Italy and [4]Nephrology Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy

Correspondence and offprint requests to: Lucio Manenti; E-mail: lmanenti@hotmail.com

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ORIGINAL ARTICLE

ABSTRACT

Background. Primary or secondary glomerulonephritis has been anecdotally reported in association with atypical haemolytic uraemic syndrome (aHUS). We here report a series of six patients who developed aHUS and glomerulopathy, and review the literature on aHUS and glomerulonephritis.

Methods. Out of all patients diagnosed at our unit with biopsy-proven glomerular diseases between March 2007 and October 2011, selected cases developing aHUS during the follow-up are presented. The following tests were performed in all six patients: serum C3 and C4 levels, ADAMTS13 activity, CFH levels and anti-CFH autoantibodies and genetic screening for *CFH*, *MCP*, *CFI*, *C3* and *CFHR1-3* mutations and risk haplotypes associated with aHUS.

Results. Two hundred and forty-eight patients received a biopsy-proven diagnosis of glomerulopathy and were followed for a median of 31 months (range 2–58). Of these, six developed aHUS, within a median of 15 months (range 1–36) of their initial diagnosis of glomerulopathy. One of these patients had focal segmental glomerulosclerosis (FSGS), two membranoproliferative glomerulonephritis (MPGN) type I, one C3 glomerulonephritis and two systemic small vessel vasculitis [one granulomatosis with polyangiitis (Wegener's), one Henoch–Schoenlein purpura]. Five patients (one of them heterozygous for a *CFH* mutation) carried, in homo- or heterozygosity, the risk haplotype *CFH*-H3 (*CFH tgtgt*), previously described to be associated with aHUS, while another one patient was homozygous for the *MCPggaac* risk haplotype predisposing to aHUS when present on both alleles.

Conclusions. Different types of glomerulopathies can be complicated by aHUS. Several mechanisms can contribute to this association, such as nephrotic-range proteinuria, mutations or aHUS-risk haplotypes involving genes encoding alternative complement regulatory proteins in some patients and inflammatory triggers associated with systemic immune-mediated diseases.

INTRODUCTION

Atypical haemolytic uraemic syndrome (aHUS) is a thrombotic microangiopathy (TMA) that often produces irreversible renal damage. It represents 5–10% of paediatric cases of HUS and the majority of adult cases. The clinical onset of the disease is often insidious [1].

In the last few years, complement alternative pathway (AP) abnormalities have been recognized to be the cause of most aHUS cases, and mutations involving AP regulatory genes were identified in ∼50% of the patients. A link has also emerged between aHUS and complement-mediated nephropathies, particularly membranoproliferative glomerulonephritis (MPGN), whose genetic background is common to that of aHUS [2], while other proteinuric glomerulopathies (such as IgA nephropathy, focal segmental glomerulosclerosis, FSGS) and vasculitis do not (at least at the same level of evidence). Intriguingly, primary or secondary glomerulopathies have been described in patients with aHUS [3–5], but the clinical significance of this association still remains elusive [6–8].

We here present a series of six patients, seen at the Nephrology Unit of our University Hospital over 4 years, who were initially diagnosed as having different types of glomerulopathies and later developed aHUS; additionally, we review the English-language literature on cases of aHUS associated with glomerulopathy and discuss the potential pathophysiological mechanisms linking glomerulopathy to aHUS.

PATIENTS AND METHODS

Selection criteria

Out of all patients diagnosed at our unit as having biopsy-proven glomerular diseases between March 2007 and October 2011, we selected the cases that developed aHUS during the follow-up. aHUS was diagnosed using the following criteria: (i) microangiopathic haemolytic anaemia as indicated by the presence of schistocytes >2% on peripheral smear, haptoglobin level <30 mg/dL (normal range 30–200 mg/dL), lactate dehydrogenase (LDH) >500 U/L (normal range 250–500 U/L), negative Coomb's test, normal ADAMTS13 activity, negative serologic testing and stool cultures as well as blood and urine culture for Shigatoxin-producing *Escherichia coli* or *Shigella dysenteriae*; (ii) progressive renal failure; (iii) thrombocytopoenia (platelet count $<150 \times 10^3/mm^3$ or reduction of >25% of previous platelet count) and (iv) renal biopsy showing typical signs of TMA, such as glomerular microthrombi composed of platelet aggregates and fibrin, peripheral capillary loops with double contour formation, endothelial cell swelling, stenosis of capillary lumens or microthrombi in the small renal arteries. We considered a clinical diagnosis of aHUS when all of the first three criteria were met; in the absence of one of the first three criteria, we confirmed the diagnosis of aHUS only in the presence of a new renal biopsy documenting TMA. We excluded from this series the patients presenting with lupus nephritis, since an association of this condition with haemolysis (microangiopathic haemolytic anaemia) is well established.

Biochemical and genetic analyses. Biochemical and genetic analyses were performed at the Laboratory of Immunology and Genetics of Transplantation and Rare Diseases, Mario Negri Institute for Pharmacological Research, Ranica, Bergamo, Italy. C3 and C4 serum levels were evaluated by kinetic nephelometry. ADAMTS13 activity was measured using the residual collagen-binding assay [9]. CFH levels were measured by enzyme-linked immunosorbent assay.

Genomic DNA was extracted from blood leukocytes (BACC2 kit; Nucleon, Amersham, UK). The coding sequence and the intronic flanking regions of complement genes—*CFH* (Factor H), *MCP* (Membrane Cofactor Protein), *CFI* (Factor I), *C3*—were directly sequenced (AB-3730-XL sequencer). CFH autoantibodies were evaluated by ELISA [10–12]. The complete CFHR1-3 deletion was searched for by the analysis of the SNP rs7542235 [13].

Literature search strategy. We searched PubMed without date limits mainly using the terms 'haemolytic uraemic syndrome', 'thrombotic microangiopathy', 'glomerulopathy', 'nephrotic syndrome', 'vasculitis', 'membranoproliferative glomerulonephritis' and 'focal segmental glomerulosclerosis'. We only selected articles published in English language; all types of articles, including reviews, were considered.

RESULTS

During the study period, 248 patients were diagnosed at our unit as having a biopsy-proven glomerulopathy (either primary or secondary); they were followed for a median of 31 months (range 2–58 months). Of these patients, six developed aHUS during the follow-up, within a median time of 15 months (range 1–36) of their initial diagnosis of glomerulopathy. One of these six patients had initially been diagnosed with FSGS), two with MPGN type I, one with C3 glomerulopathy (C3GN), and two with systemic small vessel vasculitis, namely one with granulomatosis with polyangiitis (Wegener's, GPA) and the other with Henoch–Schönlein purpura. The main clinical data at the initial presentation of glomerulopathy are reported in Table 1 [14–16].

Follow-up data and therapy for both glomerulopathy and aHUS, results of the genetic screening including complement mutations and presence of *CFH*-H3 (that identifies the *CFHtgtgt* risk haplotype) associated in homo- or heterozygosity with aHUS [14–18], and of *MCPggaac* risk haplotype, predisposing to aHUS when present in homozygosity [18], are also detailed in Table 1. The *MCPaaggt* risk haplotype, recently associated with GNC3 and MPGN I [15], was not evaluated in our patients.

Case 1 presented at the age of 57 years with nephrotic-range proteinuria (24-h proteinuria, 3.7 g) and a serum creatinine of 79 µmol/L; his renal biopsy documented FSGS. Steroid treatment was started but 1 week later Hb dropped to 6.8 g/dL, 24 h proteinuria was 40 g and acute renal failure (serum creatinine 502 µmol/L) developed. The appearance of thrombocytopoenia ($99 \times 10^3/mm^3$), increased LDH (950 UI/L), undetectable haptoglobin and the presence of schistocytes with increased circulating reticulocytes supported the diagnosis of aHUS. Direct Coomb's test, antinuclear, antiphospholipid and antiplatelet antibodies, ANCA and anti-CFH antibodies were negative. The patient recovered after 15 consecutive plasma exchange (PE) sessions. A few days after the end of PE treatment, aHUS reappeared and we decided to use

Table 1. Clinical data of the six patients at the initial presentation of glomerulopathy, of aHUS and outcome at the last follow-up after aHUS onset

ID	Age (years)	Sex	Initial glomerulopathy	IF (C3)	IF (IgG)	Time to aHUS[a] (months)	24-h proteinuria before/after aHUS (g)	Serum C3[b] (>90 mg/dL)	Serum C4[b] (>10 mg/dL)	CFH and MCP Haplotypes	Complement mutation	Focused therapy	Outcome
1	57	M	FSGS	–	–	1	3.7/40	123	28	H3/H3 (CFH) TC (MCP)	No mutation	PE, RTX, steroids	Slight proteinuria
2	13	M	MPGN I	+++	+	25	2/9	42	33	H3/H3 (CFH) TT (MCP)	CFH p.I216T; SCR4	PE, cyc, steroids	ESRD
3	22	F	MPGN I	+++	+	31	2.1/4.1	48	16	H1/H3 (CFH) TT (MCP)	No mutation	PE, cyc, steroids	ESRD
4	54	M	GN-C3	+++	–	55	0.2/0.5	26	25	H4/H7 (CFH) CC (MCP)	No mutation	Steroids, cyc	CKD
5	66	M	GPA	++	+	18	4.1/7.3	47	24	H3/H3 (CFH) TT (MCP)	No mutation	PE, steroids	ESRD, Died
6	32	M	HSP	++	+	7	10/12	131	30	H3/H3 (CFH) TC (MCP)	No mutation	Steroids, cyc azathioprine, RTX	ESRD

The *CFH*-H3 risk haplotype (that identifies the haplotype *CFH-tgtgt*) associated with aHUS was tagged by genotyping rs3753394 (c.1-332C>T) in the promoter, and rs800292 (c.184G>A; p.V62I), rs1061170 (c.1204T>C; p.Y402H), rs3753396 (c.2016A>G; p.Q672Q), rs1065489 (c.2808G>T, p.E936D) in the coding region [14, 15]. H1, H4 and H7 identify respectively the haplotypes CFH*cgcag*, CFH*cgtag* and CFH*tgtag* [15, 16]. The patients were also analysed for the last SNP rs7144 (c.2232T>C) tagging the MCP*ggaac* risk haplotype [16], also associated with aHUS when present on both alleles.

CKD, chronic kidney disease; ESRD, end stage renal disease; FSGS, focal and segmental glomerulosclerosis; GN-C3, C3 glomerulopathy; HSP, Schönlein–Henoch purpura; IF, immunofluorescence staining; GPA, granulomatosis with polyangitiis polyangiitis (Wegener); MPGN, membranoproliferative glomerulonephritis; PE, plasma exchange; Cyc, cyclophosphamide; RTX, rituximab.

[a]from initial glomerulopathy; [b]at the time of aHUS.

rituximab (RTX) (375 mg/m^2/weekly for 4 weeks); the signs of haemolysis promptly subsided and nephrotic syndrome progressively ameliorated. At 3 years follow-up, 24-h proteinuria was 0.8 g. No mutations in the *CFH*, *MCP* and *CFI* genes were identified. A homozygous deletion of *CFHR1-R3* was excluded. The patient was found to be homozygous for the aHUS-risk haplotype *CFH*-H3 (Table 1).

Three of the six patients (Cases 2, 3 and 4) had MPGN/C3GN. Serum C3 was consistently reduced in all three patients. A marked C3 deposition was also detected by immunofluorescence analysis of the kidney biopsy in all of them (Figure 1b and d).

Case 2 was diagnosed as having type I MPGN at the age of 13 years, and 3 years later developed aHUS (Figure 1a and b). Reduced CFH levels and a novel heterozygous *CFH* gene mutation in the short consensus repeat (SCR) 4 were documented (detailed description of this case is reported in [19]). The patient was also found to be homozygous for the aHUS-risk haplotype *CFH*-H3 (Table 1).

Case 3 received a biopsy-proven diagnosis of type I MPGN at the age of 22 years. Renal function remained substantially stable during the 2 years following renal biopsy. At the age of 24 years, she was hospitalized for acute renal failure due to aHUS. She was treated with PE until haemolysis disappeared;

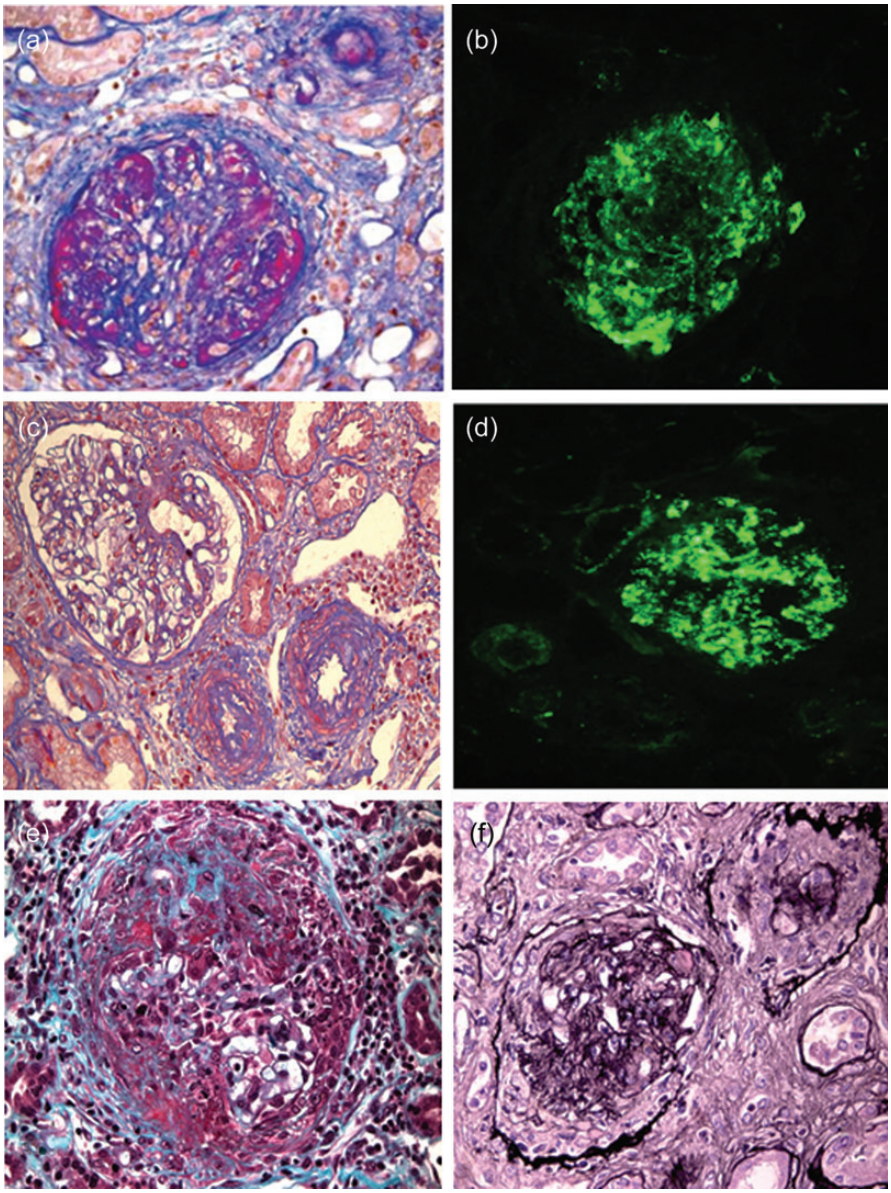

FIGURE 1: Light microscopy findings in patients who developed glomerulopathy associated with aHUS. (**a**) (acid fuchsin orange G staining ×400) Case 2 showing an accentuated lobular architecture, mesangial expansion, thickened capillary walls with double contours, intracapillary thrombi and arteriolar thrombosis and by immunofluorescence (**b**) (with anti-C3c antibody ×400) diffuse granular deposition.(**c**) (acid fuchsin orange G staining ×200) Case 4 demonstrating organized arterial TMA with multiple segments with narrowing to near-complete obliteration of lumen and by immunofluorescence (**d**) (with anti-C3c antibody ×400) diffuse granular deposition. (**e**) Case 5 (Masson thricrome stain ×400) and (**f**) Case 6 (silver staining ×400) illustrating extracapillary proliferation, fibrinoid necrosis and intracapillary thrombi and mesangial, extracapillary proliferation, intracapillary thrombi and arteriolar thrombosis respectively.

no renal function improvement was observed and the patient became haemodialysis-dependent. ADAMTS13 activity was normal. No mutations in *CFH*, *MCP, CFI* and *C3* genes were identified. Homozygous deletions of CFHR1-R3 and anti-CFH antibodies were excluded. The C3 nephritic factor was negative. The patient was found to be heterozygous for the aHUS-risk haplotype *CFH*-H3 (Table 1).

Case 4 had persistent proteinuria and microscopic haematuria since the age of 54 years and was admitted to our department at the age of 59 years for macroscopic haematuria and acute renal failure (serum creatinine from 168 to 760 μmol/L). A kidney biopsy showed diffuse tubular red cells casts but isolated mesangial C3 deposition on immunofluorescence; mesangial electron-dense deposits were disclosed by electron microscopy; altogether, these data supported the diagnosis of C3GN. During his hospital stay, the patient showed a spontaneous partial kidney function recovery (serum creatinine 176 μmol/L). Three months later he had a relapse of macroscopic haematuria and kidney function worsening (serum creatinine 592 μmol/L). A new kidney biopsy confirmed the diagnosis of C3GN with concurrent histological evidence of TMA (Figure 1c and d). He was treated with PE that was soon stopped because of an allergic reaction to plasma; three methylprednisolone boluses (500 mg each) were administered, followed by oral prednisone (1 mg/kg/day) and cyclophosphamide (1.5 mg/kg/day). aHUS remitted and an almost complete recovery of kidney function was obtained. At 12 months follow-up, both aHUS and C3GN were in remission; serum C3 was normal. ADAMTS13 activity was normal. He had no mutations in *CFH*, *MCP* and *CFI* genes. Homozygous deletions of *CFHR1-R3* and anti-CFH antibodies were excluded. The C3 nephritic factor was negative. This patient was found to be CC homozygous for the c.2232T>C SNP tagging the *MCPggaac* aHUS-risk haplotype (Table 1).

The last two patients presented with renal vasculitis. Case 5 was admitted to our department at the age of 68 years because of nephrotic-range proteinuria, haemolysis, thrombocytopoenia and acute renal failure. He had been diagnosed 2 years earlier as having GPA without renal involvement. A kidney biopsy confirmed the presence of necrotizing extracapillary proliferative glomerulonephritis with signs of TMA (Figure 1e). Immunofluorescence showed intense and diffuse C3 deposition. The patient was treated with PE, steroids and cyclophosphamide and, after 32 days, the laboratory signs of aHUS disappeared; renal function only partially recovered (serum creatinine decreased from 968 to 440 μmol/L). After 20 months, he was started on haemodialysis although no aHUS recurrence occurred and 10 months after the beginning of haemodialysis he died of sepsis.

Case 6 was admitted to our department at the age of 32 years for nephrotic syndrome (24-h proteinuria 10 g), palpable purpura involving the lower extremities, abdominal pain and diarrhoea. A kidney biopsy showed crescentic glomerulonephritis with IgA and intense C3 deposition on immunofluorescence. Adult-onset Henoch–Schoenlein purpura was diagnosed and treated with steroids and oral cyclophosphamide. During immunosuppressive therapy, nephrotic syndrome persisted and was complicated by insidious haemolysis with rapidly progressive kidney failure (serum creatinine rose from 123 to 293 μmol/L). A kidney biopsy was repeated (Figure 1f) and confirmed extracapillary proliferation associated with intracapillary thrombi and arteriolar thrombosis. The clinical picture was unresponsive to high-dose steroids and the patient refused PE. RTX (375 mg/m^2/weekly for 4 weeks) was administered. Signs of haemolysis disappeared, but renal failure and nephrotic-range proteinuria persisted. One year later the patient developed overt aHUS (severe thrombocytopoenia, anaemia and renal failure); he finally accepted to start PE and haemolysis subsided after 14 days. However, renal function did not improve and he had to start haemodialysis.

No mutations of *CFH*, *MCP* and *CFI* were identified in Cases 5 and 6, but both of them carried the aHUS-predisposing *CFH*-H3 risk haplotype in homozygosity (Table 1).

Literature review

The results of our literature review are detailed in Tables 2–4. In particular, Table 2 reports the published cases of aHUS associated with a pre-existing nephrotic syndrome, Table 3 the cases of aHUS associated with MPGN and Table 4 those associated with vasculitic syndromes.

DISCUSSION

We present here a series of six patients who had an initial diagnosis of glomerulopathy and later showed a shift to aHUS. The patients' nephropathies were etiologically distinct, but they can be grouped under three different patterns: nephrotic syndrome-causing glomerulopathy, MPGN/C3 glomerulopathy and immune-mediated/vasculitic glomerulonephritis.

To further investigate the link between glomerulopathy and aHUS, we reviewed the published cases of aHUS associated with an underlying glomerulopathy or vasculitis, and overall identified 65 cases (17 associated with nephrotic syndrome, 16 with MPGN and 32 with vasculitis syndromes).

In our case series, we excluded lupus nephritis patients since a close relationship with aHUS has already been documented, with 5–10% of lupus nephritis patients developing this complication. The aetiopathogenetic aspects linking SLE and aHUS are still unclear, but a role of complement dysregulation and CFH dysfunction in the susceptibility to SLE appears to emerge from genetic studies [13].

Five patients in our case series (one of them heterozygous for a *CFH* mutation) carried, in homo- or heterozygosity, the risk haplotype *CFH*-H3 (identifying the haplotype *CFHtgtgt*), previously described to be strongly associated with aHUS appearance [14–17], while another one patient was homozygous for the *MCPggaac* risk haplotype that has been shown to predispose to aHUS when present on both alleles [18]. Thus, it is possible that such predisposing genetic background contributed to amplifying the complement AP dysregulation triggered by glomerulopathies, thus leading to overt aHUS. In this regard, another *MCP* risk haplotype (*MCPaaggt*), not evaluated in our patients, was recently associated with C3GN and MPGN I [15], suggesting that the role of these polymorphisms

Table 2. Reported cases of nephrotic syndrome with associated aHUS

Author year	Sex	Age	Glomerulopathy	24-h proteinuria	Complement evaluation	Focused therapy	Outcome
Marie *et al.* 1969 [20]	F	7	MNG	>3.5 g	N/A	Steroids	Proteinuria
Halikowski *et al.* 1971 [21]	F	7	FSGS	>3.5 g	N/A	None	N/A
Dische *et al.* 1978 [22]	M	20	MNG	1 g	Normal levels of C3 and C4 IF: IgG deposits	Steroids	Died
Krensky *et al.* 1981 [23]	M	7	FSGS	>3.5 g	N/A	Steroids	ESRD
Krensky *et al.* 1981 [23]	N/A	N/A	FSGS	>3.5 g	N/A	Steroids	ESRD
Krensky *et al.* 1981 [23]	N/A	N/A	FSGS	>3.5 g	N/A	Steroids	CKD
Siegler *et al.* 1989 [24]	M	22	MCD	4.7 g	Normal levels of C3 and C4	Steroids	CKD
Friedlander and Jacobs 1991 [25]	N/A	N/A	MNG	N/A	N/A	N/A	N/A
Bokenkamp *et al.* 1991 [26]	M	5	FSGS	>3.5 g	Normal levels of C3 and C4	N/A	ESRD
Liapis 2003 [27]	F	31	MNG	>3.5 g	N/A	N/A	N/A
Benz *et al.* 2004 [28]	M	16	FSGS	>3.5 g	N/A	Steroids, i.v. Ig, RTX	Recovered
Koulova *et al.* 2005 [29]	M	40	MNG	10 g	Normal levels of C3, C4 and CH50	PE, steroids, VCR, RTX	Proteinuria
Benz *et al.* 2007 [30]	F	12	FSGS	>3.5 g	Normal levels of C4	Steroids	ESRD
Suri *et al.* 2008 [31]	M	11	FSGS	>3.5 g	Normal levels of C3 and C4	PE, steroids, MMF, RTX	Proteinuria
Kuppachi *et al.* 2009 [32]	M	43	MNG	10.2 g	IF: IgG deposits	PE, steroids, RTX	Proteinuria
Noris *et al.* 2010 [33]	F	31	MNG	>3.5 g	CFH mutation Reduced levels of C3	PE, steroids	ESRD
Noris *et al.* 2010 [33]	F	N/A	MCD	N/A	No complement mutations	PE, steroids, i.v. Ig	N/A

ESRD, end-stage renal disease; FSGS, focal and segmental glomerulosclerosis; i.v Ig, intravenous immunoglobulins; MCD, minimal change disease; MMF, mycophenolate mofetil; MNG, membranous glomerulonephritis; PE, plasma exchange; RTX, rituximab; VCR, vincristine.

in *CFH* and *MCP* is not limited to aHUS, in the line of the common complement-dysregulation background in aHUS and C3GN/MPGN.

We discuss our experience and the literature data organizing the collected patients on the basis of the underlying glomerulopathy.

Table 3. Reported cases of aHUS associated with MPGN

Author year	Sex	Age	Glomerulopathy	24-h proteinuria	Complement evaluation	Focused therapy	Outcome
Habib *et al.* 1969 [48]	N/A	N/A	MPGN	N/A	N/A	None	N/A
Krensky *et al.* 1981 [23]	F	1	MPGN	Elevated	N/A	Cyclophosphamide	ESRD
Krensky *et al.* 1981 [23]	M	5	MPGN	Elevated	N/A	None	ESRD
Gomez *et al.* 1984 [49]	F	3	MPGN type I	7 g	sC3 reduced	None	CKD
Pérez *et al.* 1988 [50]	F	24	MPGN type I	3 g	sC3,sC4 normal	PE	CKD
Siegler *et al.* 1989 [24]	F	1	MPGN type I	>3.5 g	Reduced sC3 and sC4. IF: C3 deposits	Steroids	ESRD
Vaziri *et al.* 2006 [51]	M	48	MPGN type I	>3.5 g	CFH mutation; sC3, sC5, CFB and properdin reduced, IF: C3 deposits	PE, steroids	Died
Vaziri *et al.* 2006 [51]	F	6	MPGN	N/A	CFH mutation sC3 reduced IF: C3-IgM deposits	PE	ESRD
Mak *et al.* 2009 [52]	F	39	MPGN	11 g	HCV+ sC3 and sC4 reduced. IF: C3, IgG, IgM, IgA deposits	PE, steroids, cyclophosphamide i. v. Ig, RTX	CKD
Noris *et al.* 2010 [33]	F	20	MPGN	N/A	no complement mutations sC3, sC4 normal	Steroids	ESRD
Noris *et al.* 2010 [33]	F	18	MPGN	5 g	CFH mutation sC3 reduced	PE, steroids	ESRD, Died
Noris *et al.* 2010 [33]	M	22	MPGN	N/A	CFI mutation sC3 reduced	PE, steroids	N/A
Noris *et al.* 2010 [33]	M	N/A	MPGN	N/A	CFP mutation	N/A	N/A
Noris *et al.* 2010 [33]	F	15	MPGN type I	N/A	C3 mutation sC3 reduced	PE, steroids	ESRD, Died
Lorcy *et al.* 2011 [53]	F	36	MPGN	>3.5 g	anti-CFH antibody; sC3 reduced	Steroids, cyclophosphamide	ESRD

Continued

Table 3. Continued

Author year	Sex	Age	Glomerulopathy	24-h proteinuria	Complement evaluation	Focused therapy	Outcome
Brackman *et al.* 2011 [54]	M	10	MPGN type I	>3.5 g	Anti-CFH antibody;CFHR1 and CFHR3 homozygous deletion; IF: C3, IgG and IgM deposits	Eculizumab	N/A
Radhakrishnan *et al.* 2012 [55]	F	16	MPGN type I	>3.5 g	sC3 undetectable, serum C3 nephritic factor, CFHR1 deficiency	Eculizumab	Recovered

CKD, chronic kidney disease; CPM, cyclophosphamide; ESRD, end-stage renal disease; MPGN, membranoproliferative glomerulonephritis; PE, plasma exchange; RTX, rituximab.

Nephrotic syndrome (minimal change disease, FSGS, membranous nephropathy)

The presentation of Case 1 is similar to the 17 patients with nephrotic syndrome reported in the literature who later evolved into aHUS (Table 2) [20–33]. These patients were all characterized by isolated nephrotic syndrome. Where complement evaluation was available [22, 24, 26, 29–31, 33], no evidence of AP hyperactivation was observed, like in Case 1, with the exception of one patient who had a *CFH* mutation and reduced serum levels of C3 [33] (Table 2). In Case 1, however, the presence of the *CFH*-H3 risk haplotype in homozygosity suggests that this patient could be genetically predisposed to aHUS.

Nephrotic-range proteinuria is associated with endothelial dysfunction as documented by increased plasma soluble thrombomodulin (TM) levels, due to shedding from damaged endothelium and the release of von Willebrand factor [34], which together with enhanced platelet aggregation create a predisposing environment for the development of aHUS [35]. TM is an endothelial glycoprotein that is involved directly in the degradation of C3a that in turn triggers inflammation and microvascular thrombosis, as was recently documented in an experimental study [36]. Moreover, severe proteinuria probably determines vascular endothelial growth factor (VEGF) reduction in the capillary lumen, by decreased size selectivity of the slit diaphragm, counteracting its diffusion from podocytes to the glomerular capillary lumen [37]. The latter finding is of relevance to understand the pathogenesis of aHUS in patients with nephrotic syndrome, since VEGF deficiency has been shown to cause TMA [38].

Moreover, it has been shown that aHUS itself aggravates proteinuria by causing podocyte fusion due to acute TMA-induced ischaemia [39]. Thus, we would speculate that in patients with aHUS superimposed to nephrotic syndrome the environment predisposing to aHUS is further deteriorated by aHUS itself, raising a possible self-perpetuating loop.

Case 1 showed a dramatic response to RTX, and we identified other four cases of nephrotic syndrome-associated aHUS with good response to RTX in the recent literature [28, 29, 31, 32] (Table 2). RTX is considered a second-line therapy for FSGS [40] and for membranous nephropathy [41] and a potential adjuvant therapy in some cases of TMA [42]. In this subgroup of RTX-treated patients, RTX appeared to be effective in preventing exacerbations when PE treatments were stopped, and also to be effective in avoiding subsequent relapses. RTX could thus break the nephrotic proteinuria-related loop that maintains haemolysis and simultaneously treat associated TMA. Indeed, an almost complete recovery of renal function was observed in the whole RTX-treated subgroup, while the non RTX-treated patients developed CKD or ESRD (Table 2).

MPGN/C3 glomerulopathy (C3GN)

We observed two cases of MPGN type I and one of C3GN. These cases recognize a similar aetiopathogenetic mechanism involving complement dysregulation. Recently, crucial advances have been made in understanding complement regulation and its implications in glomerulopathies [15, 43]. Complement AP dysregulation due to the presence of antibodies inhibiting the decay of C3 convertase (such as C3Nef) or to a genetically determined failure of CFH to control complement activation was initially reported [44]. More recently a role for antibodies against CFH, or mutations in CFH related genes (*CFHR*) and in other regulatory factors (such as *CFI, MCP* or *C3*) have been described [15, 45–47]. Loss of regulation of complement AP activity leads to different phenotypical expressions of renal disease ranging from aHUS to C3GP (a classification recently proposed to include some cases of MPGN type I, dense deposit disease-DDD, C3GN and CFHR5 nephropathy) [2]. In our MPGN/C3GN cases (Cases 2, 3, 4) ,serum C3 levels were persistently low and renal biopsy showed C3 mesangial deposition, corroborating the relationship between AP hyperactivation and both C3 glomerulopathy

Table 4. Reported cases of aHUS associated with vasculitis syndromes

Author year	Sex	Age	Vasculitis	24 h-proteinuria	Complement evaluation	Focused therapy	Outcome
Benitez *et al.* 1964 [59]	N/A	N/A	MPA	N/A	N/A	N/A	N/A
Stefani *et al.* 1978 [60]	F	23	MPA	2 g	N/A	Steroids	N/A
Stefani *et al.* 1978 [60]	M	16	MPA	N/A	N/A	N/A	N/A
Jordan *et al.* 1986 [61]	N/A	N/A	GPA	N/A	N/A	N/A	N/A
Kuroda *et al.* 1986 [62]	N/A	N/A	MPA	N/A	N/A	N/A	N/A
Green *et al.* 1988 [63]	F	18	MPA	N/A	N/A	PE	ESRD
Heptinstall 1992 [64]	N/A	N/A	MPA	N/A	N/A	N/A	N/A
Hirsch *et al.* 1995 [65]	F	66	MPA	1.4 g	Normal sC3, sC4	PE, steroids, cyclophosphamide	ESRD
Filler *et al.* 1997 [66]	F	10	HSP	>3.5 g	Reduced sC3	PE, steroids	ESRD
Stefanidis *et al.* 1998 [67]	F	68	MPA	6 g	IF: no C3 deposits	PE, steroids, cyclophosphamide	ESRD
Hollenbeck *et al.*1998 [68]	N/A	N/A	MPA	N/A	N/A	PE, steroids	N/A
Hollenbeck *et al.*1998 [68]	N/A	N/A	MPA	N/A	N/A	PE, steroids	N/A
Lim *et al.* 1998 [69]	F	66	GPA	N/A	Normal sC3 , sC4	PE, steroids, cyclophosphamide	CKD
Rizvi *et al*2000 [70]	N/A	N/A	GPA	N/A	N/A	PE, cyclophosphamide	N/A
Yamasaki *et al.* 2001 [71]	F	56	MPA	N/A	N/A	PE, steroids, cyclophosphamide	Died
Sato *et al.* 2002 [72]	F	50	MPA	N/A	N/A	PI, steroids, cyclophosphamide	Recovered
Sato *et al.* 2002 [72]	F	68	MPA/ GPS	N/A	N/A	PE, steroids, CPM	Died
Suzuki *et al.* 2004 [73]	F	73	MPA	N/A	N/A	PE, steroids, CPM	Died
Al-Toma et al. 2005 [74]	F	40	HSP	<3 g	Normal sC3,C4 IF: C3 deposits	PE, steroids	CKD
Fujimura *et al.* 2006 [75]	F	76	MPA	N/A	N/A	PI, steroids	Died
Yamazaki *et al.* 2007 [76]	F	61	GPA	<3 g	Normal sC3, sC4	PE, steroids	CKD
Yoshioka *et al.* 2007 [77]	F	78	MPA	<3 g	Normal sC3, sC4	Steroids, cyclophosphamide	Recovered

Continued

Table 4. Continued

Author year	Sex	Age	Vasculitis	24 h-proteinuria	Complement evaluation	Focused therapy	Outcome
Nagai *et al.* 2008 [78]	F	77	MPA	<3 g	27% of ADAMTS13 activity	PE, steroids	CKD
Zhang *et al.*2009 [79]	N/A	N/A	MPA	N/A	N/A	PE, steroids, cyclophosphamide	N/A
Zhang *et al* 2009 [79]	N/A	N/A	MPA	N/A	N/A	PE, steroids, cyclophosphamide	N/A
Zhang *et al* 2009 [79]	N/A	N/A	HSP	N/A	N/A	PE, steroids, cyclophosphamide	N/A
Kobayashi *et al.* 2009 [80]	F	49	MPA	N/A	N/A	PI, steroids, cyclophosphamide	ESRD
Kobayashi *et al.* 2009 [80]	F	67	MPA/GPS	N/A	N/A	Steroids, cyclophosphamide	Died
Watanabe *et al.* 2010 [81]	F	61	MPA/GPS	No	IF: C3 deposits	PE, steroids	Died
Asamiya *et al.* 2010 [82]	F	59	MPA	<3 g	Normal sC3, sC4	PE, steroids, cyclophosphamide, RTX	ESRD
Yamauchi *et al.* 2010 [83]	F	59	MPA	<3 g	IF: no C3 deposits	PE, steroids	CKD
Mandai *et al.* 2011 [84]	M	40	MPA	<3 g	IF: no C3 deposits	PE, steroids, CPM	ESRD

AZA, azathioprine; CKD, chronic kidney disease; ESRD, end-stage renal disease; GPA, granulomatosis with polyangiitis (Wegener's); GPS, Goodpasture's syndrome; HSP, Henoch–Schoenlein purpura; IF, immunofluorescence staining; MPA, microscopic polyangiitis; PE, plasma exchange; PI, plasma infusion; RTX, rituximab.

and aHUS. A single case (Case 2) carried a *CFH* genetic alteration that would have predisposed to both MPGN and to aHUS [18], but he was also found to be homozygous for the risk haplotype *CFH*-H3 that could have led to overt aHUS; moreover the other two cases carried respectively the *CFH*-H3 (in heterozygosity) and the *MCPggaac* (in homozigosity) aHUS-risk haplotypes, that could have genetically predisposed to aHUS.

In our literature review (Table 3) [23, 24, 33, 48–55], we found 17 cases of aHUS associated with MPGN. Complement mutations were not investigated in the earliest reports but, by the time genetic and immunological complement analyses became available, mutations in *CFH*, *CFI*, *C3*, and in *CFP* (encoding for properdin, which stabilizes the AP C3 convertase) [56] were identified in six patients with MPGN/aHUS [33,51,54], whereas anti-CFH antibodies were found in other two patients [53, 54]. Thus, in particular, *CFH, CFI, C3* mutations and anti-CFH antibodies are emerging as predisposing factors not only for aHUS but also for MPGN, and some authors consider that, as expression of a single aetiopathogenesis, aHUS and MPGN would be two faces of the same medal [2, 46]; in keeping with this view, it was recently shown that MPGN can switch into aHUS and *vice versa* without discontinuity [53, 56, 19].

The clinical outcome and the renal prognosis (where reported) were poor in ∼50% of the cases (Table 3). We found a single case, a silent HCV carrier, treated with RTX. A complete recovery from nephrotic syndrome and a partial rescue of renal function were observed. Other cases were treated with eculizumab, a humanized monoclonal antibody against complement protein C5 that inhibits activation of the terminal complement pathway; long-term follow-up data are not available in these patients [54, 55]. Eculizumab, stopping the chronic hyperactivation of complement AP, represents a promising therapeutic option that could change the renal prognosis of these patients.

Immune-mediated/vasculitic glomerulonephritis

Recently AP hyperactivation has been shown to play an important role in ANCA-associated rapidly progressive glomerulonephritis. Indeed disease progression could be prevented by C3 depletion in animal models, and human neutrophils involved in ANCA-associated vasculitis have been shown to activate AP and release C5 fragments, which further amplify neutrophil pro-inflammatory response [2]. Our two cases showed intense mesangial deposits of C3, and one of them also reduced serum C3 levels. So we can hypothesize that vasculitis cases developed aHUS because of an intense AP activation. This mechanism is quite similar to that described for Shiga toxin-associated HUS that, determining an exuberant C3a formation, triggers microvascular thrombosis [35]. Moreover we could speculate that our two patients were genetically predisposed to develop aHUS, since both were homozygous for the aHUS-risk haplotype *CFH*-H3.

Another possible pathogenic mechanism, similar to that involved in microangiopathic haemolytic anaemia in SLE patients, would be that glomerulonephritis itself could trigger aHUS [57, 58], because it produces endothelial damage and red cell fragmentation in the glomerular bed thus favouring the development of TMA.

In our two patients, haemolysis appeared despite treatment with steroids and cyclophosphamide. We used PE or RTX but we obtained exclusively remission of haemolysis, without recovery of renal function.

In the literature, we identified 32 cases of renal vasculitis complicated by aHUS (Table 4) [59–84]. About 80% of such cases were microscopic polyangiitis (MPA); rarely other renal vasculitis was identified (GPA and adult-onset Henoch–Schoenlein purpura). In the follow-up, ESRD or death occurred in 60% of the cases whose follow-up was available. One patient was treated with RTX, which determined a prompt arrest of PE-resistant aHUS, but the patient remained haemodialysis-dependent. It is arguable that an early treatment with RTX or with eculizumab would ameliorate the prognosis of these patients.

In conclusion, taking together the glomerulopathies that trigger complement hyperactivation–dysregulation, the prevalence of associated aHUS could emerge as a relevant issue. Indeed TMA associates with lupus nephritis, MPGN and C3 glomerulopathies, and also with IgA nephropathy [6]. Very likely, renal vasculitis shares a similar relationship with TMA. More difficult to explain is the link between idiopathic nephrotic syndrome and aHUS. We hypothesize that in some cases, as in our patients, mutations or aHUS-risk haplotypes in genes encoding complement regulatory proteins (*CFH* and *MCP*) and/or local predisposing environment with endothelial dysfunction would trigger aHUS. Nephrologists should therefore keep a high index of suspicion of underlying complement dysfunction and TMA in glomerulopathic patients who show sudden anaemia, low platelet counts and LDH increase [85] (Figure 2).

An early recognition of aHUS may allow appropriate management and prevention of life-threatening consequences. In selected cases, an early application of PE and/ or of RTX showed efficacy in silencing haemolysis and contemporarily treating the underlying glomerulopathy [40–42, 86]. Moreover, in nephrotic aHUS patients treated with RTX, the drug was able to stop the loop of heavy proteinuria-aHUS and to reverse positively the road to a rapid decline of renal function. Obviously, the emerging anti-C5 biological agent eculizumab, which showed remarkable results in aHUS [87] and more recently also in C3 glomerulopathies [88], would represent an adjunctive therapy for this subtle clinical association.

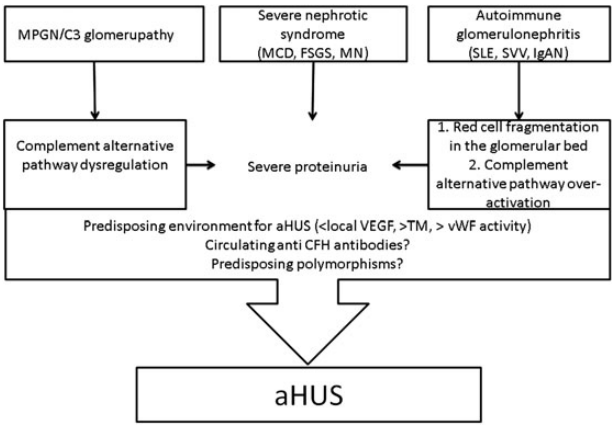

FIGURE 2: Proposed aetiopathogenesis for glomerulopathies-associated aHUS.

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CONFLICT OF INTEREST STATEMENT

None declared

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