Collapsing Glomerulopathy in Systemic Lupus Erythematosus: An Extreme Form of Lupus Podocytopathy?

Mark Haas

Clin J Am Soc Nephrol 7: 878–880, 2012. doi: 10.2215/CJN.03590412

Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California

Correspondence: Dr. Mark Haas, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room 8742, Los Angeles, CA 90048. Email: mark.haas@cshs.org

Collapsing glomerulopathy (CG) describes a pattern of glomerular injury, the main feature of which is severe injury to podocytes with loss of markers of differentiation, proliferation of podocytes and/or parietal epithelial cells filling Bowman's space, and global or segmental collapse of the capillary tuft (1–4). Multiple etiologies of CG have been described, including certain viral infections (most notably HIV but also parvovirus B19 and hepatitis C), drugs, gene mutations, and vascular occlusion, in addition to idiopathic forms (4–6). In this issue of *CJASN*, Salvatore *et al.* (7) report a retrospective series of 19 patients with systemic lupus erythematosus (SLE), none known to be positive for HIV, hepatitis C, or parvovirus, who underwent a renal biopsy for an indication of proteinuria and often renal insufficiency that showed CG, with or without concurrent lupus nephritis. These findings raise important questions regarding the pathogenesis of CG in this clinical setting and the relationship of these lesions to the previously described entity of lupus podocytopathy (8), as well as issues of differential diagnosis on renal biopsy.

As detailed by Salvatore *et al.* (7), CG occurring in the setting of SLE shares certain demographic, clinical, morphologic, and immunohistologic features with idiopathic and HIV-associated CG (HIVAN): a strong association with persons of African descent; a typical clinical presentation with heavy proteinuria and often renal insufficiency; frequent progression to ESRD, especially in the absence of a therapy-induced remission of proteinuria; frequent tubular injury and tubulointerstitial scarring in addition to the characteristic glomerular lesions of CG; loss of certain podocyte differentiation markers, especially in glomeruli with CG lesions; and proliferation of glomerular epithelial cells as indicated by Ki67 staining. However, there are also differences, especially at a molecular level, that suggest unique pathogenic aspects of CG in SLE. In the majority of cases of the latter, glomerular staining for WT-1 was preserved, and loss of synaptopodin was not global as is typical in idiopathic CG and HIVAN (4), but rather limited to collapsed segments (7). This more limited loss of podocyte differentiation markers is seen in "reactive" lesions of CG such as those associated with vascular occlusion (4), although in only 1 of the 19 cases of Salvatore *et al.* could the CG be potentially attributed to a thrombotic microangiopathy.

The pathogenesis of the remaining cases of CG in patients with SLE presented by Salvatore *et al.*, as well as in prior reports (8–14), remains unclear, although it should be noted that the great majority of these patients had active systemic disease (often a lupus flare) and a significant number had concurrent lupus nephritis, albeit usually mild (most often International Society of Nephrology/Renal Pathology Society class II). This certainly suggests involvement of humoral and/or cell-mediated immunity, both of which have been implicated in the pathogenesis of podocytopathies and of SLE (15–19). The relative contributions of various immune pathways may play a key role in determining the responsiveness of these lesions of CG to therapy. In this regard, it is of interest that, among those patients of Salvatore *et al.* with follow-up data, four of five who had CG with concurrent lupus nephritis had a complete or partial response to therapy (pulse steroids ± mycophenolate mofetil, intravenous immunoglobulin [IVIG], plaquenil, and/or azathioprine), with only one of five developing ESRD. By contrast, only two of six treated patients without concurrent lupus nephritis had a complete or partial therapeutic response, with four of six developing ESRD. Deciphering the involved pathways of cell-mediated and humoral immunity, as well as cytokines and other mediators involved, may thus offer clinicians insight as to which therapeutic approaches might be most effective in treating patients with SLE and CG, with or without concurrent lupus nephritis. The treatments given the patients of Salvatore *et al.*, with the exception of one patient given IVIG, appear directed more at T cell–mediated than antibody-mediated processes, and the one patient treated with IVIG did show a substantial reduction in proteinuria and stable, although reduced, renal function 2 years after biopsy. However, this patient, like the majority of those who did not develop ESRD, had reasonably preserved renal function (serum creatinine <2 mg/dl) at the time of biopsy.

A number of authors have previously described glomerular lesions in patients with SLE characterized by proteinuria and extensive podocyte foot process effacement with minimal changes, noncollapsing focal

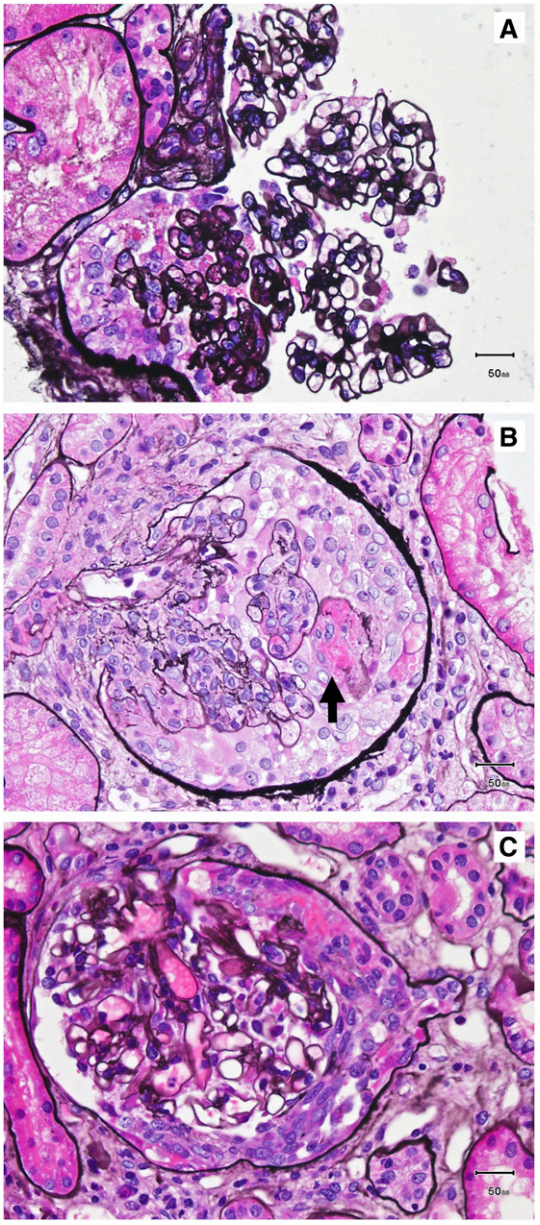

Figure 1. | Collapsing glomerulopathy (CG) and lesions that may resemble CG histologically in renal biopsies from patients with systemic lupus erythematosus. (A) CG. There is segmental collapse of the capillary tuft with overlying swollen and hyperplastic epithelial cells, some of which contain protein resorption droplets. (B) Lupus nephritis with a cellular crescent. In this glomerulus, the cells of the crescent are plump and not spindle-shaped, which can lead to the impression of CG. However, there is endocapillary proliferation, as well as somewhat subtle, segmental fibrinoid necrosis with disruption of the glomerular basement membrane (arrow), which are not features seen in CG. Electron microscopy (not shown) demonstrated mesangial and segmental subendothelial deposits. (C) Pauci-immune crescentic GN. Portions of the glomerulus not involved by the crescent do not show endocapillary hypercellularity, a feature that is also seen with CG. However, note the spindle shape of some of the cells, as well as some fibrin within the cellular crescent, features much more typical of true crescents than of the "pseudocrescents" of CG. All three panels show tissue stained with Jones methenamine silver stain.(Original magnification, ×400; Bar, 50 μm.)

segmental glomerulosclerosis (FSGS), or mesangial proliferative GN by light microscopy without subepithelial or subendothelial immune deposits—so-called lupus podocytopathy (8,9,20–23). Unlike the case with CG in patients with SLE, patients with lupus podocytopathy most often show some therapeutic response to steroids and/or other immunosuppressive therapy and only infrequently progress to ESRD within the first few months to years after biopsy, although the responses are often only partial remissions, even in patients with minimal histologic lesions (8,9,20,21). The relationship between lupus podocytopathy and the CG lesions described by Salvatore *et al.* and others (7–14) remains unclear, much as is the case with collapsing and noncollapsing forms of idiopathic FSGS, although in all of these lesions the primary target of injury is likely to be the podocyte, and indeed CG may represent an extreme form of lupus podocytopathy.

Finally, the pathologic diagnosis of CG on renal biopsy in patients with SLE is not always straightforward, especially if there is concurrent lupus nephritis, as illustrated in Figure 1. The proliferated epithelial cells in Bowman's space in CG (Figure 1A) often have a crescent-like appearance (thus the term "pseudocrescent"), raising the differential diagnosis of lupus nephritis with crescents (Figure 1B) in biopsies showing concurrent lupus nephritis and of pauci-immune (anti–neutrophil cytoplasmic antibody [ANCA] associated) crescentic GN in biopsies without significant endocapillary cell proliferation and few or no immune complex deposits without subendothelial deposits; the latter (Figure 1C) has been described in a small subset of patients with SLE (24). There are certain morphologic features that are useful in differentiating these lesions even by light microscopy, such as prominent protein resorption droplets within glomerular epithelial cells in CG (Figure 1A), endocapillary proliferation in lupus nephritis (Figure 1B), and frequent but variable presence of fibrinoid necrosis (Figure 1B), spindle-shaped cells, and fibrin (Figure 1C), as well as segmental breaks in Bowman's capsule in true crescentic lesions. However, even with immunofluorescence and electron microscopy, some biopsies may still prove quite difficult to interpret, noting that these lesions may potentially occur concurrently, that a small fraction of cases of lupus nephritis with crescents may have few immune complex deposits (25), that modest numbers of such deposits may be present in ANCA-associated crescentic GN (26), and that 10%–20% of cases of pauci-immune crescentic GN are ANCA negative (27). It should be stressed here that CG appears to represent a rather uncommon renal manifestation of SLE; the 19 patients in the series of Salvatore *et al.* (7) were pooled from five large referral centers over an 8-year interval. However, the therapeutic and prognostic implications of correctly identifying this lesion and differentiating it from lupus nephritis with crescents and pauci-immune crescentic GN are potentially important, particularly as we continue to learn more about the underlying molecular pathology of both lupus nephritis and CG in the setting of SLE.

Disclosures

None.

References

1. Laurinavicius A, Rennke HG: Collapsing glomerulopathy—A new pattern of renal injury. *Semin Diagn Pathol* 19: 106–115, 2002

2. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC: Pathologic classification of focal segmental glomerulosclerosis: A working proposal. *Am J Kidney Dis* 43: 368–382, 2004
3. Barisoni L, Kriz W, Mundel P, D'Agati V: The dysregulated podocyte phenotype: a novel concept in the pathogenesis of collapsing idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 10: 51–61, 1999
4. Albaqumi M, Barisoni L: Current views on collapsing glomerulopathy. *J Am Soc Nephrol* 19: 1276–1281, 2008
5. Cohen AH, Sun NC, Shapshak P, Imagawa DT: Demonstration of human immunodeficiency virus in renal epithelium in HIV-associated nephropathy. *Mod Pathol* 2: 125–128, 1989
6. Haas M: Collapsing glomerulopathy: Many means to a similar end. *Kidney Int* 73: 669–671, 2008
7. Salvatore SP, Barisoni LMC, Herzenberg AM, Chander PN, Nickeleit V, Seshan SV: Collapsing glomerulopathy in 19 patients with systemic lupus erythematosus or lupus-like disease. *Clin J Am Soc Nephrol* 7: 914–925, 2012
8. Kraft SW, Schwartz MM, Korbet SM, Lewis EJ: Glomerular podocytopathy in patients with systemic lupus erythematosus. *J Am Soc Nephrol* 16: 175–179, 2005
9. Hertig A, Droz D, Lesavre P, Grünfeld J-P, Rieu P: SLE and idiopathic nephrotic syndrome: Coincidence or not? *Am J Kidney Dis* 40: 1179–1184, 2002
10. Marques LP, Pacheco GG, Rioja LS, Nunes SN, Velone ST, Santos OR: Can systemic lupus erythematosus be the cause of collapsing glomerulopathy? *Lupus* 14: 853–855, 2005
11. Amoura Z, Georgin-Lavialle S, Haroche J, Merrien D, Brocheriou I, Beaufils H, Piette J-C: Collapsing glomerulopathy in systemic autoimmune disorders: A case occurring in the course of full blown systemic lupus erythematosus. *Ann Rheum Dis* 65: 277–278, 2006
12. Melo NC, Malheiros DM, Barros RT, Woronik V: Collapsing glomerulopathy associated with proliferative lupus nephritis: Reversible acute kidney injury. *Lupus* 20: 98–101, 2011
13. Gupta R, Sharma A, Bhowmik D, Gupta S, Agarwal S, Gupta R, Dinda A: Collapsing glomerulopathy occurring in HIV-negative patients with systemic lupus erythematosus: Report of three cases and brief review of the literature. *Lupus* 20: 866–870, 2011
14. Tungekar MF, Waller S, Clothier JC: Collapsing glomerulopathy in a girl with systemic lupus erythematosus. *Pediatr Nephrol* 26: 809–813, 2011
15. Dayal AK, Kammer GM: The T cell enigma in lupus. *Arthritis Rheum* 39: 23–33, 1996
16. Cunard R, Kelly CJ: T cells and minimal change disease. *J Am Soc Nephrol* 13: 1409–1411, 2002
17. McCarthy ET, Sharma M, Sharma R, Falk RJ, Jennette JC: Sera from patients with collapsing focal segmental glomerulosclerosis increase albumin permeability of isolated glomeruli. *J Lab Clin Med* 143: 225–229, 2004
18. Avila-Casado MC, Perez-Torres I, Auron A, Soto V, Fortoul TI, Herrera-Acosta J: Proteinuria in rats induced by serum from patients with collapsing glomerulopathy. *Kidney Int* 66: 133–143, 2004
19. Smeets B, Te Loeke NAJM, Dijkman HBPM, Steenbergen MLM, Lensen JFM, Begieneman MPV, van Kuppevelt TH, Wetzels JFM, Steenbergen EJ: The parietal epithelial cell: A key player in the pathogenesis of focal segmental glomerulosclerosis in Thy-1.1 transgenic mice. *J Am Soc Nephrol* 15: 928–939, 2004
20. Dube GK, Markowitz GS, Radhakrishnan J, Appel GB, D'Agati VD: Minimal change disease in systemic lupus erythematosus. *Clin Nephrol* 57: 120–126, 2002
21. Nishihara G, Nakamoto M, Yasunaga C, Takeda K, Matsuo K, Urabe M, Goya T, Sakemi T: Systemic lupus erythematosus in a patient with remitting minimal change nephrotic syndrome. *Clin Nephrol* 48: 327–330, 1997
22. Stankeviciute N, Jao W, Bakir A, Lash JP: Mesangial lupus nephritis with associated nephrotic syndrome. *J Am Soc Nephrol* 8: 1199–1204, 1997
23. Baranowska-Daca E, Choi Y-J, Barrios R, Nassar G, Suki WN, Truong LD: Nonlupus nephritides in patients with systemic lupus erythematosus: A comprehensive clinicopathologic study and review of the literature. *Hum Pathol* 32: 1125–1135, 2001
24. Nasr SH, D'Agati VD, Park H-R, Sterman PL, Goyzueta JD, Dressler RM, Hazlett SM, Pursell RN, Caputo C, Markowitz GS: Necrotizing and crescentic lupus nephritis with antineutrophil cytoplasmic antibody seropositivity. *Clin J Am Soc Nephrol* 3: 682–690, 2008
25. Charney DA, Nassar G, Truong L, Nadasdy T: "Pauci-Immune" proliferative and necrotizing glomerulonephritis with thrombotic microangiopathy in patients with systemic lupus erythematosus and lupus-like syndrome. *Am J Kidney Dis* 35: 1193–1206, 2000
26. Haas M, Eustace JA: Immune complex deposits in ANCA-associated crescentic glomerulonephritis: A study of 126 cases. *Kidney Int* 65: 2145–2152, 2004
27. Hagen EC, Daha MR, Hermans J, Andrassy K, Csernok E, Gaskin G, Lesavre P, Lüdemann J, Rasmussen N, Sinico RA, Wiik A, van der Woude FJ: Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int* 53: 743–753, 1998

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Collapsing Glomerulopathy in 19 Patients with Systemic Lupus Erythematosus or Lupus-Like Disease," on pages 914–925.