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CORRESPONDENCE

Patterns of podocyte infolding glomerulopathy and collapsing glomerulopathy seen in a patient with systemic lupus erythematosus: a case study

To the Editor,

Podocyte infolding glomerulopathy (PIG) is a rare histological finding in renal biopsies, first described in Japan in 2008. It is characterised by the infolding of podocytes into the glomerular basement membrane (GBM), leading to the formation of microspheres and/or microtubules within thickened GBM visualised on electron microscopy (EM).[1] These cases have been commonly associated with autoimmune diseases with 70% having a history of systemic lupus erythematosus (SLE) or Sjögren's syndrome. They typically present with proteinuria, ranging from mild to nephrotic range, with or without haematuria, or with signs or symptoms of the systemic autoimmune disease.

Collapsing focal segmental glomerulosclerosis (cFSGS), also known as collapsing glomerulopathy (CG) is currently considered a variant of FSGS, but its morphological features are distinct.[2] It is traditionally known to be associated with human immunodeficiency virus (HIV) infection but is also recognised in non-HIV patients.[3] CG is defined by at least one glomerulus with segmental or global collapse and overlying podocyte hypertrophy and hyperplasia.[4] This can occur in patients with SLE with or without lupus nephritis and can result in nephrotic-range proteinuria and rapidly progressive renal failure.[5]

Herein, we report the first case of chronic glomerulopathy showing features of PIG and CG in a patient with serologically quiescent SLE who progressed to end-stage renal failure, requiring a kidney transplant, despite re-induction immunosuppressive therapy. Informed written consent was obtained from the patient.

This was a 33-year-old female who had a history of SLE, which was first diagnosed in India at age 20 and manifested as sub-nephrotic range proteinuria, positive anti-nuclear antibodies (ANA) and low C3 and C4 complement levels. A renal biopsy performed 5 years after the onset showed features consistent with class IV lupus nephritis. The disease remained quiescent on prednisolone 7.5 mg, azathioprine 50 mg daily and hydroxychloroquine 400 mg daily. Fig. 1 shows the timeline of events relating to this patient.

She presented to the hospital with a ruptured appendicitis requiring open appendicectomy, after which multiple intravenous and oral antibiotics including amoxicillin, metronidazole, gentamicin, cephalexin and ciprofloxacin were given. Peritoneal fluid cultured *Escherichia coli* and *Pseudomonas aeruginosa*. Serum creatinine on discharge was 80 µmol/L. Ten days after hospital discharge, the patient represented to the emergency with profuse vomiting and diarrhoea, bilateral leg swelling, and reduced urine output. She was tachycardic at 110 beats per minute, hypertensive at 150/80 mmHg, and clinically fluid overloaded. Biochemistry revealed an elevated serum creatinine at 810 µmol/L, hypoalbuminaemia (16g/L), hyperkalaemia (6.1 mmol/L) and metabolic acidosis (pH 7.24, bicarbonate 16 mmol/L). Abdominal computed tomography did not reveal any new intra-abdominal pathology.

The provisional diagnosis of her oliguric renal failure was acute tubular necrosis (ATN) in the setting of gastroenteritis, with recent intravenous contrast and antibiotics use. Azathioprine and perindopril were ceased and stress dose corticosteroids were commenced. Continuous renal replacement therapy was undertaken when she remained oliguric (10−20 mL/h) despite fluid resuscitation. Serological studies demonstrated positive ANA (speckled at 1:160 titre), negative anti-double stranded DNA, low C3 at 0.67 g/L but normal C4 at 0.20 g/L. A kidney biopsy was performed as the patient remained dialysis dependent for 2 weeks.

Light microscopy (LM) showed florid ATN and changes suggestive of class IV lupus nephritis with 12 of the 15 glomeruli displaying crescent-like changes, including a cellular proliferation filling Bowman's space and collapsed capillary loops (Fig. 2A). IF revealed linear and non-specific mesangial and capillary loop staining with IgG (Fig. 2B), while there was granular, weak and patchy mesangial and capillary loop staining with C3 (Fig. 2C). It showed weak staining with IgM, and IgA and C1q were negative. EM exhibited thickening of the GBM, foot process effacement, microspherules and atypical podocytes displaying vacuolation, nuclear atypia, and microvillous transformation (Fig. 2D,E). There were also myelinosomes with curvilinear bodies within the tubular epithelial cells seen concerning for hydroxychloroquine toxicity. No electron-dense deposits were seen.

The renal biopsy did not exhibit an exudative glomerulonephritis pattern with an increase in neutrophils or subepithelial humps on EM, which are seen in a typical post-infectious glomerulonephritis. However, there were presence of low C3 levels, proliferative changes in glomeruli and weak staining of IgG, IgM and C3 on immunofluorescence. In the setting of these changes along with the history of gastroenteritis and positive growth of *E. coli* and *P. aeruginosa* on the peritoneal fluid culture, atypical post-infectious glomerulonephritis with activation of alternate complement pathway was considered. Azathioprine was reintroduced and hydroxychloroquine was withheld. She was discharged home on 10 mg of prednisolone after a quick tapering regime. Her diarrhoea resolved completely after high dose corticosteroids with normalisation of C3 levels.

She remained dialysis dependent for a further 4 weeks and a repeat kidney biopsy was performed. This was almost identical to the first biopsy, but in addition, there was evolving fibrosis with tubular atrophy, consistent with a chronic pathological process. On review, the cellular epithelial proliferation was favoured to be of a podocyte nature in line with the EM findings. With these new histological findings, the diagnosis was deemed as chronic glomerulopathy showing features of PIG and 'pseudo-crescent' formation, which in retrospect, were features of CG. The patient was commenced on induction weekly cyclophosphamide therapy and high dose corticosteroids. Native urine output improved to 1.5 L/day following four doses of

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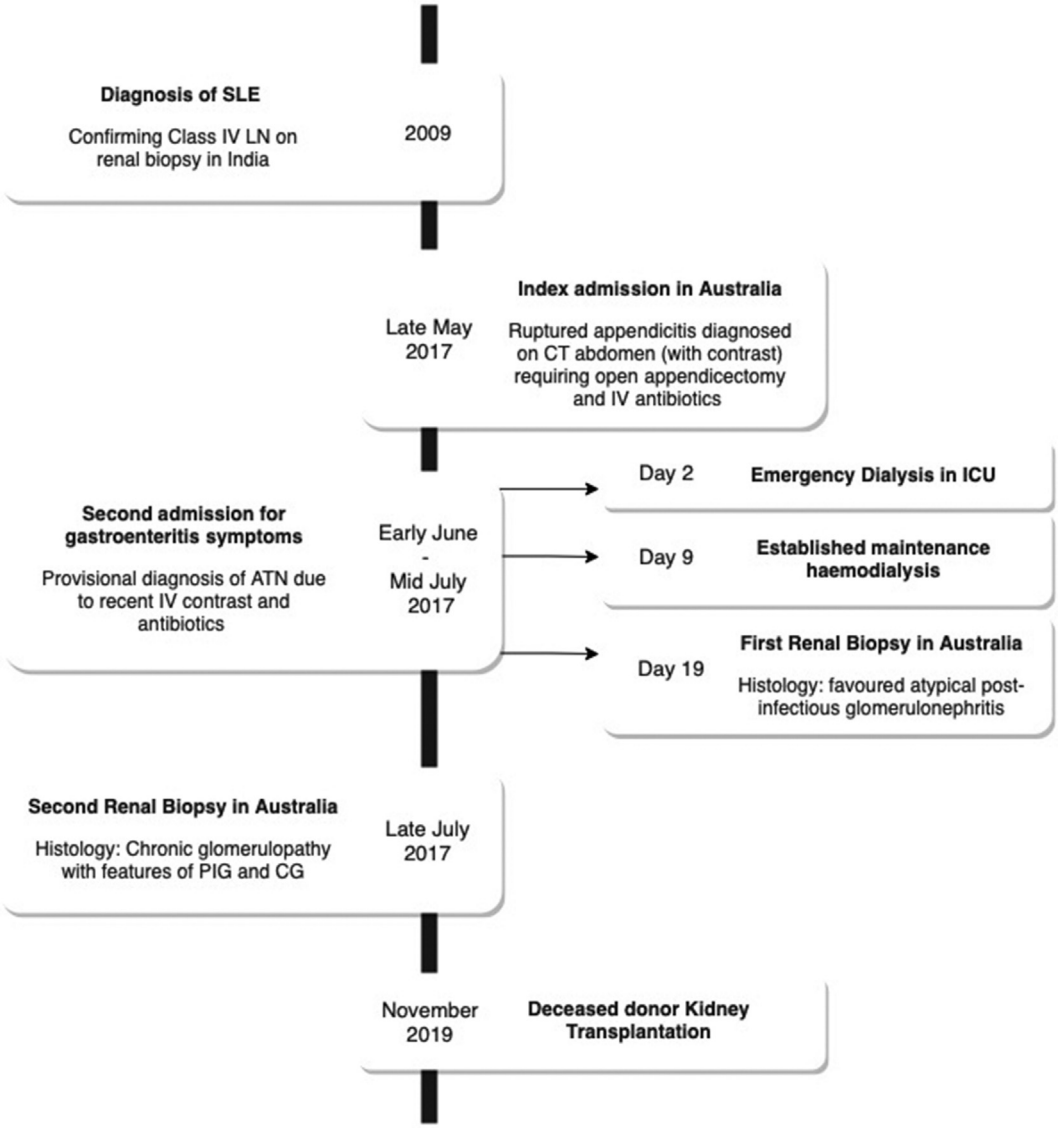

Fig. 1 Flow chart showing a timeline of events relating to the patient.

cyclophosphamide, but she remained dialysis dependent due to poor clearances. She received a deceased donor kidney transplant after 2 years.

We describe a young female with SLE presenting with acute renal failure, whose kidney biopsies were not pathognomonic of lupus nephritis, leading to uncertainties in her medical management. EM revealed GBM thickening and transmural involvement by microspherules, which is seen in PIG. PIG is defined as diffuse podocyte infolding into the GBM associated with ultrastructurally identifiable microspherular aggregates.[6] Our case showed podocyte infolding, but due to the features of CG also being present, it was more appropriate to describe it as a PIG pattern rather than a diagnostic entity. Wostmann *et al.*[7] stated that PIG should be considered as a pattern of injury rather than an aetiologically defined diagnosis, as the aetiology of PIG is still unclear. While only a few cases have been documented so far, PIG is known to have a high remission rate and a favourable prognosis with appropriate immunosuppressive therapy in patients with autoimmune disease.[6,8]

Conversely, the features of CG confer a poorer prognosis and it is associated with high rates of end-stage renal failure.[2] Retrospectively, these were likely present during the first renal biopsy where it was initially reported as cellular epithelial proliferation within Bowman's spaces, favoured to be podocytic hyperplasia. LM revealed crescent-like changes with the differential remaining between true crescentic formation and 'pseudo-crescent formation' with podocyte hyperplasia in more than 50% of the entire glomeruli. Podocytes are normally terminally differentiated in normal adult kidneys, but in cases of podocyte damage, they undergo dedifferentiation and loss of expression of maturity markers, such as synaptopodin and podocin. This is accompanied by morphological alterations, such as the loss of foot processes and an increase in the cytoplasm with protein-resorption droplets and microvillous transformation. Furthermore, they

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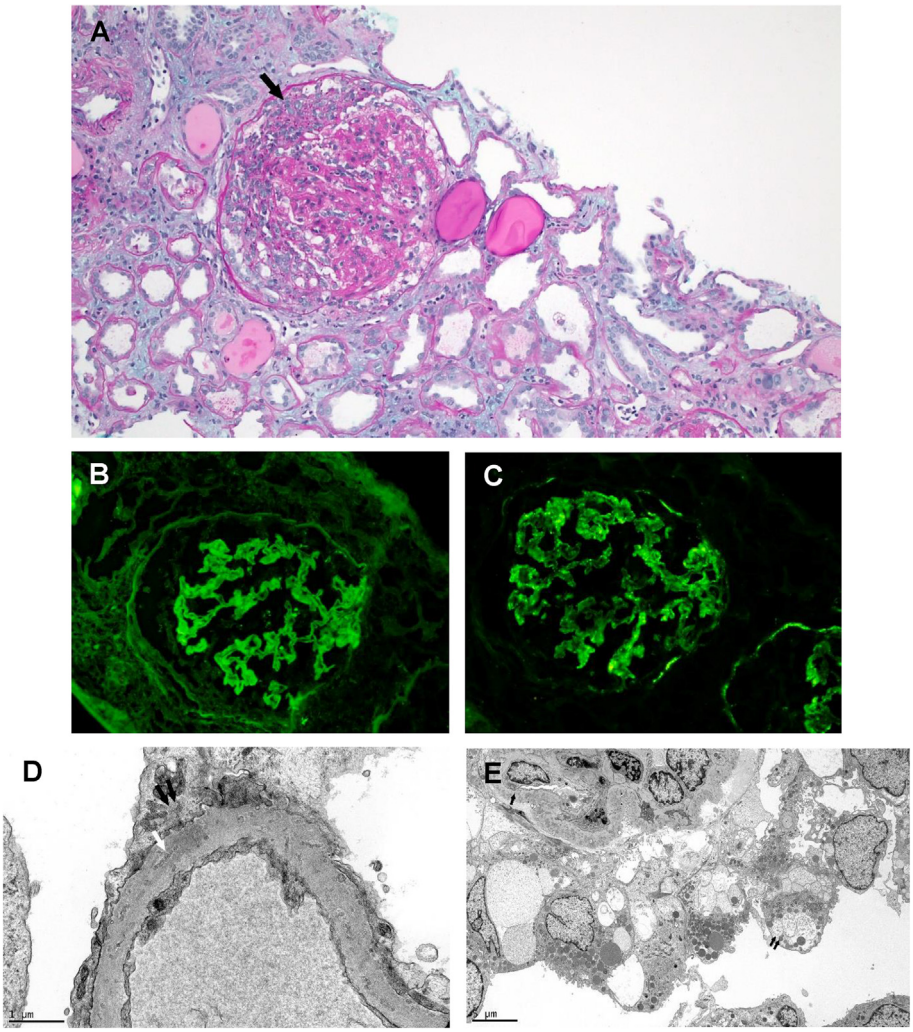

Fig. 2 (A) The glomerulus shows mesangial expansion and hypercellularity. Note the cellular proliferation filling the Bowman's space, displaying crescent-like changes (arrow) (periodic acid−Schiff, medium power). (B) There is linear, non-specific mesangial and capillary loop staining with IgG (immunofluorescence, higher power). (C) There is granular, weak and patchy, mesangial and capillary loop staining with C3 (immunofluorescence, higher power). (D) The GBM shows thickening and transmural involvement by microspherules (arrow). No electron dense deposit is identified. The podocytes show effacement and focal actin aggregation (double arrows), consistent with a podocyte injury (electron microscopy, ×25,000). (E) There is a glomerular tuft at the top of the figure showing a collapsed appearance (arrow) and a cellular proliferation of podocytes exhibiting vacuolation and frequent lysosomal activity (double arrow) (electron microscopy, ×5,000).

lose contact with GBM, filling the Bowman's space.[2] While true crescent formation was considered especially in the setting of known SLE, there was no fibrin or nuclear debris within the proliferation to validate this.

Immunofluorescence did not show a 'full house' pattern to clearly suggest lupus nephritis as a cause of her glomerulopathy. Membranous nephropathy was considered due to the weak positivity with IgG and C3, and a pattern of PIG can be seen in membranous nephropathy.[9] However, LM did not show classic 'spikes' or a rigid appearance of the capillary loops. Furthermore, there were no electron-dense deposits and the microspherules were distributed in a transmural and randomly scattered fashion on EM. The weak non-specific staining may suggest that an undefined immune abnormality rather than immune complex deposition is involved in the pathogenesis of PIG.[10]

The presence of ATN may also be a contributing factor to oliguric renal failure. There has been one other published PIG case associated with ATN, in which a 59-year-old man presented with acute renal failure due to tumour lysis syndrome on a background of recent chemotherapy.[11] Similar to this case, the patient had a normal premorbid renal function which rapidly deteriorated necessitating dialysis.

In our case, the patient did not improve with induction immunosuppression and ultimately required a renal transplant. Although PIG is usually associated with a favourable prognosis, the features of CG seen in our patient may have accounted for the poor prognosis, with CG mostly associated with high rates of end-stage renal failure.[2] A delay in induction immunosuppression due to the initial diagnosis of PIG conferring a favourable prognosis could also be a factor.

In summary, PIG is a rare histopathological finding in which understanding of its aetiology, pathophysiology and clinical implications are still evolving. This is the first case reported in Australia and one of the only two cases in the world where the patient required dialysis. The case is unique because both features of PIG and CG were demonstrated on kidney biopsy. We recommend evaluating for PIG changes and concurrent findings, such as CG and ATN as they may have a poorer prognosis and may require early immunosuppressive therapy in this subset of patients.

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