CASE REPORT

Collapsing glomerulopathy in systemic lupus erythematosus

Kerolos Abadeer,¹ Ali A Alsaad,² Xochiquetzal J Geiger,³ Ivan E Porter⁴¹Department of Nephrology and Hypertension, Mayo Clinic Florida, Jacksonville, Florida, USA²Department of Internal Medicine, Mayo Clinic Florida, Jacksonville, Florida, USA³Department of Pathology and Laboratory Medicine, Mayo Clinic Florida, Jacksonville, Florida, USA⁴Department of Nephrology and Hypertension, Mayo Clinic, Jacksonville, Florida, USA

Correspondence to

Dr Ali A Alsaad,
alsaad.ali@mayo.edu

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SUMMARY

Collapsing glomerulopathy (CG) is a rare disease that can be associated with multiple other disorders. It usually leads to poor prognosis with a high percentage of patients progressing to end-stage renal disease. In this article, we illustrate a clinical case of CG associated with systemic lupus erythematosus that had a prompt response to mycophenolate and prednisone. The condition started after sudden cessation of the already established mycophenolate treatment regimen. The patient then presented with acute kidney injury due to kidney biopsy-proven CG. In that circumstance, we hypothesised that mycophenolate may play a role in prevention and development of CG.

BACKGROUND

Collapsing glomerulopathy (CG) has been recognised as an increasingly serious risk factor for end-stage renal disease (ESRD). The pathogenesis and treatment of this rare disease is still elusive. It has been described in the literature as a rare form of glomerular injury affecting podocytes, characterised by global or segmental collapse of the glomerular capillary tuft overlaid by visceral epithelial hypertrophy. It also affects the basement membrane in the form of retraction and wrinkling.¹

As a primary form of podocytopathy, CG has been seen in patients of African descent.² Furthermore, it has been associated with numerous other conditions including viral infections (HIV, parvovirus B19 and hepatitis C virus), bacteria (tuberculosis), drugs (interferon α , pamidronate) and autoimmune conditions (systemic lupus erythematosus (SLE) and mixed connective tissue disease).³

The role of mycophenolate in the treatment of CG in our case was critical; we hypothesised the possibility that this condition was precipitated by the cessation of mycophenolate treatment. To the best of our knowledge, this is the first reported case of CG in SLE occurring immediately following the cessation of mycophenolate treatment regimen, which endorses our hypothesis that mycophenolate, can have a prophylactic effect against CG development in cases of SLE.

CASE PRESENTATION

A 36-year-old African-American woman with a history of SLE and overlapping lupus nephritis presented to our facility for evaluation and follow-up. Her medical history was not remarkable. She had no history of hypertension but she was placed on losartan for proteinuria that was discontinued due to hypotension. The patient's condition was initially

diagnosed following her first pregnancy at the age of 33. At that time, her 24-hour urine protein level was 18 g (reference range 0–20 mg/dL) and her serum creatinine level was 4 mg/dL (reference range 0.5–1.2 mg/dL). The patient underwent a kidney biopsy which revealed class IV diffuse proliferative lupus nephritis with inclusions and subendothelial cells along with endothelial deposits. The patient had persistently positive double-stranded DNA antibodies over a year. She was treated thereafter with a regimen which included intravenous cyclophosphamide for ~18 months, which helped to bring her serum creatinine level to 0.7 mg/dL. She was then treated with high-dose prednisone and azathioprine was also introduced as a maintenance therapy afterwards to reduce her prednisone dose to 10 mg per day. Inflammatory and disease severity markers were negative at that point indicating a well-controlled disease.

Subsequently, the patient developed pancytopenia and candida oesophagitis after 2 months of treatment initiation with azathioprine. Bone marrow biopsy revealed classic bone marrow suppression with no other abnormalities suggestive of primary bone marrow disease or malignancy. Thus, azathioprine was discontinued and mycophenolate was started at a dose of 2 g/day. Subsequently, mycophenolate dose was gradually reduced to 1 g/day.

At her previous follow-up visit, and due to gastrointestinal side effects, the patient had decided to decrease the mycophenolate dose to 250 mg/day and continued prednisone 5 mg/day. During the visit, the patient denied any haematuria, dysuria or other genitourinary symptoms. No fever, rash, inflammatory arthritis, pleuritic chest pain or fatigue was reported. Inflammatory markers

Figure 1 Lupus class I with minimal mesangial expansion and open capillary loops with mesangial deposits detected by electron microscopy (Jones methenamine silver, original magnification $\times 400$).

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including erythrocytes sedimentation rate and C reactive protein along with double-stranded DNA antibodies and C3-C4 complements were all within normal reference range. Serum creatinine was 0.8 mg/dL and 24-hour protein urea was 0.84 g during that visit. With the absence of clinical and laboratory signs of disease activity or flares, the decision was made to allow the patient to stop mycophenolate and maintain prednisone with a follow-up visit scheduled for 4 weeks, which she did not keep.

The patient was seen in the emergency department 2 months later with an abrupt onset of nausea, vomiting and diarrhoea. She lacked any symptoms of her typical lupus flares such as joint pain or rash, but did present with macroscopic haematuria and oliguria. The patient was noted to have acute kidney injury with a serum creatinine level around 2.0 mg/dL (from baseline 0.8 mg/dL), +4 proteinuria and a 24-hour urine protein level of 8.8 g. The patient confirmed that she stopped taking mycophenolate as instructed and continued to take prednisone 5 mg/day. Intravenous fluids were initiated in the emergency room with 100 mg of hydrocortisone.

INVESTIGATIONS

Kidney biopsy was performed, and the biopsy results were discussed at a joint nephrology–pathology conference. The renal biopsy revealed minimal residual lupus nephritis (class I) with diffuse foot process effacement consistent with lupus podocytopathy and CG. Tuft retraction and prominent visceral epithelial hyperplasia was also noted. A diagnosis of CG associated with SLE was made. HIV 1 and 2 and parvovirus B19 tests were negative.

KIDNEY BIOPSY PATHOLOGY ANALYSIS

The renal biopsy contained 25 glomeruli, 4 globally sclerosed and 2 with hilar segmental sclerosis. There was minimal segmental mesangial expansion with no glomerular basement membrane spikes, holes, splitting, thrombi, crescents or necrotising lesions (figure 1). Six glomeruli showed collapsing features with tuft retraction, capillary loop wrinkling, epithelial cell proliferation and prominent protein resorption droplets (figure 2). There was moderate tubulointerstitial oedema with a mild lymphocytic infiltrate and patchy tubulitis, occasional eosinophils, and acute tubular epithelial cell injury with tubular protein resorption droplets. No viral-type inclusions or cytopathic changes were seen. Cytomegalovirus and BK virus (a member of the polyomavirus family) immunohistochemistry were negative. Smaller vessels had segmental hyaline deposition, and larger vessels showed mild-to-moderate arteriosclerosis. There was no vasculitis.

Two glomeruli were present for immunofluorescence studies. There was trace to 1+ (of 3+) segmental mesangial IgG, IgM, and C3 and strong tubular nuclear staining for IgG (figure 3). There was no tubular basement membrane staining and IgA, C1q, κ and λ light chains were negative.

Two glomeruli were examined by electron microscopy, one of these with segmental tuft retraction and early sclerosis (figure 4). There was mild glomerular basement membrane thickening with diffuse, near-complete podocyte foot process effacement, microvillus transformation and mild capillary loop corrugation. A few capillary loops had early paramesangial splitting and mesangial interposition. There were no subepithelial or subendothelial immune complex deposits. Endothelial cells contained small reticular aggregates. The mesangium was mildly expanded with scattered small to occasional medium-size immune complex deposits. There were no tubular basement membrane deposits.

The mentioned findings were suggestive of minimal mesangial lupus nephritis, corresponding to the International Society of Nephrology/Renal Pathology Society class I, and CG, the latter likely representing a severe form of lupus podocytopathy.

DIFFERENTIAL DIAGNOSIS

CG has a characteristic pathological morphology in the renal biopsy. Nevertheless, there are a few other conditions that can resemble CG, and so, should be considered as a differential diagnosis, including crescentic glomerulonephritis and cellular focal segmental glomerulosclerosis; cellular glomerulonephritis and CG have hypertrophy and hyperplasia of podocytes in common.⁴

TREATMENT

The treatment options were discussed with the patient in details including high-dose glucocorticoids, a repeat of cyclophosphamide directed at SLE in addition to high-dose glucocorticoids or cyclosporine therapy. Resuming mycophenolate therapy was among the options as well. A review of the literature revealed the risk of ESRD in cases of CG, and given the rare nature of this disease, no evidence-based treatment has been reported. Therefore, the need for an effective treatment regimen was critical. The inciting event for the patient's CG was determined to be the previous alteration in the patient's mycophenolate treatment regimen. After a decision sharing with the patient, mycophenolate was restarted to a dose of 1.5 g/day, and prednisone was increased to 40 mg/day with a taper over 4 weeks.

OUTCOME AND FOLLOW-UP

The prompt response that was encountered in just 3 days following treatment with higher dose prednisone and restoration of mycophenolate therapy was very encouraging. Improvement in symptoms, clinical examination and creatinine level (from 2.0 to 1.7 mg/dL) within 72 hours was encountered. Over the following month, the patient's serum creatinine resolved to a level of 1.3 mg/dL and 24-hour protein urea level improved to 3.5 g. The patient continued her treatment regimen of daily doses of 1 g of mycophenolate and 10 mg of prednisone. We have followed up

Figure 2 Global collapsing glomerulopathy with tuft retraction, glomerular membrane wrinkling and epithelial cell proliferation containing prominent protein resorption droplets. There is adjacent acute tubular cell injury and interstitial chronic inflammation (Jones methenamine silver, original magnification $\times 200$).

Figure 3 Immunofluorescence findings of segmental mesangial immune complex deposits and tubular nuclear staining representing tissue manifestation of antinuclear antibody (anti-IgG, original magnification $\times 400$).

with the patient frequently over the next 24 months, and she remains clinically stable with an average creatinine level of 1.2 mg/dL and a 24-hour protein urea of nearly 1.1 g. Although the reason to stop mycophenolate initially was gastrointestinal side effects, the patient was able to tolerate the treatment in the second round with minimal gastrointestinal symptoms.

DISCUSSION

CG is a well-recognised risk factor of ESRD. In our case, the patient had been monitored for years without any changes in her lupus nephritis condition. But with mycophenolate cessation, she experienced CG with acute kidney injury manifested clinically as nephrotic syndrome with heavy proteinuria. The timeframe to

Figure 4 Extensive podocyte foot process effacement with microvillus transformation and mesangial immune complex deposits indicated by the black arrow (electron microscopy, original magnification $\times 6800$).

develop CG in lupus can be variable and depends on the associated immune suppression medications use. Our patient reduced the dose of mycophenolate from 2 to 250 mg/day and was instructed to discontinue mycophenolate therapy after ~ 1 month from the treatment initiation. She missed the 1 month follow-up appointment but presented to the emergency room after 2 months with acute kidney injury and was diagnosed with a biopsy-proven CG. Therefore, CG had happened in 2–3 months within the mycophenolate therapy discontinuation timeframe and ~ 2 years after the initial diagnoses of SLE.

The patient was at great risk of developing ESRD as a result of her CG condition. Resolution of the patient's renal injury occurred immediately following the restoration of the mycophenolate regimen. Given the substantial effect of mycophenolate in the treatment of CG in our index case, mycophenolate may play a critical role in preventing CG from developing, and further research is warranted.

To the best of our knowledge, this is the first case report describing the association between CG and lupus nephritis occurring after the cessation of mycophenolate treatment regimen. In 2012, Salvatore and colleagues conducted the largest study, 19 patients with SLE-associated CG. The study showed that most of the patients were of African descent (17/19; 89%), which is reflected in our index case.² The relation between SLE and CG is not fully understood, and the prognosis is usually poor with most cases developing ESRD irrespective of treatment.^{5,6} Other than SLE, CG has been described in association with other conditions including HIV and parvovirus B19, and with medications such as pamidronate.³ In our index case, HIV and parvovirus B19 were excluded.

The pathological characteristics of CG demonstrate hypertrophy and hyperplasia of the podocytes as a part of the podocytopathy associated with CG. Additionally, studies have shown deregulation of the podocytes phenotype with overexpression of molecular markers expressed on immature podocytes such as cytokeratin and desmi.^{7,8} On the other hand, a decrease has been noticed in the markers of the podocytes maturity such as Wilm's tumour, common acute lymphocytic leukaemia antigen, nephrin and synaptopodin.⁷ Therefore, the capillary collapse may be caused by the rapid increase in the number and size of podocytes.

Given the unique features of this rare entity, there is currently no evidence-based treatment. All of the current recommendations depend mainly on expert opinions and published studies.^{7,9} Overall, prognosis of this condition is not promising with only 10% achieving full remission and about 50% progressing to ESRD.¹⁰ Literature review shows no use of mycophenolate for treatment in previous studies, but our patient had a dramatically positive response and maintenance of remission with the use of mycophenolate. An important step in our case is that glucocorticoids (hydrocortisone) were given at the time of presentation to the emergency room with no mycophenolate. A step that if happened could have altered the results of the kidney biopsy.

Literature on this topic is fairly limited and there is no strong evidence-based treatment that has been described for this condition. CG does not always respond to mycophenolate treatment or other medications. Ramachandran *et al*¹¹ described a case of CG that responded to rituximab therapy, an option that can be considered based on an individualised case in the literature. Therefore, treating CG has remained a clinical challenge and further case reports and studies are warranted.

In this case, the overall reduction in immunosuppression rather than the mycophenolate itself could have been the cause for the encountered CG. The same principle could be true for the treatment response and outcome as mycophenolate-increased

immunosuppression may play a role in development and treatment of the disease. We also do not have specific information on the patient's compliance with steroids, which could be another factor that caused and treated CG. CG is seen rarely in SLE and many patients with lupus are not on mycophenolate therapy, but they do not present with CG. Therefore, the biopsy-proven case illustrated in this article makes the correlation between the two entities a rare, but existing possibility.

Moreover, the rarity of CG as a manifestation of SLE drives the fact that there is no strong evidence-based treatment for this condition. Although we have used a standard therapeutic

approach (glucocorticoids and an immunosuppressive agent) to treat CG, the rapid improvement of the patient's condition can be attributed to the glucocorticoid effect alone and/or the synergistic effect of mycophenolate.

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Contributors KA and AAA wrote the manuscript. XJG provided the pathology images and its interpretation. IEP critically reviewed the manuscript. AAA reviewed and coordinated the submission and manuscript revision process. All authors approved the manuscript before submission.

Competing interests None declared.

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Patient's perspective

I am grateful that my kidneys are working again. I am using the same treatment I was taking before my kidney disease and it is working.

Learning points

- ▶ Collapsing glomerulopathy is a rare disease with no current gold standard treatment.
- ▶ Collapsing glomerulopathy can be associated with systemic lupus erythematosus following the cessation of mycophenolate.
- ▶ Mycophenolate may play a role in preventing the development of collapsing glomerulopathy; however, this hypothesis needs further evaluation.
- ▶ More case reports and case series are needed to characterise the role of mycophenolate in the treatment of collapsing glomerulopathy.

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