nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Letters to the Editor

A minimal change disease compatible with C1q nephropathy in a paediatric patient. Evolution and treatment of a difficult pathology☆

Enfermedad de cambios mínimos compatible con nefropatía C1q en paciente pediátrico. Evolución y tratamiento de una enfermedad complicada

Dear Editor,

C1q nephropathy is a controversial disease as some authors consider it to be indistinguishable from minimal change disease (MCD), while others believe it is a between minimal changes and focal segmental glomerulosclerosis (FSGS).[1,2] The criteria for diagnosis of the disease include predominant C1q deposits by immunofluorescence and no clinical or laboratory evidence of systemic lupus erythematosus.[3,4] Microscopically, in contrast to lupus, there should be no tubulointerstitial disease in C1q nephropathy.[5,6]

We present a case of a 21-year-old patient, referred to Nephrology from the Paediatric Department in March 2010, when he was 14 years old, due to steroid-resistant nephrotic syndrome. Paediatricians had previously been diagnosed the patient as a likely case of minimal change disease, and treatment was started with corticosteroids at a dose of 80 mg/day.

The first visit to Nephrology revealed the following values: albumin 2 g/dl; total protein 4.9 g/dl; haemoglobin 15.9 g/dl; creatinine 0.18 mg/dl and electrolytes were normal. Proteinuria was 4.9 g in 24 h, and C3 and C4 levels were, 162 and 22.9 mg/g. An ultrasound revealed that both kidneys were enlarged with increased renal parenchyma related to the nephrotic syndrome. It was decided to maintain steroid treatment and the patient was seen in clinic in January 2011; then, proteinuria was increased despite treatment. The immunological study was negative for ANA, ANCA, ENA, DNA, anticardiolipin antibodies and GBM antibodies. *Immunoglobulins*: IgG 135 mg/dl and the rest of immunoglobulins were within normal range. No data indicating anaemia were observed and kidney function remained normal. It was decided to perform a kidney biopsy (Fig. 1): 30 glomeruli, with a slight increase in mesangial cells; no evidence of basement membrane thickening or spikes, and matrix clusters or capillary collapses were not observed. There were no abnormalities in the vascular and tubular components. A dense mesangial C1q deposit was observed on direct immunofluorescence, while a more limited quantity of deposits of C3 and IgG were observed. It was negative for the remaining immunoglobulins, light chains and fibrinogen. *Diagnosis*: minimal change disease with predominant C1q deposit, compatible with C1q nephropathy.

Treatment was initiated with tacrolimus to maintain levels between 6 and 8 μg/l and genetic testing was ordered to rule out diseases related to the WT1 gene (WAGR syndrome, Denys-Drash syndrome and Fraser syndrome). They were all negative and there was no response to the treatment. In February 2012 the patient was started on mycophenolate mofetil with increasing doses up to a maximum of 1 g/12 h, and again without response. He presented in January 2015 with proteinuria of 9.4 g/24 h and impaired kidney function, negative autoimmune testing (ANA, ANCA, DNA, ENA, GBM and cryoglobulins). A second biopsy was indicated: 19 glomeruli, of which 50% (9) were completely sclerosed, six did not present abnormalities and the remaining four presented variable degrees of sclerosis,

DOI of original article:
https://doi.org/10.1016/j.nefro.2018.05.004.

☆ Please cite this article as: Romaniouk Jakovler I, Mouzo Javier R, Perez Nieto C, Romero A, Simal F, Castañon B. Enfermedad de cambios mínimos compatible con nefropatía C1q en paciente pediátrico. Evolución y tratamiento de una enfermedad complicada. Nefrologia. 2019;39:84–86.

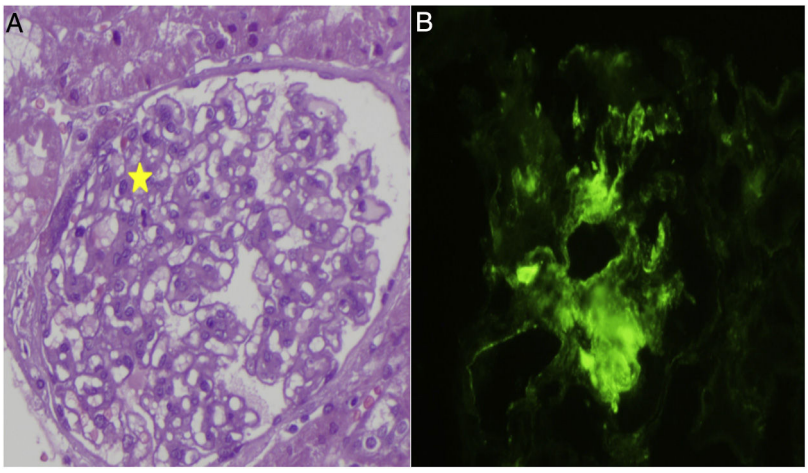

Fig. 1 – (A) Kidney biopsy. Morphologically, a slight increase in mesangial cells is observed in some glomeruli. (B) Direct immunofluorescence study in which C1q deposits are observed.

Table 1 – Relationship between treatment, proteinuria and kidney function from March 2010 to July 2017 in a patient with a diagnosis of C1q nephropathy.

Date	03/2010	01/2011	02/2012	01/2013	01/2014	01/2015	06/2015	06/2017
Age of the patient (years)	14	15	15	16	17	17	18	21
Creatinine (mg/dl)	0.18	0.57	0.58	0.72	0.65	1.2	1.71	3.9
Proteinuria (g/dl)	4.9	3	5	5.4	9.7	12.7	10	14
Prednisone 80 mg/day								
Tacrolimus for levels of 6–8 μg/l								
Mycophenolate mofetil 1 g/12 h								
Rituximab								

Over time, and according to the kidney disease stage, the patient received treatment with: acetylsalicylic acid, hidroferol 0.266 μg, statins, proton-pump inhibitors, phosphate binders and antihypertensive drugs.

in two glomeruli the slclerosis was also surrounded the Bowman's capsule. Immunofluorescence did not reveal deposits of complement, immunoglobulins, light chains or fibrinogen were observed in any of the structures. Despite the disappearance of C1q deposits in this biopsy, the patient underwent five years of treatment with a progressive decline in kidney function. It was therefore decided to start a fourth line of treatment with rituximab, receiving four weekly boluses in June 2015 with no improvement in proteinuria and significantly impairment of kidney function (Table 1). All possible treatment lines had therefore been exhausted and the patient's status progressed to advanced chronic kidney disease (CKD).

Anti-C1q antibodies target the first complement component. The majority of them are of the IgG subtype, predominantly IgG1 and IgG2, demonstrating a strong correlation between their presence and kidney damage. The mechanisms through which C1q is found in kidney biopsies would be: (1) that it is bound to the Fc portion of the implanted Ig or of the circulating immune complexes; (2) apoptotic remains could capture C1q facilitating their clearance; (3) C1q could bind to C-reactive protein, amyloid or Ig trapped in the glomerulus; (4) specific and direct binding of C1q to renal parenchyma cells; (5) passive entrapment, and (6) cross-reaction with antigens similar to C1q.[1,7–9] This therefore explains why every time we are faced with nephropathy involving the classical complement pathway, C1q deposits can be observed in the biopsy.

Therefore, patients who have C1q nephropathy and FSGS are more likely to progress to end-stage kidney disease. There are no randomised trials which have evaluated the treatment of C1q nephropathy. Therapy involves treatment of the underlying microscopic lesion.

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https://doi.org/10.1016/j.nefroe.2018.05.007

Eculizumab as a treatment for atypical hemolytic uremic syndrome secondary to carfilzomib☆

Síndrome hemolítico urémico atípico secundario al uso de carfilzomib tratado con eculizumab

Dear Editor,

Carfilzomib is a proteasome inhibitor drug with antiproliferative and pro-apoptotic activity. It is one of the drugs used in the treatment of refractory multiple myeloma.[1–4] The onset of atypical haemolytic uremic syndrome (aHUS) associated with the use of carfilzomib is a complication previously described in the literature.[5–10] We describe a case of aHUS secondary to carfilzomib effectively treated with eculizumab.

This case involves a 71-year-old woman with refractory Bence-Jones Kappa multiple myeloma treated with carfilzomib, daratumumab and dexamethasone (KdD). The patient was admitted to the Haematology Department due to onset of malaise and fever 2 days after receiving the second cycle of KdD. Despite negative microbiology results, her blood pressure increased to over 180/100 mmHg on the fourth day. Blood tests found a decrease in haemoglobin of up to 6.8 g/dl and in platelets of up to 12,000, with an increase in LDH of up to 900 IU/l, accompanied by a deterioration of renal function, with serum creatinine levels of 2.6 mg/dl. Suspecting thrombotic microangiopathy (TMA), treatment with prednisone (1 mg/kg/day) and fresh plasma was started, with no improvement, and the patient was referred to the Nephrology Department for assessment.

Studies performed by the Nephrology Department showed 5–6% schistocytes per field on peripheral blood smear, no signs of malignant arterial hypertension on fundoscopy, undetectable haptoglobin in blood, and negative direct Coombs test. ADAMTS13 test was normal (ADAMTS13 > 50%). Other causes of aHUS and typical haemolytic uraemic syndrome (*STEC-HUS*) were ruled out, and genetic studies were not performed due to the high suspicion of a pharmacological cause. Carfilzomib was discontinued and treatment with eculizumab was started after administration of meningococcal prophylaxis with oral penicillin. Plasmapheresis was not performed due to the poor status of the patient and to avoid the comorbidity associated with the technique. One week after the third dose of eculizumab, serum creatinine levels had normalised (1.1 mg/dl) without the need for any haemodialysis sessions, and schistocytes had disappeared. From a haematological point of view, partial improvement was observed in haemoglobin and platelet levels, probably due to the underlying disease, although no schistocytes were found. The patient received 3 weekly doses of 900 mg of eculizumab, which was discontinued after improvement of renal function and stabilisation of haemolysis parameters.

Based on the accumulated evidence relating to the pathogenesis of this condition, we wonder whether treatment with

DOI of original article:
https://doi.org/10.1016/j.nefro.2018.02.005.
☆ Please cite this article as: Moliz C, Gutiérrez E, Cavero T, Redondo B, Praga M. Síndrome hemolítico urémico atípico secundario al uso de carfilzomib tratado con eculizumab. Nefrologia. 2019;39:86–88.