



Collapsing glomerulopathy in a patient with APOL1 intermediate-risk genotype triggered by lupus nephritis and SARS-CoV-2 infection: lessons for the clinical nephrologist

Christophe Masset¹ · Karine Renaudin^{2,3} · Delphine Kervella¹ · Agnès Chapelet¹ · Clément Deltombe¹ · Simon Ville^{1,2}

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The case

A 21-year-old woman of African ancestry presented with skin rash and joint pain associated with edema. Her BMI was 20.2 kg/m². Laboratory tests revealed nephrotic syndrome (protein-to-creatinine ratio (PCR) of 8.5 g/g, serum albumin 1.8 g/dL) without normal kidney function (serum creatinine (SCr) 0.7 mg/dl, estimated GFR by MDRD was 130 ml/min/1.73m²). Immunology work-up revealed a high antinuclear antibody titer (> 1:2560; normal range < 1:80) and positive anti-double-stranded DNA antibody (> 400 IU/ml; normal range < 30), C3 and C4 serum levels were decreased (0.27 g/L; normal range 0.9–1.8 and 0.09 g/L; normal range 0.1–0.4 g/L, respectively). Renal biopsy found active class IV lupus nephritis: all glomeruli showed global subendothelial deposits (wire-loops), hyaline thrombi, hematoxylin bodies and 50% glomerular endocapillary hypercellularity (Fig. 2A). Immunofluorescence microscopy showed full house bright staining (supplementary Figure). As summarized in Fig. 1, the patient was started on steroids (1 mg/kg orally, tapered by 25% every 2 weeks, then continued at 10 mg/day) and mycophenolate mofetil (2 g/day). Treatment was switched to cyclophosphamide (500 mg/15 days, i.v.) owing to the onset of neurological involvement (cranial

neuropathy) and increase in serum creatinine. Whilst clinical and serological parameters improved, she presented with necrotizing fasciitis complicated by septic shock. This led to the discontinuation of immunosuppressants, except for steroids (hydrocortisone hemisuccinate i.v. in intensive care, then the resumption of prednisone at 10 mg/day). After a 1-month stay in intensive care, following surgical treatment of the infection, she was admitted to the division of physical medicine and rehabilitation. Another month later, while double-stranded DNA antibody levels increased again (307 IU/mL) clinical activity remained low and renal parameters were consistent with remission (PCR 3.0 g/g, serum gamma globulin 7.6 g/L, SCr 1.2 mg/dL). One week after this reassuring work-up, she presented with fever without any other symptoms, and SARS-CoV-2 infection was diagnosed. She had no respiratory involvement and no specific treatment was administered, however within a week edema recurred, and proteinuria and serum creatinine increased again (PCR 6.0 g/g, SCr 1.3 mg/dL). A second renal biopsy was performed. Glomeruli showed focal active lesions of lupus nephritis different from those of the first biopsy: karyorrhexis and/or neutrophils without necrosis in 46%, glomerular endocapillary hypercellularity and subendothelial deposits in 8%. Otherwise, all showed glomerular sclerosis with segmental or global collapse of the glomerular tuft associated with adhesions to Bowman's capsule and podocyte hypertrophy. Twenty-three percent of glomeruli presented extracapillary hypercellularity and pseudocrescents with striking podocyte hypertrophy/hyperplasia, attributable to concurrent collapsing glomerulopathy (CG) (Fig. 2B, C). Finally, glomerular full house immunostaining was present, as in the first biopsy, with a lower intensity. APOL1 genotype was assessed and revealed intermediate risk (G2

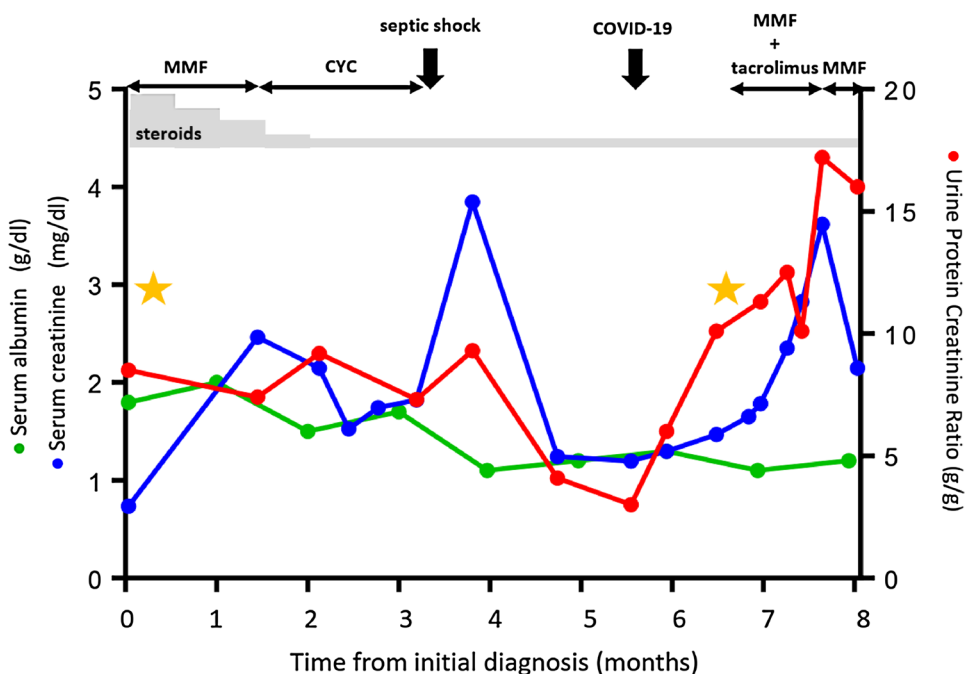
✉ Simon Ville
simon.ville@chu-nantes.fr

¹ Department of Nephrology and Transplantation, Institut de Transplantation Urologie Néphrologie (ITUN), CHU de Nantes, 30 boulevard Jean Monnet, 44000 Nantes, France

² Centre de Recherche en Transplantation et Immunologie UMR1064, INSERM, Université de Nantes, Nantes, France

³ Department of Pathology, CHU Nantes, Nantes, France

Fig. 1 Evolution of renal parameters and treatments in a patient with lupus nephropathy complicated by septic shock and SARS-CoV-2 infection. The yellow stars indicate the time of the kidney biopsies. *MMF* mycophenolate mofetil, *CYC* cyclophosphamide, *COVID-19* coronavirus disease 2019. (Color figure online)



deletion/wild type). We concluded that the glomerular injuries were active lupus nephritis associated with collapsing glomerulopathy presumably due to concomitant mechanisms: (1) the SLE flare itself, (2) SARS-CoV-2 infection, against a background of genetic predisposition. We resumed immunosuppressant therapy with steroids, mycophenolate mofetil and low dose tacrolimus. However, due to a rapid increase in serum creatinine suggestive of nephrotoxicity, tacrolimus was discontinued. Current serological activity is low, but renal function has only partially improved while proteinuria remains unchanged.

Lessons for the clinical nephrologist

Collapsing glomerulopathy (CG) is a pattern of glomerular injury characterized by shriveling of the glomerular tuft in the setting of focal segmental glomerulosclerosis (FSGS) [1]. It most often occurs in subjects of African ancestry with a genetic predisposition, who carry an APOL1 high-risk genotype (homozygous for G1 or G2 or compound G1/G2 heterozygotes) and triggering diseases behave like a ‘second hit’ leading to clinical manifestation of CG. Lupus nephritis is on the list of known triggers [2], to which SARS-CoV-2 infection was added more recently [3]. We report the case of a patient with CG in whom these two factors were combined.

APOL1 genotype assessment found intermediate risk (G2 deletion/wild type).

This case illustrates that differentiating CG from crescentic lupus nephritis can be challenging. Indeed, unlike lupus podocytopathy, characterized by podocyte injury without peripheral capillary wall immune deposits and glomerular proliferation [4], CG associated with SLE occurs in patients with an active lupus flare and often with immune complex-mediated lupus nephritis [2]. For example, Larsen et al. previously found that in renal biopsies from African American patients with SLE, CG and non-necrotizing crescents were associated with the APOL1 high-risk genotype. This suggests that it was a result of the morphological similarity between a florid ‘crescent-like’ collapsing lesion and cellular crescent formation which may lead to confusion and under-diagnosis of CG lesions in such patients [5]. A morphological feature allowing the differentiation of pseudo-crescents from genuine crescents of parietal cell origin is the absence of spindled cellular morphology, pericellular matrix and fibrin, as in our patient.

An additional argument supporting CG was the close association between the onset of the SARS-CoV-2 infection and the recurrence of massive proteinuria in a patient with APOL1 intermediate-risk genotype. Indeed, collapsing glomerulopathy is the most common glomerular disorder reported in SARS-CoV-2 infected patients and it occurs early in the course of the disease [3, 6, 7]. In line with HIVAN, proposals have been made to term this new

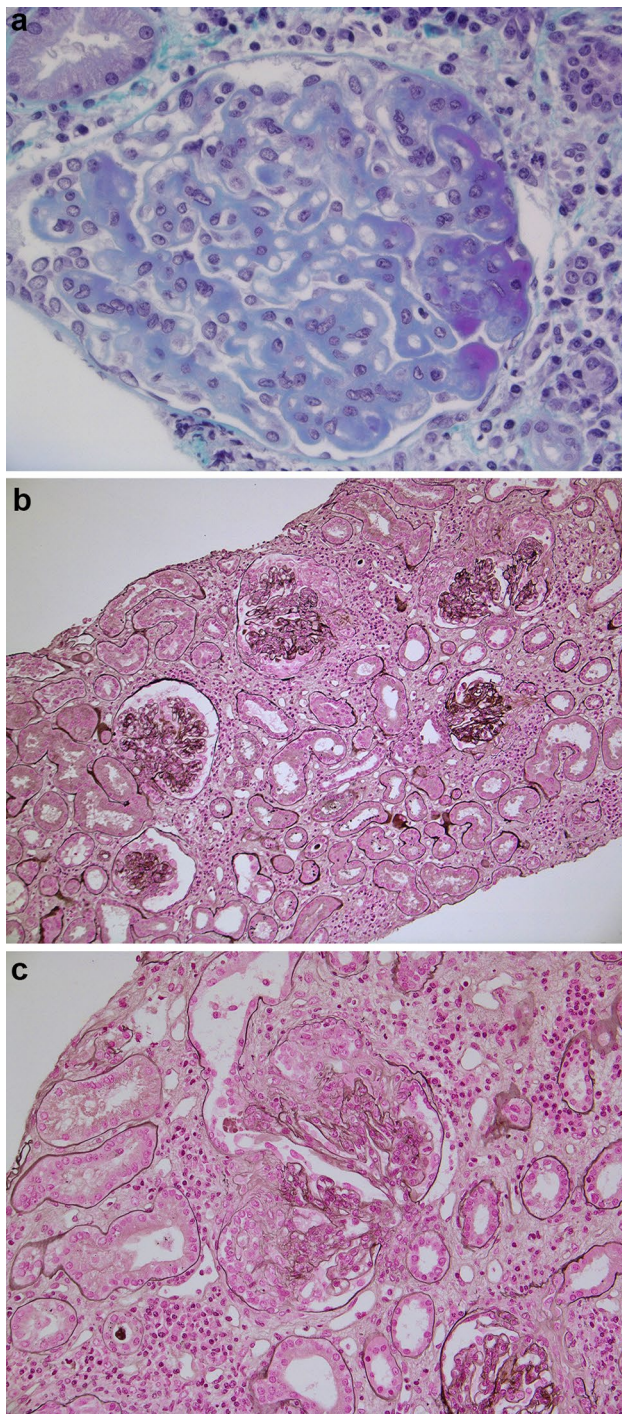


Fig. 2 **A** Diffuse subendothelial deposits, hematocytin bodies and segmental endocapillary hypercellularity (Masson trichrome stain $\times 400$). **B** Diffuse lesions of glomerular sclerosis with segmental or global collapse of the glomerular tuft associated with adhesions and podocyte hypertrophy (Marinozzi methenamine silver stain $\times 100$). **C** Collapsing glomerulopathy with pseudocrescents due to podocyte hypertrophy and hyperplasia

entity COVID-19-Associated Nephropathy (COVAN) [8]. As with HIVAN, COVAN impacts patients with APOL1 high risk genotype, who represent 14% of the African American population and more generally of people of West African ancestry, whilst up to 50% have one risk allele. To date, all patients with COVAN in whom the APOL1 genotype was assessed had two risk alleles, except for the intriguing case of a kidney transplant recipient with a germline APOL1 high-risk genotype but with allograft carrying only one risk allele [7]. This case, as well as ours, suggests that the presence of a single APOL1 risk allele may be sufficient to confer risk in extreme conditions such as simultaneous SLE flare and COVID-19 that may have been synergistic. The common theme in both conditions is an increase in interferon-mediated inflammatory signaling, a feature shared by most triggers of CG, as illustrated by the archetypal example of CG occurring in a patient with APOL1 high-risk genotype and treated with interferon [9]. Otherwise, even though it is less frequent than in patients with SLE and APOL1 high-risk genotype, CG may occur in patients with one risk allele while it is exceptional in patients with zero risk alleles [5].

We chose to resume immunosuppressive drugs with multitarget therapy (combination of mycophenolate mofetil and tacrolimus) to avoid increasing steroid dosage and resuming cyclophosphamide, and because mycophenolate mofetil alone seemed insufficient. The poor response to treatment seen in our patient is also evocative of CG lesions, known to have a worse prognosis compared to classical lupus nephritis.

Our report raises concerns about the potential risk of COVAN in people of West African ancestry, including those with APOL1 intermediate-risk genotype, when other promoting factors for CG overlap. We cannot rule out that CG was not related to the SARS-Cov-2 infection in our patient, therefore it would be of great importance, should similar cases occur, to report them to better appreciate the risk these patients are exposed to when they contract COVID-19.

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Declarations

Conflict of interest None of the authors have any conflicts to disclose with regard to this work.

Ethical statement The patient has given her consent for us to report her case.

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