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BRIEF REPORT

Favorable outcome in a case of *Mycoplasma pneumoniae*-associated crescentic glomerulonephritis

Anne-Laure Adra · Marie-Gabrielle Vigue · Fabienne Dalla Vale · Lydia Ichay · Pierre Raynaud · Aude Mariani · Denis Morin

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Abstract *Mycoplasma pneumoniae*-associated nephritis has been reported in children with various pathological findings. It nevertheless remains an uncommon disease and, within this clinical context, endo-and extracapillary glomerulonephritis in a child has never been described. We report here a case of a 3-year-old girl diagnosed with severe crescentic glomerulonephritis associated with *M. pneumoniae* infection who presented with nephrotic syndrome and impaired renal function. The serum C3 complement level was initially low but returned to normal after 1 month. Two courses of three methylprednisolone pulses were administered in association with plasmapheresis and, secondarily, mycophenolate mophetil. This treatment regimen led to disease remission and a favorable renal outcome at the 6-month follow-up. However, the treatment guidelines in this situation remain debatable.

Keywords Endo- and extracapillary glomerulonephritis · *Mycoplasma pneumoniae* · Nephrotic syndrome · Plasmapheresis

A.-L. Adra · M.-G. Vigue · F. Dalla Vale · L. Ichay · A. Mariani · D. Morin (✉)
Néphrologie Pédiatrique-Centre de Référence des Maladies rénales rares du Sud-Ouest-CHU Montpellier,
Université Montpellier I,
Montpellier, France
e-mail: d-morin@chu-montpellier.fr

P. Raynaud
Anatomo-pathologie-CHU Montpellier, Université Montpellier I,
Montpellier, France

D. Morin
IGF-CNRS, UMR5203-INSERM U661,
Montpellier, France

Introduction

Various types of *Mycoplasma pneumoniae*-associated acute glomerulonephritis have been reported in the literature. It is known to be a rare situation with a variety of pathological findings, including membranoproliferative glomerulonephritis (MPGN), proliferative endocapillary glomerulonephritis, minimal change disease, endo-and extracapillary glomerulonephritis, tubulo-interstitial nephritis, and even immunoglobulin A (IgA) nephropathy [1–6]. The pathogenesis of the disease remains unclear although it is thought to be an immune complex-mediated nephritis due to circulating immune complexes containing either mycoplasmal or autologous antigens [1].

In their review of 19 cases of *M. pneumoniae*-associated nephritis, Said et al. showed that end-stage renal failure or chronic renal failure occurred in nearly 40% of patients, mostly in those with MPGN [1]. In this context, rapidly progressive glomerulonephritis has been reported only once, in an adult patient, who continued to display chronic renal insufficiency despite treatment with steroid pulses, oral cyclophosphamide, and plasma exchanges [6].

To the best of our knowledge, we report here for the first time a case of acute *M. pneumoniae*-associated glomerulonephritis in a 3-year-old girl, characterized by severe endo-and extracapillary proliferation and an early relapse of proteinuria. The outcome was favorable following steroid therapy, plasmapheresis, and immunosuppressive therapy. The treatment, which remains mainly supportive in this situation, is still debatable.

Case report

A 3-year-old girl was admitted to our department with features of severe acute glomerulonephritis. Two weeks

earlier, macroscopic hematuria had been diagnosed as cystitis and she had received oral amoxicillin. She then became febrile with cough and developed marked edema. On admission, her temperature was 39°C and her blood pressure was normal. Physical examination showed impressive edema with ascites, and the chest X-ray revealed a typical aspect of *M. pneumoniae*-associated pneumonia with peribronchial infiltrates. Urinalysis demonstrated macroscopic hematuria and proteinuria up to 11 g/24 hours. Blood chemistry studies yielded the following values: urea nitrogen, 19.7 mmol/l; creatinine, 90 μmol/l; serum total protein, 40 g/l; albumin, 17 g/l. Hemoglobin was 9.1 g/dl, platelets 395,000/μl, and white blood cells (WBC) 12,100/μl. The C-reactive protein was 3.4 mg/l. The renal ultrasound scan showed enlarged hyperechoic kidneys (biological data and treatment are summarized in Table 1).

A PCR analysis for detecting *M. pneumoniae* in a nasopharyngeal swab was positive (*adhesin P1* gene), and the repeat studies of the complement fixation reaction for *M. pneumoniae* showed a significant increase in the serum titer. Both results supported the diagnosis of a recent *M. pneumoniae* infection in this young girl. She then received oral macrolides.

The serum complement study showed a C3 level of 0.44 g/l (normal range 0.7–1.2 g/l) and a C4 level of 0.16 g/l (normal range 0.1–0.2 g/l). The search for antinuclear factor, antineutrophil cytoplasmic antibodies, and antiphospholipid antibodies was negative. The serum anti-streptococcal antibody titers remained low.

Microscopic examination of a renal biopsy specimen revealed 22 glomeruli, with diffuse global endocapillary proliferation in 20/22 glomeruli and cellular crescent in 10/22 glomeruli (Fig. 1). Rare aspects of double-outline capillary basement membrane were also observed. There was strongly positive immunofluorescence staining, with both global and diffuse glomerular staining, for IgA, IgG, and C3 as well as the glomerular basement membrane, and slightly positive staining for IgM and C1q in the same area. The deposits did not have a "hump" appearance. The suspected diagnosis was either severe type I MPGN with crescents or immunocomplex endo-and extracapillary glomerulonephritis. Reverse transcriptase-PCR on renal biopsy specimens for the detection of *M. pneumoniae* RNA was negative. No electron microscopic study was performed.

Because of a possible diagnosis of severe MPGN, additional studies of the complement system were performed. The results for serum factor H, factor I, and factor B antigen levels were normal as was that for the membrane expression of the membrane cofactor protein (CD46). The search for C3 nephritic factor (C3Nef) was also negative (these studies were performed in the Laboratoire d'Immunologie Biologique-HEGP-Paris) [7].

Three methylprednisolone (MP) pulses were administered (1 g/1.73 m^2 body surface area/dose) followed by oral prednisone 2 mg/kg/day. Blood and urine studies showed the persistence of heavy proteinuria and a low total serum protein level. The child's renal function improved slightly with this treatment, but her creatinine plasma level remained high (70 μmol/l). Consequently, six plasmapheresis (PP) (80 ml/kg with albumin and fresh frozen plasma) procedures were performed. She was also maintained on oral steroid therapy. One month after admission, she was discharged with no edema; the proteinuria was 3.4 g/24 h, blood urea nitrogen was 5.1 mmol/l, and serum creatinine was 35 μmol/l. The serum complement C3 had returned to a normal level.

Unfortunately, she had to be readmitted 3 weeks later with a relapse of marked edema, macroscopic hematuria, increased proteinuria, and a plasma creatinine level of 137 μmol/l with a blood urea nitrogen level of 34 mmol/l, all of which were apparently triggered by a transient viral episode. The serum complement remained normal. A new renal biopsy showed 17 glomeruli with diffuse endocapillary proliferation and cellular crescents in 14/17 glomeruli. No further aspects of a double-outline capillary basement membrane were seen, excluding the diagnosis of MPGN. Immunofluorescence staining on the second biopsy specimen was unchanged in comparison with that on the first one, apart from a significant decrease in C3 deposits. Based on observations of these two renal biopsies, we suspected immunocomplex endo-and extracapillary glomerulonephritis.

A new course of three MP pulses was administered (1 g/1.73 m^2/dose), and three PP procedures a week were performed for the first 3 weeks followed by once a week for 4 weeks. She also received a first bolus of intravenous (IV) cyclophosphamide (500 mg/m^2), which was discontinued because of severe and prolonged neutropenia after the cyclophosphamide infusion. After recovery of a normal WBC count, she was started on mycophenolate mophetil (MMF; 1200 mg/m^2 body surface area/day) and maintained on daily oral prednisone and an angiotensin-converting enzyme inhibitor (enalapril 0.5 mg/kg/day). Her condition improved and at the end of the PP sessions, her plasma creatinine level was 35 μmol/l and the proteinuria was 0.35 g/l. The prednisone dose was progressively tapered.

After 6 months, she was still receiving oral MMF, prednisone 0.5 mg/kg/day, and enalapril (0.5 mg/kg/day). Her renal function was normal, and the level of proteinuria remained stable at around 0.3 g/l.

Discussion

Fewer than 25 cases of *M. pneumoniae*-associated glomerulonephritis have been reported in children during the past

Table 1 Laboratory data and treatment used at presentation and follow-up

	Presentation		Relapse		Follow-up
	↓		↓		↓
Days	0	30	45	90	180
Biological findings					
Creatinine (μmol/l)	90	35	137	37	35
Albumin (g/l)	17	24	15	35	34
Hematuria	macro	micro	macro	micro	micro
Proteinuria (g/day)	11	3.4	12	0.37	0.35
C3 (g/l)	0.44	0.92	0.95	0.94	0.97
Treatment					
MP pulses (1g/1.73m^2)	♦♦♦		♦♦♦		
Oral prednisone	----------	----------	----------	----------	---------- →
PP	||| |||		||| ||| ||| | | | |		
Cyclophosphamide (500 mg/m^2)			•		
MMF (1200 mg/m^2/day)			----------	----------	---------- →

MP methylprednisolone, *PP* plasmapheresis, *MMF* mycophenolate mophetil

30 years [1–6]. The clinical presentation has mostly been acute nephritis, with or without nephrotic syndrome, but interstitial nephritis and isolated gross hematuria have also been reported [1]. A severe presentation with acute renal failure and nephrotic syndrome is possible in this clinical context, but severe endo-and extracapillary proliferation has only been reported once, in an adult [6]. To the best of our knowledge, this condition has never been described in children. Thus, guidelines for treatment in such a situation are lacking.

In the present case, the diagnosis of *M. pneumoniae* infection was suspected from the chest X-ray and proven by the positive PCR for *M. pneumoniae* in the nasopharyngeal swab from our patient [8] and the increase in serum complement fixation titer for *M. pneumoniae* in two consecutive samples. RT-PCR did not detect this bacterium in the renal biopsy specimen, which was unsurprising as other studies have noted that *M. pneumoniae* antigens in kidney tissue are rarely positive in this situation [1, 3].

The results of published studies indicate that a low C3 complement level is frequently found in patients with *M. pneumoniae*-associated glomerulonephritis [1], and in at least one case, a decreased C3 level was associated with C3NeF, an IgG autoantibody that binds to the alternative pathway, C3 convertase [9, 10]. In one study, all of the patients who maintained a persistently low C3 complement level during follow-up had MPGN on renal biopsy and a poor renal outcome [1]. In our case, the C3 complement

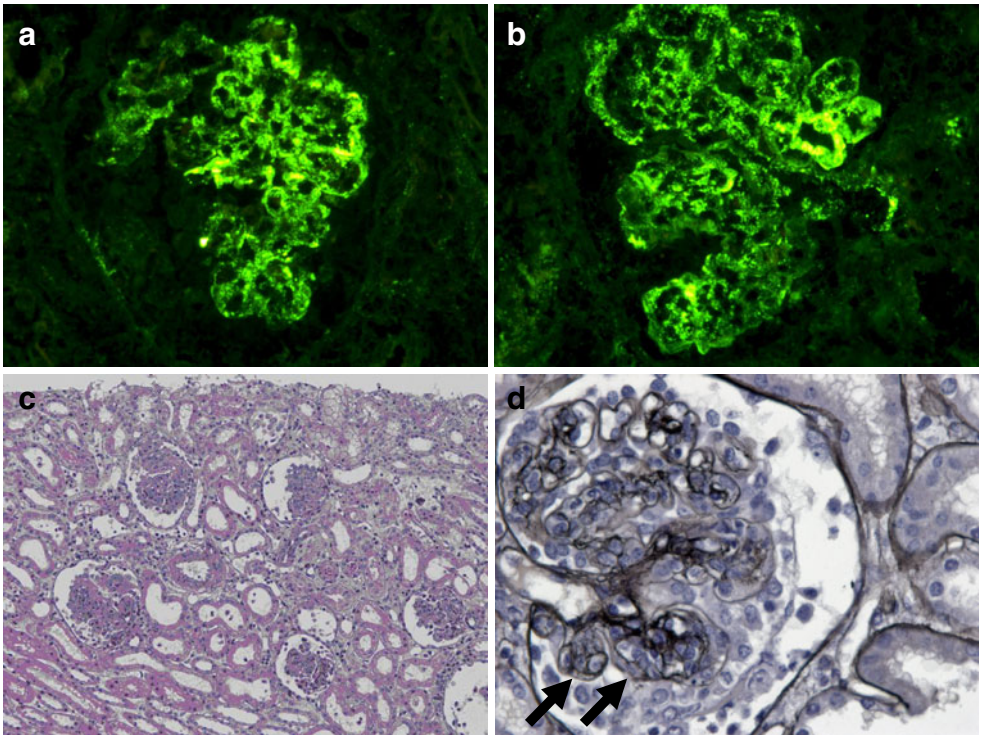

Fig. 1 First renal biopsy specimen. **a**, **b** Immunofluorescence findings with intense granular deposits of C3 and immunoglobulin G distributed in the both mesangium and peripheral capillary walls, with a prominent subendothelial pattern. **c** Glomeruli with endocapillary proliferation with cellular crescents (light microscopy, hematoxylin staining). **d** Glomerular endocapillary hypercellularity with focal basement membrane duplication (*arrows*) and a crescent formation (high power microscopic view, Marinozzi silver stain)

level was low at presentation but returned to the normal range within 1 month. The explanation for this phenomenon is not clear. We can hypothesize that complement activation mostly occurred via the alternative pathway due to a breakdown in control mechanisms, as is the case in acute post-streptococcal glomerulonephritis [11]. To the best of our knowledge, all of the various reports of cases with transient hypocomplementemia recorded a good renal prognosis, even when the initial presentation was acute renal failure. These data suggest that the pathophysiology of *M. pneumoniae*-associated nephritis varies and thus may cause several types of nephritis and a range of renal outcomes.

We performed an extensive complement analysis in our patient because the results of the first renal biopsy suggested severe MPGN. Our aim was to detect any acquired or hereditary complement dysregulation in the alternative complement pathway, as MPGN is known to be possibly associated with various types of complement regulatory protein abnormalities. These abnormalities may be acquired, as evidenced with the finding of C3NeF, or hereditary, as in complement factor H deficiency, which is also associated with a decreased C3 level [12]. In both cases, these findings have important treatment consequences as the patients would clearly benefit from plasma exchanges or plasmapheresis.

Our patient was also characterized by a severe clinical presentation, namely, gross hematuria, acute renal failure, heavy proteinuria, and diffuse and active extracapillary proliferation in 50% of the glomeruli, as revealed by renal biopsy. This latter finding raised the fear of poor renal prognosis, especially when the relapse of heavy proteinuria and acute renal failure, triggered by a viral episode, occurred after the first course of treatment (Table 1). The second renal biopsy showed the persistence of active renal proliferation, both endo-or extracapillary. In the literature, the only patient described with the same pattern on renal biopsy was an adult, and the outcome was very poor [6].

In crescentic glomerulonephritis, the prognosis depends on the severity of the histopathological findings and the underlying disease [13]. In our case, PP was performed after the first MP pulses because of persistantly impaired renal function with a high level of proteinuria and the severity of the renal biopsy results. After the early relapse of severe proteinuria and renal failure, the decision was made to add new MP pulses, PP and cyclophosphamide, and then MMF to the treatment regimen in response to the impaired renal function and the persistently severe cellular proliferative lesions on the second renal biopsy. This latter finding was surprising, given the recent immunosuppressive treatment. The choice of this therapeutic approach was also based on the severity of the nephrotic syndrome, which is known to be a predictor of poor renal prognosis in crescentic glomerulonephritis [14].

Severe *M. pneumoniae*-associated nephritis is a rare condition, and there is, therefore, a lack of good data in the literature to guide the choice of treatment regimen. The only published case described an adult patient who presented with diffuse proliferative glomerulonephritis that had led to acute renal failure. This patient had to be

hemodialysed, and the treatment consisted of MP, oral cyclophosphamide, and PP. The patient was able to stop dialysis under this treatment regimen, but he unfortunately remained with chronic renal insufficiency and eventually died of severe infectious disease [6].

In conclusion, to the best of our knowledge, this is the first report of a child presenting with severe immunocomplex endo-and extracapillary glomerulonephritis associated with *M. pneumonia* infection. The question of whether this newly described association in a single child is coincidental remains to be resolved. The treatment, mainly based on MP and PP, was associated with good short-term renal prognosis, although long-term renal follow-up is needed in this young girl. As in the other cases of post-infectious crescentic glomerulonephritis, and in the absence of clear treatment guidelines, the severity of the histopathological findings seems to remain the most important factor in determining the intensity of the immunosuppressive treatment.

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