www.nephropathol.com DOI: 10.15171/jnp.2019.28 J Nephropathol. 2019;8(3):e28

Journal of Nephropathology

# A rare case of focal segmental glomerular sclerosis and subsequent necrotizing crescentic glomerulonephritis in the same patient

Jake Cho[1,2*], Erika Lara[1,2], Izuchukwu Nwakoby[3,4]

[1]University of Central Florida College of Medicine, Graduate Medical Education, Orlando, Florida, USA
[2]Ocala Regional Medical Center, Internal Medicine Residency Program, Ocala, Florida, USA
[3]Ocala Regional Medical Center, Nephrology Department, Ocala, Florida, USA
[4]The Ocala Kidney Group, Ocala, Florida, USA

## ARTICLE INFO

*Article type:*
Case Report

*Article history:*
Received: 18 May 2018
Accepted: 3 July 2019
Published online: 25 July 2019

*Keywords:*
Chronic kidney disease, End stage renal disease, Rapidly progressive glomerulonephritis, Pauci-immune crescentic glomerulonephritis, Focal segmental glomerular sclerosis, Glomerulonephritis

## ABSTRACT

*Background:* Focal segmental glomerular sclerosis (FSGS) and necrotizing crescentic glomerulonephritis is a rare combination of diagnoses in the same patient. We report on a patient with FSGS who 10 years later developed anti-neutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis.

*Case Presentation:* Patient is a 60-year-old female with chronic kidney disease stage 3, osteopenia and anemia. In 2007, she was positive for ANCA proteinase-3 antibody, but kidney biopsy revealed FSGS. She was treated with high-dose oral steroids with tapered dose and went into remission. In 2017, she developed acute renal failure with increased proteinuria. Despite prior FSGS diagnosis, her new kidney biopsy revealed pauci-immune necrotizing glomerulonephritis. Patient was treated with methylprednisolone 250 mg IV for three days and high dose oral steroids with tapered dose. She was also started on rituximab 375 mg/m2 IV once weekly for 4 doses. Given the extent of kidney damage, the patient decided to start peritoneal dialysis and she is also on the kidney transplant list.

*Conclusions:* The rare concurrence of FSGS and ANCA associated glomerulonephritis has not yet been reported. The case also emphasizes the significance of screening for ANCA or obtaining kidney biopsy when indicated not only as the gold standard for diagnosis but also as prognostic value.

Case Report

*Implication for health policy/practice/research/medical education:*
This case presents a first reported occurrence of dual glomerulopathy consisting of focal segmental glomerular sclerosis and ANCA-associated vasculitis. Although both are rare conditions, if dual glomerulopathy is suspected in the setting of acute renal failure with an active urine sediment, then pauci-immune crescentic glomerulonephritis should be considered in the differential diagnosis. The clinical significance of "double positive" renal disease is that it often portends worse prognosis and more challenging treatment. Workup should include screening for ANCA as well as obtaining renal biopsy to avoid diagnostic anchoring bias and obtain an accurate diagnosis to begin timely treatment and preserve renal function.

*Please cite this paper as:* Cho J, Lara E, Nwakoby I. A rare case of focal segmental glomerular sclerosis and subsequent necrotizing crescentic glomerulonephritis in the same patient. J Nephropathol. 2019;8(3):e28. DOI: 10.15171/jnp.2019.28.

## 1. Background

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting the structure and function of the kidney (1). CKD affects 11% of the U.S. population (2) and is generally associated with old age, diabetes, hypertension, obesity, and cardiovascular disease. Diabetic glomerulosclerosis and hypertensive nephrosclerosis are the two most common causes of CKD (1). The presence of red blood cell or white blood cell casts or proteinuria suggest glomerular and tubulointerstitial diseases (1). Primary focal segmental glomerular sclerosis (FSGS), resulting from podocyte injury, is the most common cause of nephrotic syndrome in the US, accounting for about 4% of end stage renal disease (ESRD) (3). Rapidly progressive glomerulonephritis (RPGN) is a syndrome noted for the precipitous loss of

*Corresponding author: Jake Cho, Email: Jake.Cho@ucf.edu

renal function with features of glomerulonephritis and proteinuria (4). RPGN is further divided into pauci-immune crescentic glomerulonephritis (PICG), anti-glomerular basement membrane GN (anti-GBM GN) and immune complex GN. Pauci-immune crescentic glomerulonephritis accounts for up to 80% of cases of RPGN, with an estimated incidence of 7 to 10 cases per million people per year in the United States (5). In this case report, we describe a rare dual glomerulopathy in a patient who was initially diagnosed with FSGS in 2007 and then developed PICG in 2017.

## 2. Case Presentation

Patient is a 60-year-old female with history of right breast cancer status post lumpectomy in 2010, hypertension, CKD stage 4, anemia, secondary hyperparathyroidism and osteopenia. Patient was initially evaluated for acute renal failure in 2007 with clinic records from 2011 showing elevated blood urea nitrogen (BUN) of 55 mg/dL, creatinine of 2.21 mg/dL and urine protein to creatinine ratio of 161 mg/gm. She also had positive serology for proteinase-3 anti-neutrophil cytoplasmic antibody (ANCA) (PR-3 antibody) and an erythrocyte sedimentation rate (ESR) of 4 mm/hour as documented in the earliest clinic records from 2011. CT guided core needle renal biopsy was obtained and analyzed by the pathologist using both light microscopy and immunofluorescence which revealed focal sclerosing glomerulopathy (Figure 1A, B and C). Pathology specimens were also reviewed by an academic medical institution using electron microscopy which confirmed the diagnosis of FSGS (Supplementary Table 1). The PR3-ANCA positivity was of unclear significance without renal involvement and followed clinically. Treatment consisted of oral prednisone 60 mg daily for 2 months. She responded well and she was weaned off the steroids and remained in remission over the next 10 years with stable creatinine of 1.8 to 2.0 mg/dL and a GFR of 28 to 31 mL/min. During recent clinic visits in 2017, she showed signs of acute on CKD with creatinine increased to 2.78 mg/dL, GFR decreased to 18 mL/min and recurring proteinuria. Her anemia also worsened to hemoglobin of 7.2 g/dL during this admission.

### *2.1. Physical examination results*

On examination, the patient had a blood pressure of 119/72 mm Hg, heart rate 71 to 89 bpm, temperature of 98.8°F and respiratory rate 16 to 20 per minute. She was in no acute distress. Her lungs were clear to auscultation and cardiac exam was within normal limits. Her abdominal exam was non-tender and soft without costovertebral angle tenderness. Bilateral lower legs were normal without edema or rash. Her head exam was negative for sinus congestion, rhinorrhea or sinus tenderness. Of note, a few months prior to admission, the patient experienced +2 pitting edema in her legs along with a palpable purpura rash consistent with leukocytoclastic vasculitis (Supplementary Figure 1). The edema and rash lasted about 3 weeks and resolved prior to admission.

### *2.2. Clinical course*

The patient had a CT abdomen and pelvis prior to admission that did not show hydronephrosis, radiopaque kidney stones or renal cysts, however, renal cortical thickness was diminished compared to imaging from 2005. Given the active urine sediment, prior ANCA serology and acute renal failure, additional imaging was done to evaluate for granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss). CT sinus showed clear paranasal sinuses, without sinusitis. CT chest showed no evidence of mediastinal lymphadenopathy or mass. The lungs demonstrated patchy areas of interstitial infiltrates possibly inflammatory vasculitis or edema (Supplementary Figure 2). Urinalysis (Table 1) was significant for microscopic hematuria and urine protein of 161 mg/dL and urine creatinine of 68.7 mg/dL for a protein/creatinine ratio of 2343 mg/g (sub nephrotic range < 3000 mg/gm). Renal function panel was significant for BUN 59 mg/dL, Creatinine 3.90 mg/dL and eGFR of 11 mL/min. Given her prior FSGS, the patient was presumed to have acute glomerulonephritis secondary to FSGS exacerbation. Instead, repeat biopsy showed severe tubular atrophy and interstitial fibrosis along with diffuse global glomerulosclerosis (Figure 1D, E, F). There was no significant immune complex by immunofluorescence (IF) or electron microscopy (Supplementary Table 2) but staining was positive for C-ANCA (cytoplasmic) pattern and negative for P-ANCA (perinuclear). Serology was positive for anti-proteinase 3 (PR3) but negative for anti-myeloperoxidase (MPO). Given the pattern of C-ANCA, anti-PR3 vasculitis, she was diagnosed with pauci-immune crescentic glomerulonephritis. The patient was started on methylprednisolone 250 mg IV daily for three days and then transitioned to prednisone PO 60 mg daily for 4 weeks with taper over a 6-week period. Of note, she was also started on rituximab IV 375 mg/m$^2$ once weekly for four doses. By discharge, her creatinine improved to 3.10 mg/dL and eGFR to 15 mL/min. ESR decreased to 57 mm/h. However, given the extent of glomerulosclerosis and tubulointerstitial fibrosis, the patient eventually underwent peritoneal dialysis catheter placement and she is currently on the kidney transplant list.

## 3. Discussion

The clinical significance of combined renal pathologies is

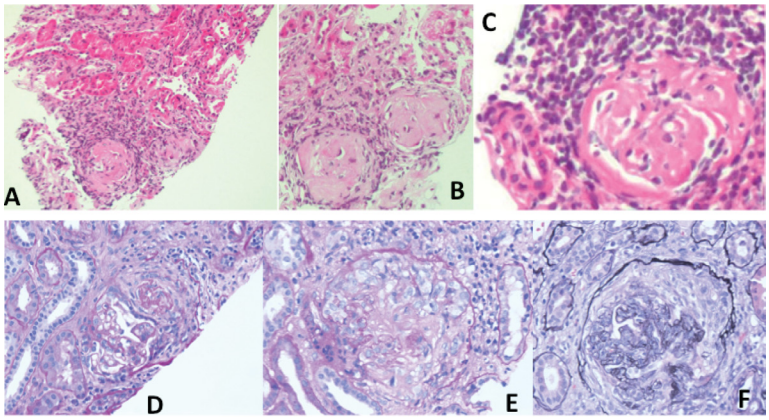


**Figure 1. (A,B,C)**: 2007 Renal Biopsy: Light Microscopy, Low/medium mag, dense glomerular scars with greater than 50% degree of segmental sclerosis and adhesions onto Bowman's capsule. **(Fig 1C)**: 2007 Renal Biopsy: High mag, No cellular proliferative changes: Focal Segmental Sclerosing Glomerulopathy (FSGS). **(D,E,F)**: 2017 Renal Biopsy: Light Microscopy, Low/medium mag: Glomeruli show mesangial normocellularity. Glomerulus contains cellular crescent with segmental, small fibrinoid nebrosis. **(Fig 1F)**: 2017 Renal Biopsy: Glomeruli show segmental scarring with cellular crescent. Tubular atrophy and interstitial fibrosis are severe. Pauci-immune Crescentic Necrotizing Glomerulonephritis (PICG).

variable as some reports comment on the pathophysiology while others focus on clinical outcomes. For instance, the Gu 2016 retrospective observational study analyzed 20 patients with both membranous nephropathy (MN) and FSGS lesions (6). Along with the mechanism of anti-phospholipase A2 (PLA2R) receptor antibody podocyte deposition, the Gu 2016 study also examined the role of soluble urokinase-type plasminogen activator receptor (suPAR). Research suggests that suPAR levels act as a circulating permeability factor in the pathogenesis of primary FSGS by promoting the detachment of podocytes from the GBM. Patients with combined MN and FSGS presented with features of advanced MN with greater tubulointerstitial damage and interstitial fibrosis than primary MN. On the other hand, patients with combined lesions showed features of FSGS more consistent with secondary FSGS and normal urinary suPAR levels. Cellular variants, which are common in primary FSGS, were not seen in any patient with combination lesions suggesting that the FSGS lesions may be secondary to primary MN and contribute independently to the tubulointerstitial injury (6). The Nasr 2008 case series (7) followed the clinical outcomes of 23 patients with pauci-immune crescentic glomerulonephritis superimposed on diabetic glomerulosclerosis. The study found that prognosis was considerably worse for patients with combined disease. At a mean follow-up of 14.6 months, in the cohort of 21 patients, 8 patients had died and 8 patients had reached ESRD (7). In contrast, the study by Gu et al found that patients with combined MN and FSGS lesions had more benign characteristics and lower degree of renal dysfunction than primary FSGS (6). It is beyond the scope of this report to comment on the pathophysiology of combined FSGS and ANCA renal disease. However, it can be argued that since the patient was ANCA positive at the time of FSGS diagnosis, that perhaps the FSGS was secondary to predisposed pauci-immune crescentic glomerulonephritis (3). However, PICG was not seen on initial renal biopsy (Table 1, Figure 1 A,B,C). Second, the patient was successfully treated for FSGS with oral steroids and remained in remission. Glucocorticoid monotherapy would have been inadequate in the treatment of ANCA vasculitis renal disease (8, 9). Hence, it is very unlikely that the patient had acute ANCA renal vasculitis prior to the FSGS. To avoid long-term high dose steroid monotherapy, treatment consists of two phases; induction of remission and maintenance of remission. In the past, induction was most commonly achieved with IV methylprednisolone for 3 to 5 days coupled with pulsed intravenous cyclophosphamide. The 2010, non-inferiority, rituximab for ANCA-associated vasculitis trial (RAVE) demonstrated that 64% of patients treated with rituximab compared with 53% of those treated with cyclophosphamide achieved remission at six months (10,11). Hence, in this case, the patient was given high-dose corticosteroids for three days, followed by rituximab (375 mg/m$^2$ once a week for 4 weeks). She was also given high dose prednisone PO 60 mg daily with taper over 10 weeks.

## 4. Conclusions

FSGS and ANCA-associated vasculitis are rare conditions, with estimated incidences in the US of 5.3 patients per million for FSGS (12) and 10 cases per million people for rapidly progressive glomerulonephritis (5). Examples of reported double-positive glomerular

**Table 1.** Relevant Admission Labs and Urinalysis

| | | |
|---|---|---|
| • Color yellow, clear<br>• pH 6.0 (ref. range 5.0 - 9.0)<br>• Specific Gravity 1.010 USG (ref. range 1.005 - 1.030)<br>• Glucose negative (mg/dL)<br>• Ketones negative (mg/dL)<br>• Nitrite negative<br>• Leukocyte esterase negative | • Bilirubin: negative (mg/dL)<br>• Urobilinogen 0.2 mg/dL (ref. < = 1 mg/dL)<br>• Bacteria: few (0/hpf)<br>• Epithelial Cells: moderate (ref. 0/hpf) | Active Sediment:<br>• RBC 25-50 (0/hpf)<br>• WBC 5-10 (0/hpf)<br>• Protein 100 mg/dL (ref. < 15 mg/dL)<br>• Hemoglobin; large (ref. negative) |
| **Special urine studies** | • Random Protein 161 mg/dL (ref. range 5-24 mg/dL)<br>• Random Creatinine 68.7 mg/dL (ref. range 20-320 mg/dL)<br>• Random Sodium 70 mmol/L (ref. range 20 mmol/L) | • Protein/Creatinine ratio; 2343 mg/g (ref. range < 160 mg/g) |
| **CBC** | **Admission labs** | **Reference Range** |
| Leukocytes | 4.5 thou/mm$^3$ | (3.5-11) thou/mm$^3$ |
| Eosinophils | 10.6% / 0.5 thou/mcL | (0–3%) / (0–0.7) thou/mcL |
| RBC | 2.32 m/mcL | (3.40 - 5.10) m/mcL |
| Hemoglobin | 7.2 g/dL | (12–16) g/dL |
| Hematocrit | 22.5 % | (36–46%) % |
| Platelets | 246 thou/mm$^3$ | (150–440) thou/mm$^3$ |
| **Renal Function Panel** | **Admission labs** | **Reference Range** |
| Sodium | 140 (mEq/L) | (135–145) (mEq/L) |
| Potassium | 4.9 (mEq/L) | (3.5–5.1) (mEq/L) |
| Chloride | 105 (mEq/L) | (98–108) (mEq/L) |
| Bicarbonate | 23 (mEq/L) | (22–34) (mEq/L) |
| Calcium | 8.7 (mg/dL) | (8.8 - 10.5) (mg/dL) |
| Glucose | 134 (mg/dL) | (70 – 110) (mg/dL) |
| BUN | 59 (mg/dL) | (7–18) (mg/dL) |
| Creatinine | 3.90 (mg/dL) | (0.60–1.30) (mg/dL) |
| Est. GFR (non Af.Am) | 11 (ml/min) | (> 60) (ml/min) |
| **Hepatic function panel** | **Admission labs** | **Reference Range** |
| Albumin | 3.6 (g/dL) | (3.5–5.5) (g/dL) |
| AST | 26 (IU/L) | (12–37) (IU/L) |
| ALT | 29 (IU/L) | (17–63) (IU/L) |
| Total bilirubin | 0.3 (mg/dL) | (0.2–1.5) (mg/dL) |
| Alkaline phosphatase | 51 (IU/L) | (38 – 126) (IU/L) |
| **Autoimmune Studies 2012** | | |
| ANCA profile | 2012 (earliest clinic record) | **Reference Range** |
| MPO antibody | <6 U/mL | < 6.0 U/mL |
| PR3 antibody | 79 U/mL | 0.0-3.5 U/mL |
| **Autoimmune Studies 2017** | | |
| ANCA profile | 2017 (Admission workup) | **Reference Range** |
| ESR | 103, (mm/h) | (0 – 20) (mm/hr) |
| C-ANCA | 1:320, titer | Neg: <1:20 titer |
| P-ANCA | <1:20 titer | Neg: <1:20 titer |
| Atypical P-ANCA | <1:20 titer | Neg: <1:20 titer |
| MPO Antibody | <9.0 U/mL | 0.0-9.0 U/mL |
| PR3 Antibody | >100.0 U/mL | 0.0-3.5 U/mL |

Abbreviations: ref. (reference), RBC (red blood cell count), WBC (white blood cell count), BUN (blood urea nitrogen), AST (aspartate aminotransferase), ALT (alanine aminotransferase), GFR (glomerular Filtration Rate), ESR (erythrocyte sedimentation rate), C-ANCA (cytoplasmic anti-neutrophilic cytoplasmic antibodies), P-ANCA (peri-nuclear anti-neutrophilic cytoplasmic antibodies), MPO (Myeloperoxidase), PR3 (Proteinase-3).

lesions include combined anti-glomerular basement membrane disease and ANCA glomerulonephritis (13), combined membranous nephropathy and FSGS (6), concurrent ANCA glomerulonephritis and membranous nephropathy (14), as well as PICG superimposed on diabetic glomerulosclerosis (7). This case report provides a first reported occurrence of combined FSGS and ANCA renal disease. If dual glomerulopathy is suspected, then pauci-immune crescentic glomerulonephritis should be considered in the differential diagnosis in the setting of acute renal failure with an active urine sediment (7). Workup should include screening for ANCA as well as obtaining renal biopsy to achieve an accurate diagnosis and begin timely treatment in order to preserve renal function.

## Authors' contribution

**JC:** Data curation; obtained the relevant clinical labs and imaging including pictures of the lower leg edema. Formal Analysis; Applied clinical analysis to the labs, urinalysis with microscopy, renal function panels, autoimmune studies including ANCA profile and images. Investigation; Conducted research and investigation into discussion topics. Validation; verification of the facts in the case report, verification of references. Writing; prepared the original draft. Writing; review and editing of the manuscript. **EL:** Formal Analysis; assisted in the interpretation of the clinical labs, assisted in the discussion of focal segmental glomerular sclerosis and rapidly progressive glomerulonephritis. Validation; verification of facts presented in the case report. Writing; contributed to the documentation of the clinical course. **IN:** Data curation; assisted in obtaining clinic progress notes prior to hospital admission, obtained immune fluorescence microscopy and electron microscopy images from external consulting services. Validation; verification of the facts and key concepts in the case report, verification of references. Writing; reviewed and edited the manuscript, in particular the section emphasizing the rarity of finding a dual combined glomerulopathy.

## Conflicts of interest

The primary author and lead investigator and associated authors do not have any have conflicts of interest to declare or financial disclosures. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA or any of its affiliated entities.

## Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. Written informed consent was obtained from the patient for the publication of this case report along with the accompanying images.

## Funding/Support

This research was supported (in whole or in part) by HCA and/or an HCA affiliated entity.

## Supplementary Materials

Supplementary file 1 contains supplementary Figures 1 & 2 and Tables 1 & 2.

## References

1. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379(9811):165-80. doi: 10.1016/S0140-6736(11)60178-5.
2. Hayek SS, Sever S, Ko YA, Trachtman H, Awad M, Wadhwani S, et al. Soluble urokinase receptor and chronic kidney disease. N Engl J Med. 2015;373(20):1916-25. doi: 10.1056/NEJMoa1506362.
3. Fogo AB. Causes and pathogenesis of focal segmental glomerulosclerosis. Nat Rev Nephrol. 2015;11(2):76-87. doi: 10.1038/nrneph.2014.216.
4. Kambham N. Crescentic glomerulonephritis: an update on Pauci-immune and anti-GBM diseases. Adv Anat Pathol. 2012;19(2):111-24. doi: 10.1097/PAP.0b013e318248b7a1.
5. Syed R, Rehman A, Valecha G, El-Sayegh S. Pauci-immune crescentic glomerulonephritis: an ANCA-associated vasculitis. Biomed Res Int. 2015;2015:402826. doi: 10.1155/2015/402826.
6. Gu QH, Cui Z, Huang J, Zhang YM, Qu Z, Wang F, et al. Patients with combined membranous nephropathy and focal segmental glomerulosclerosis have comparable clinical and autoantibody profiles with primary membranous nephropathy: a retrospective observational study. Medicine (Baltimore). 2016;95(21):e3786. doi: 10.1097/MD.0000000000003786.
7. Nasr SH, D'Agati VD, Said SM, Stokes MB, Appel GB, Valeri AM, et al. Pauci-immune crescentic glomerulonephritis superimposed on diabetic glomerulosclerosis. Clin J Am Soc Nephrol. 2008;3(5):1282-8. doi: 10.2215/CJN.00740208.
8. McCabe C, Jones Q, Nikolopoulou A, Wathen C, Luqmani R. Pulmonary-renal syndromes: an update for respiratory physicians. Respir Med. 2011;105(10):1413-21. doi: 10.1016/j.rmed.2011.05.012.
9. Abeer Kaldas IW, Sharma Prabhakar. ANCA associated glomerulonephritis- an in-depth review. J Nephrol Ther. 2013;4(147). doi: 10.4172/21610959.1000147
10. Shah S, Hruskova Z, Segelmark M, Morgan MD, Hogan J, Lee SK, et al. Treatment of severe renal disease in ANCA positive and negative small vessel vasculitis with rituximab. Am J Nephrol. 2015;41(4-5):296-301. doi: 10.1159/000431336.
11. Moiseev S, Novikov P, Jayne D, Mukhin N. End-stage

renal disease in ANCA-associated vasculitis. Nephrol Dial Transplant. 2017;32(2):248-53. doi: 10.1093/ndt/gfw046.
12. Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2017;12(3):502-17. doi: 10.2215/CJN.05960616.
13. McAdoo SP, Tanna A, Hruskova Z, Holm L, Weiner M, Arulkumaran N, et al. Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients. Kidney Int. 2017;92(3):693-702. doi: 10.1016/j.kint.2017.03.014.
14. Zou R, Liu G, Cui Z, Chen M, Zhao MH. Clinical and immunologic characteristics of patients with ANCA-associated glomerulonephritis combined with membranous nephropathy: a retrospective cohort study in a single Chinese center. Medicine (Baltimore). 2015;94(37):e1472. doi: 10.1097/MD.0000000000001472.