



One of the few reported cases of fibrillary glomerulonephritis in lupus nephropathy

Uno de los pocos casos reportados de glomerulonefritis fibrilar en nefropatía lúpica

Dear Editor,

We report a case of the onset of lupus nephritis (LN) in the form of fibrillary glomerulonephritis (FGN).

In August 2021 a 17-year-old girl of Romanian origin developed malar erythema and inflammatory gonalgia. Her primary care physician confirmed a preserved renal function with positive ANA and anti-DNA, microhematuria and albuminuria. The patient was referred to our clinic. Fever, weight loss, other arthralgias, arthritis, uveitis, Raynaud's and aphthae were all absent. She had regular menstruation and was not obese. She had no other relevant medical history. Her mother suffered from arterial hypertension, psoriasis and autoimmune hypothyroidism. A skin biopsy was performed on the malar erythema and results confirmed acute cutaneous lupus. A complete blood count and biochemistry study were ordered. The hemogram and biochemistry results were all within normal values except for total protein: 5.6 g/dl and serum albumin: 2.5 g/dl. Urinalysis showed proteinuria (30 mg/dl), red blood cells (3–10 per high power field); CrCl: 246 ml/min/1.73 m² and proteinuria: 2.4 g/24 h.

Autoimmunity: positive for a homogeneous ANA pattern AC1 420 titer 1:160, Anti-DNA native antibodies: positive (titer 243.3). Anti-double stranded DNA antibodies (*Crithidia luciliae*): positive. The rest, including antiphospholipid antibodies and β -2 glycoprotein 1, were negative. C₃: 61 mg/dl, C₄: 9 mg/dl. Thyroid profile with normal TSH and antimicrosomal antibodies (TPO) 107.60 IU/mL (normal values: 0.0–60.0). Neck ultrasound was normal. Immunoglobulin (Ig) G positive and IgM negative for EBV, rubella, HHV type 6, varicella zoster. Quantiferon and serology negative for *Leishmania*, *Leptospira*, *Trypanosoma cruzi*, *Borrelia*, *Strongyloides*, parvovirus, lupus, cytomegalovirus, toxoplasma, HBV, HCV, HIV, *Brucella* and *Bartonella*.

A renal biopsy was performed (Fig. 1). The results showed 19 glomeruli per sample, 1 with global sclerosis of the capillary mass (5%). The preserved glomeruli were normal in size and lobulation. Fine and permeable capillary loops. There were no wire loop deposits, hyaline pseudothrombi, necrotizing lesions, karyorrhexis, neutrophils or endo-

extra-capillary hypercellularity. Slight mesangial expansion without increased cellularity. In 2 glomeruli, with segmental distribution, images suggest projections without basement membrane (BM) vacuolization or clear subepithelial deposits by direct immunofluorescence (DIF). No significant alterations of the tubule. No lesions on the muscle wall vessels or arterioles. No intimal fibrosis, arteriolar hyalinosis or amyloid material with Congo red. DIF: mesangial and subendothelial granular deposits of IgG (++) and C3 (+++) in capillary loops, and mesangial granular deposits of IgM (+) and C1q (++) with a slight predominance of kappa light chains over lambda. Diagnosis: class III LN. Activity score: 0/24. Chronicity score: 1/12.

We started treatment with ACE inhibitors, hydroxychloroquine, corticosteroids and mycophenolate. After 6 months of follow-up treatment, renal function remains stable and proteinuria has decreased to 0.65 g/24 h.

The results of electron microscopy were then received (Fig. 2): There were 4 glomeruli with distorted general architecture. Podocytes presenting villous transformation in the cytoplasm; no intracytoplasmic deposits. Focal pedicel fusion affecting 30% of the total pedicellar extension and rearrangement of the intermediate filaments towards the cell's basal pole. BM with irregular contours and diffusely thickened, lamina densa thickness between 700 and 925 nm (average 863 nm, NV: 300–400 nm), moderately electron dense diffuse deposits, arranged as fibrils ranging in diameter from 10.60 to 35.65 nm (average 18.32 nm), embedded in the lamina densa and causing a spiculate reaction of the glomerular BM, but not embedded in the lamina densa. Few subendothelial deposits. Endothelia with a normal shape, clearly visible fenestrations and tubuloreticular inclusions. Moderately enlarged mesangium at the expense of the matrix and with frequent electron dense deposits of the same characteristics described above. No ultrastructural lesions of tubules or vessels. No deposits in the tubular or vascular BM. In view of these findings, an immunohistochemical staining for DNAJB9 was performed. The result was positive for a granular pattern in the subepithelial aspect of the BM, which led to a diagnosis of fibrillary glomerulonephritis.

Given the good initial response, immunosuppressive treatment was maintained pending evolution of the patient's condition.

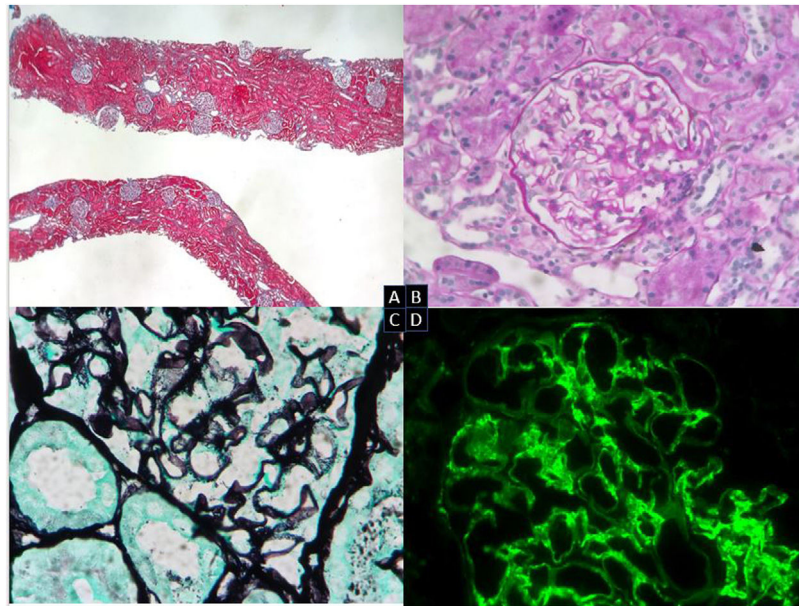


Fig. 1 – Renal biopsy. Optical microscopy. (A) Renal cortical parenchyma with preserved general architecture and without significant chronic changes (Masson's trichrome). **(B)** Glomeruli with no mesangial expansion, proliferative lesions or other morphological alterations (PAS, 20×). **(C)** Glomerulus with very focal spikes of basement membrane (silver, 40×). **(D)** DIF: IgG and granular mesangial C3 deposits in capillary loops and IgM and mesangial C1q deposits (IgG, 40×).

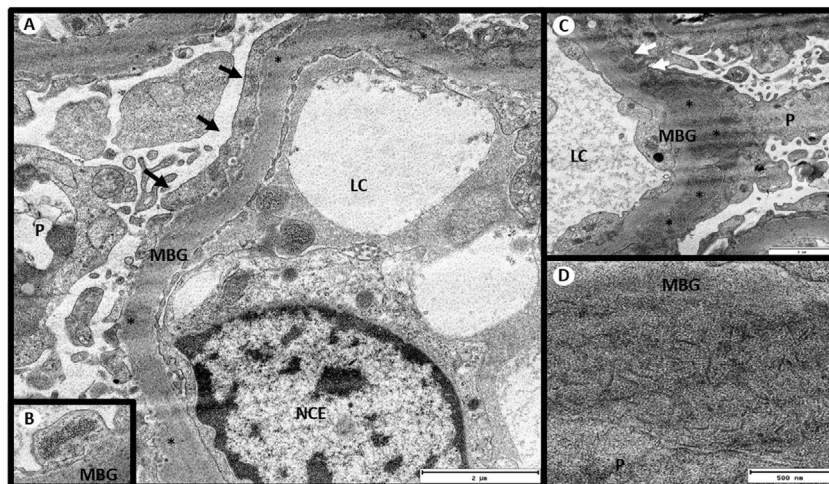


Fig. 2 – Electron microscopy. (A) Glomerulus with massive pedicel fusion (black arrows). **(B)** Presence of tubuloreticular inclusions in the endothelium. **(C)** Moderately electron-dense deposits in the subepithelium (*) with spiculated reaction of the lamina densa (white arrows). **(D)** Deposits organized in the form of fibrils. Transmission electron microscopy A and C: 5,000×, B: 8,000×, D: 1,2000×. CL: capillary lumen; GBM: glomerular basement membrane; ECN: endothelial cell nucleus; P: podocyte.

The DNA protein JB9 is a cochaperone located in the endoplasmic reticulum of many cells. It is activated by stress and is involved in protein folding. In FGN^{1,2} with immunocomplex deposition, Ig has been shown to be restricted for IgG4 and IgG1. This explains why Ig is the protein deposited or why it deposits a misfolded JB9 DNA protein at glomerular level, which will trigger the subsequent inflam-

matory response. The mechanism depends on complement activation through the classical pathway (C4 positive in generalized staining). The largest published series of FGN³ describes 23% of cases associated with tumors that started between 15 years before and 10 years after (multiple myeloma, chronic myelomonocytic leukemia; thyroid, hepatocellular, lung, uterine, prostate, colon or renal cancer; melanoma),

15% associated with unspecified autoimmune diseases (lupus, Sjogren's, Crohn's disease, Graves-Basedow, primary biliary cholangitis, idiopathic thrombocytopenic purpura and ankylosing spondylitis), 3% with chronic hepatitis C, 20% with diabetes, 9% with chronic ischemic heart disease, 5% with COPD and 17% with monoclonal gammopathy. Clinically, 71% of cases presented with HTN, 59% with edema, 41% with proteinuria (mean 3.1 g/day), 62% with hypoalbuminemia, 38% with hypercholesterolemia, 62% with full-blown nephrotic syndrome, 52% with hematuria, 29% with leukocyturia and 2% with hypocomplementemia.

The association of FGN with LN⁴⁻¹⁰ has only been reported rarely in relapses following renal transplantation in cases of LN without systemic lupus and in one case of neuropsychiatric lupus, which resulted in a diagnosis of class 4 LN.

In a review of 223 renal biopsies of LN with organized electron-dense deposits¹¹, investigators identified 3 cases with tubular deposits and 2 cases with fibril deposits, with the structural features of immunotactoid glomerulopathy and FGN.

Regarding the prognosis, there is no conclusive data given the low number of cases, although FGN progresses to end-stage renal disease in 50% of cases after 5 years. For the same reason, there is no evidence regarding treatment, although the use of rituximab is recommended.

In our case, and given the short time of evolution, we can report a partial response after 2 months of treatment.

Funding

This article has no source of funding.

REFERENCES

- Rosenstock JL, Markowitz GS, Valeri AM, et al. Fibrillary and immunotactoid glomerulonephritis: distinct entities with different clinical and pathologic features. *Kidney Int.* 2003;63:1450-61.
- Nasr SH, Vrana JA, Dasari S, et al. DNAJB9 is a specific immunohistochemical marker for fibrillary glomerulonephritis. *Kidney Int Rep.* 2017;3:56-64.
- Nasr SH, Valeri AM, Cornell LD, et al. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. *Clin J Am Soc Nephrol.* 2011;6:775-84.
- Bhat ZY, Zeng X, Hingorani J, Khan S, Mohanty MJ. Fibrillary glomerulonephritis in a patient with systemic lupus erythematosus: a rare association. *Int Urol Nephrol.* 2013;45:281-4, <http://dx.doi.org/10.1007/s11255-011-0073-0>. Epub 2011 Nov 19. PMID: 22102086.
- Menon S, Zeng X, Valentini R. Fibrillary glomerulonephritis and renal failure in a child with systemic lupus erythematosus. *Pediatr Nephrol.* 2009;24:1577-81, <http://dx.doi.org/10.1007/s00467-009-1168-z>. Epub 2009 Mar 24. PMID:19308460.
- Touzot M, Terrier CS, Faguer S, Masson I, François H, Couzi L, et al., Groupe Coopératif sur le Lupus Rénal (GCLR). Proliferative lupus nephritis in the absence of overt systemic lupus erythematosus: a historical study of 12 adult patients. *Medicine (Baltimore).* 2017;96:e9017, <http://dx.doi.org/10.1097/MD.00000000000009017>. PMID: 29310419; PMCID: PMC5728820.
- Ponticelli C, Moroni G, Glasscock RJ. Recurrence of secondary glomerular disease after renal transplantation. *Clin J Am Soc Nephrol.* 2011;6:1214-21, <http://dx.doi.org/10.2215/CJN.09381010>. Epub 2011 Apr 14. PMID: 21493742.
- Isaac J, Shihab FS. Recurrent lupus nephritis in the second allograft of a patient with systemic lupus erythematosus. *Nephron.* 2002;92:947-9, <http://dx.doi.org/10.1159/000065458>. PMID: 12399648.
- Perez O, Dave K, Almanzar A, Prodhan T, Concepcion L. Primary psychiatric disorder masking the diagnosis of neuropsychiatric lupus in a patient with altered mental status: a case report. *Cureus.* 2017;9:e1793, <http://dx.doi.org/10.7759/cureus.1793>. PMID: 29423350; PMCID: PMC5794200.
- Isaac J, Herrera GA, Shihab FS. De novo fibrillary glomerulopathy in the renal allograft of a patient with systemic lupus erythematosus. *Nephron.* 2001;87:365-8, <http://dx.doi.org/10.1159/000045944>. PMID: 11287782.
- Hvala A, Kobenter T, Ferluga D. Fingerprint and other organised deposits in lupus nephritis. *Wien Klin Wochenschr.* 2000;112:711-5. PMID: 11020962.

Martín Navarro Juan A.^{a,*}, Matías de la Mano M. Angeles^b, Roldán Cortés David^c, Díaz-Crespo Francisco^d, Procaccini Fabio L.^a, Muñoz Rodríguez Jorge^c, Medina Zahonero Laura^a, Ortega-Díaz Mayra^a, Puerta Carretero Marta^a, Barba Teba Raquel^a, Chavarría Mur Eva^e, Alcázar Arroyo Roberto^a

^a Su^o de Nefrología Hospital Universitario Infanta Leonor, Spain

^b Su^o de Reumatología Hospital Universitario Infanta Leonor, Spain

^c Su^o de Anatomía Patológica Hospital Universitario Infanta Leonor, Spain

^d Su^o Anatomía Patológica H.G.U. Gregorio Marañón, Spain

^e Su^o de Dermatología Hospital Universitario Infanta Leonor, Spain

* Corresponding author.

2013-2514/© 2022 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.nefro.2022.12.003>