The many faces of lupus nephritis

When kidneys are involved in SLE

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Renal involvement occurs in at least half of cases of systemic lupus erythematosus (SLE). Four cases are discussed illustrating the diagnosis of the various types of lupus nephritis and their treatment. Early treatment with the combination of corticosteroids, hydroxychloroquine and either cyclophosphamide or mycophenolate mofetil is appropriate.

KEY POINTS

- Most patients with extrarenal systemic lupus erythematosus (SLE) will develop renal involvement and need lifelong six-monthly screening for urinary abnormalities to allow prompt and successful treatment.
- The finding of haematuria in pregnancy and other health checks should be followed up with serological testing for lupus nephritis, particularly in people of Southeast Asian and Asian descent.
- With the advent of mycophenolate mofetil and rituximab treatments for lupus nephritis, successful treatment of severe disease in young people now does not require the use of agents that cause long-term infertility (e.g. cyclophosphamide).
- The burden of disease and medications needed can lead to noncompliance and resultant severe flares of SLE that have a high morbidity when subsequently treated.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect almost any organ system.[1] Its presentation and course are highly variable, ranging from indolent to fulminant.[1-3] SLE has many types of manifestations, including constitutional, musculoskeletal and dermatological, and presentation may be with signs of any of these, such as malar rash, ulcers/mucocutaneous involvement, seizures, thrombocytopenia, haemolytic anaemia, fever and lymphadenopathy.[1] Treatment of patients with SLE includes disease-modifying therapy to control the disease and reduce the frequency of flares and also management of complications of the disease, including nephritis.

Renal involvement is clinically apparent in most cases of SLE, and usually develops within a few years of SLE onset. SLE (lupus) nephritis presents mainly with urinary abnormalities of red cells and protein, although it can present with an aggressive nephritic syndrome (deteriorating renal function and hypertension) or nephrotic syndrome (gross unexplained oedema).[1] The main goal

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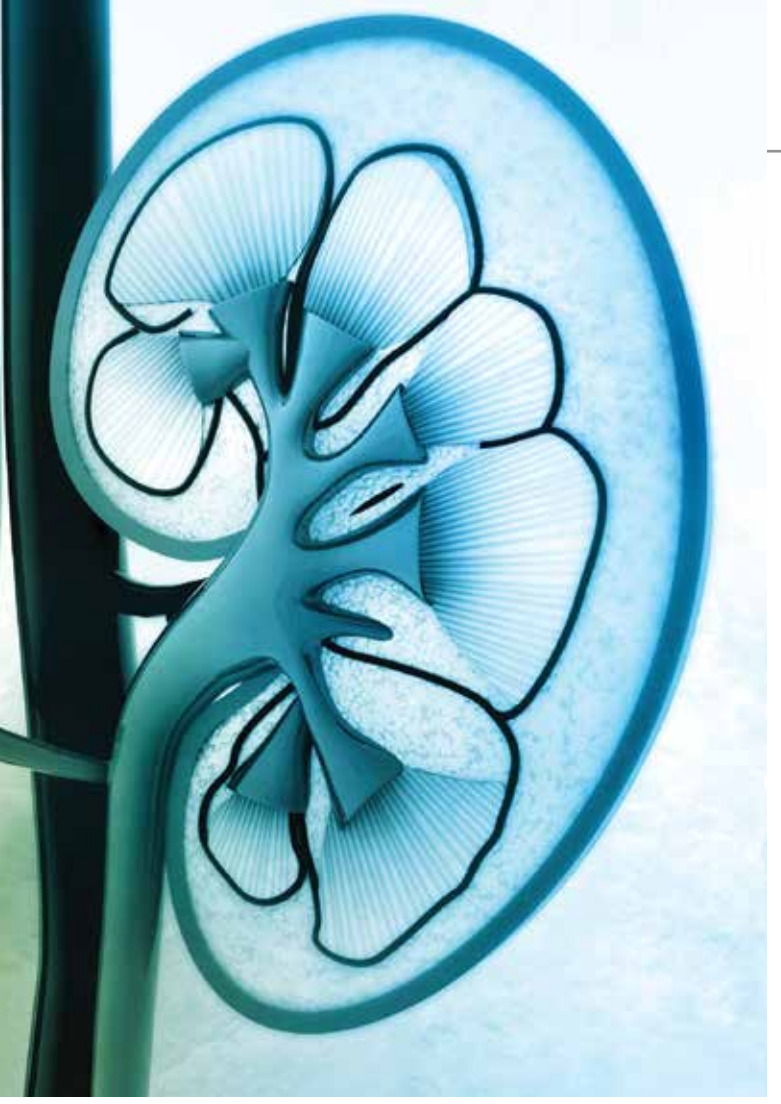

of treatment, which depends on the type of lupus nephritis, is normalisation of renal function or, at least, prevention of further loss of renal function. Rates of renal involvement and patient survival are improving with the use of newer more aggressive immunosuppressive and supportive therapies.

This review describes four cases of lupus nephritis, covering new diagnoses and flares of existing disease, with the lessons learnt and treatment provided additional to standard extrarenal SLE treatment in each case. The classification and treatment of lupus nephritis is summarised in the Table.[2-5]

Case 1: Lupus nephritis found in preconception check up

Case scenario

A 19-year-old woman of Southeast Asian origin presented to her GP for a preconception check up. She was found to be well, with normal clinical examination. Her family history was relevant for a grandmother having SLE (unclear how severe). There was mild proteinuria quantified as 350 mg/24 h collection (normal, <150 mg/24 h) and haematuria of 50 red blood cells per high-power field (normal, <10 rbc/hpf).

The patient was referred to a nephrologist for a renal biopsy, which demonstrated the presence of class II lupus nephritis (Table). She was offered long-term six-monthly reviews for her mild nephritis and was also counselled for potential flares of SLE during any future pregnancy or at other times. As she had no other clinical signs of SLE, she was not offered any immunosuppression treatment.

Discussion

The finding of an active urinary sediment and then lupus nephritis incidentally during a preconception workup is unusual but more common in women of Southeast Asian or Asian (Indian and Sri Lankan) origin. It is recommended that women with urine abnormalities identified on preconception workup have renal biopsies to delineate the cause of the active urinary sediment. Lifelong observation and reassessment is the key to therapy in patients with class I or II lupus nephritis as almost all patients will eventually require treatment due to worsening of their disease.[1]

Case 2: A presentation of severe disease

Case scenario

A 17-year-old Caucasian man presented to his GP with two weeks of constitutional symptoms (sore throat, cough, night sweats and loss of appetite), a malar rash with marked photosensitivity and marked peripheral oedema that extended up to his lower abdominal wall and included gross and painful scrotal oedema. The oedema was a classic sign of a severe nephrotic syndrome presentation. He initially presented hypertensive with blood pressures of 150–170/90–100 mmHg.

Investigations confirmed acute kidney injury with an elevated creatinine level of 178 µmol/L (normal range, 35 to 90 µmol/L), an albumin level of 15 g/L (normal, 34 to 46 g/L), urine microscopy showing 327 rbc/hpf (normal, <10 rbc/hpf) and a 24-hour protein excretion of 3870 mg/24 h (normal, <150 mg/24 h). His auto-antibody screen included an anti-dsDNA antibody level of 657 IU/mL (normal, <5 IU/mL), antinuclear antibody (ANA) level of 640 IU/mL and low levels of C3 (0.29 g/L; normal, 0.9 to 1.8 g/L) and C4 (0.06 g/L; normal, 0.16 to 0.50 g/L); findings of elevated antibodies to double-stranded DNA and decreased C3 and C4 complement levels often correlate with active SLE disease and particularly lupus nephritis. Urgent renal biopsy was performed and severe class IV lupus nephritis found (Table and Figures 1a to e).

Because of the patient's young age and the likely toxicity from use of cyclophosphamide, he was treated with intravenous methylprednisolone (1000 mg daily for three days) followed by prednisolone 60 mg daily and mycophenolate mofetil 720 mg three times daily (high dose for induction in severe disease) for his lupus nephritis. He was also given hydroxychloroquine 200 mg twice daily for his extrarenal SLE, and high-dose frusemide and spironolactone for the gross oedema. Sperm banking was performed before treatment was initiated.

The patient was very slow to respond to this therapy, achieving only a partial remission. This included a fall in his creatinine level, a fall in his anti-dsDNA antibody level to 116 IU/mL and a return

TABLE. LUPUS NEPHRITIS: RENAL BIOPSY CLASSIFICATION, USUAL TREATMENT AND OUTCOMES[2-5]

Renal biopsy classification		Usual treatment offered*	Usual outcome from treatment
Classification	**Histology on light microscopy**		
Class I – Minimal mesangial lupus nephritis	Normal	Observation for the renal lesion	Regular follow up required as may transform over 20 years
Class II – Mesangial proliferative lupus nephritis	Mild mesangial proliferation	Observation for the renal lesion	Regular follow up required as the proteinuria may need a ACE inhibitor and the nephritis may transform over 20 years
Class III – Focal lupus nephritis	Focal mesangial proliferative changes (≥50% of glomeruli affected)	Prednisolone and mycophenolate	If remission, good outcome
Class IV – Diffuse lupus nephritis	Diffuse mesangial proliferative changes (≥50% of glomeruli affected) – often with crescents	Prednisolone and mycophenolate; consider cyclophosphamide	If remission, often good outcome; may lead to ESRD
Class V – Membranous lupus nephritis	Membranous appearance	Prednisolone and mycophenolate; consider cyclophosphamide	If remission, often good outcome; may lead to ESRD
Class VI† – Advanced sclerosing lupus nephritis	≥90% of glomeruli globally sclerosed without residual activity	Dialysis for low eGFR	Transplantation for those suitable medically after waiting a few years on dialysis

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; SLE = systemic lupus erythematosus.

* Patients with lupus nephritis and extrarenal symptoms or signs of SLE should receive hydroxychloroquine unless contraindicated.

† Class VI is endstage renal disease in some classifications.

to normal of his complement levels. Despite the oedema being controlled, his albumin level remained low and he had continued heavy proteinuria (up to 10 g/24 h).

A repeat biopsy after six months of this regimen showed improvement in the patient's mesangial proliferative change, so adjunct rituximab was given in two doses to attempt to induce remission. At 12 months following rituximab administration, the patient was well with a normal creatinine level (90 µmol /L), and was in remission serologically from his SLE markers with minimal proteinuria and red blood cells in the urine.

Discussion

It is often the case that despite the patient presenting with what seems to be clinical nephrotic syndrome, the renal biopsy shows a class III /IV lesion and treatment is based on histology not clinical presentation.

This case demonstrates the more severe and treatment-resistant lupus nephritis that often occurs in Caucasian men. Because of this patient's young age, the decision was made to treat his class IV lupus nephritis with high-dose mycophenolate mofetil and corticosteroids, avoiding cyclophosphamide because of its associated long-term sterility and toxicity issues. Sperm banking was performed in case treatment with mycophenolate mofetil was unsuccessful and cyclophosphamide needed to be used. The partial response to treatment allowed the use of rituximab, which induced a full remission, and the patient returned to normal renal function for his age group.

Case 3: Development of renal involvement in SLE

Case scenario

A 40-year-old Caucasian man presented to a new GP with multiple constitutional symptoms of fevers, myalgia, arthralgia, right-sided pleurisy and a malar rash. He had previously been diagnosed with SLE involving the skin and joints and an episode of pericarditis, treated with long-term prednisolone and intermittent methotrexate.

On this presentation, lupus nephritis was newly diagnosed on screening the urine for protein (4+ dipstick positive). Although his serum creatinine level of 87 µmol/L was within the normal range (normal, 60 to 110 µmol/L), he had a proteinuria of 5700 mg/24 h (normal, <150 mg/24 h) and a haematuria of 100 rbc/hpf. This flare was accompanied by an elevated anti-dsDNA antibody level of 516 IU/mL (normal, <5 IU/mL), but complement levels were normal. A renal biopsy demonstrated mixed class IV and V lupus nephritis (Table).

The patient was treated with intravenous cyclophosphamide

1.5 g monthly, intravenous methylprednisolone at a dose of 1000 mg daily for three days, followed by oral prednisolone 50 mg once daily and hydroxychloroquine 200 mg twice daily. This rapidly led to a partial remission at two months, with resolution of symptoms and a reduction in proteinuria to 790 mg/24 h and haematuria to 20 rbc/hpf, as well as a fall in anti-dsDNA antibody level to 133 IU/mL. After three months of cyclophosphamide, he was converted to mycophenolate mofetil 720 mg twice daily and his dose of prednisolone was gradually reduced. Six months later, his renal function had remained normal and his proteinuria was

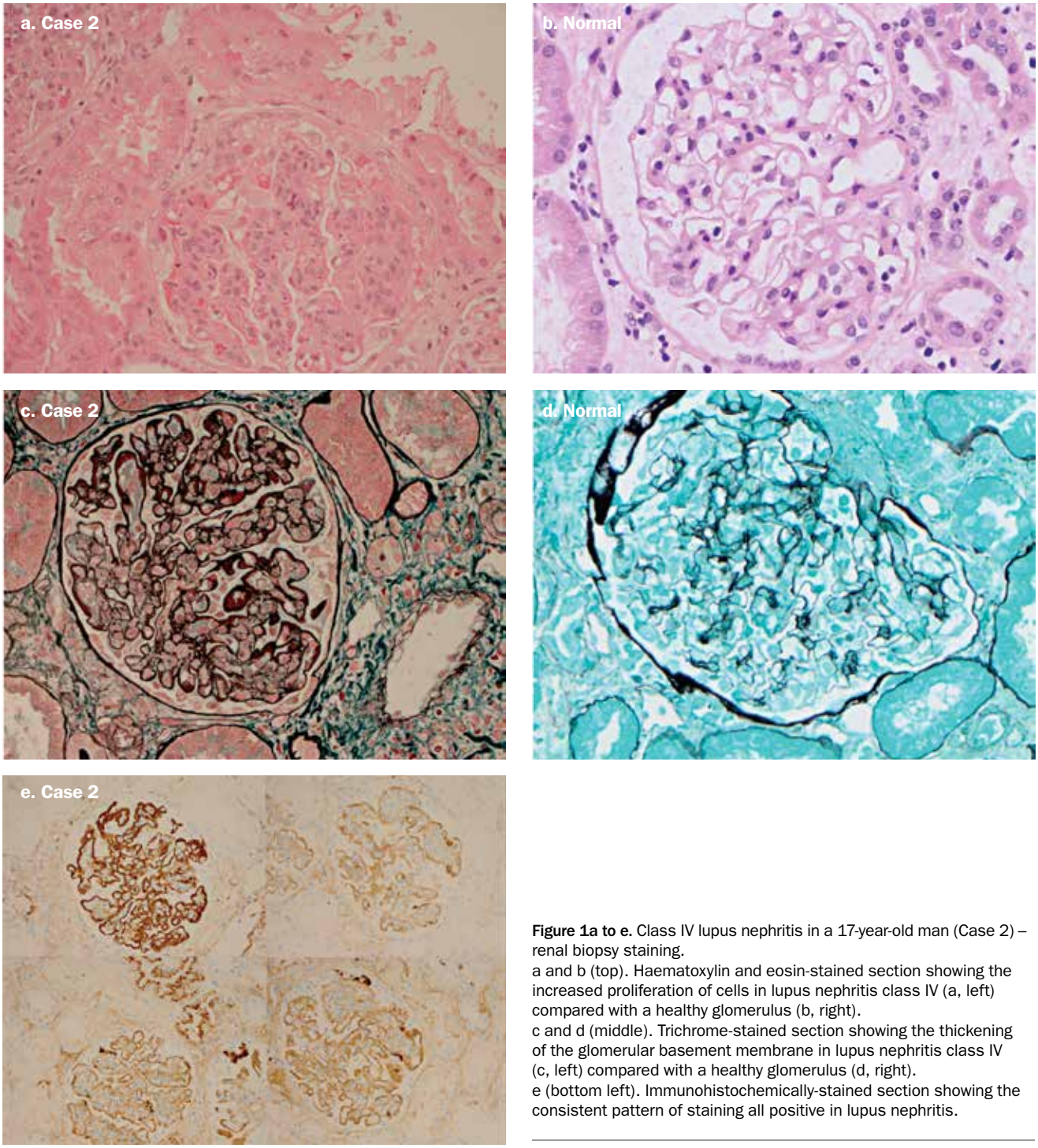

Figure 1a to e. Class IV lupus nephritis in a 17-year-old man (Case 2) – renal biopsy staining.
a and b (top). Haematoxylin and eosin-stained section showing the increased proliferation of cells in lupus nephritis class IV (a, left) compared with a healthy glomerulus (b, right).
c and d (middle). Trichrome-stained section showing the thickening of the glomerular basement membrane in lupus nephritis class IV (c, left) compared with a healthy glomerulus (d, right).
e (bottom left). Immunohistochemically-stained section showing the consistent pattern of staining all positive in lupus nephritis.

below 100 mg/24 h, although he had had another flare of his pericarditis requiring further oral prednisolone pulsing.

Discussion

This case demonstrates that part of the regular follow up in patients with extrarenal SLE is an assessment of urine to detect silent lupus nephritis (particularly in any flares of extrarenal disease). Patients with SLE often do not have their urine spot-tested in follow-up appointments. Lupus flares in the kidney are common and treated differently to extrarenal SLE; if they are caught and treated early, significant acute kidney injuries can be avoided.[1]

Case 4: A fulminant flare due to medication noncompliance

Case scenario

A 40-year-old Caucasian woman was admitted to hospital with constitutional symptoms of lethargy, arthralgia, fevers, nausea, vomiting and diarrhoea. She was known to have a 20-year history of SLE involving her joints, with recurrent rashes, intermittent alopecia, pleural serositis and class IV nephritis (Table). She was also positive for anticardiolipin antibody. She had been treated in recent years with mycophenolate mofetil and prednisolone. Due to social stressors and psychological fatigue with her chronic disease she had periods of noncompliance, and before this presentation had taken no medications for four months.

This presentation was a flare of her lupus nephritis, with her creatinine level elevated at 185 µmol/L (normal range, 45 to 90 µmol/L) and albumin level decreased at 19 g/L (normal range, 32 to 45 g/L). Her urine only had 15 rbc/hpf (normal, <10 rbc/hpf) but 4.5 g/24 h of protein (normal, <150 mg/24 h). Serologically her complement levels were depressed (C3, 0.33 g/L [normal, 0.9 to 1.8 g/L] and C4, 0.06 g/L [normal, 0.16 to 0.50 g/L]) and her anti-dsDNA antibody level was elevated at 657 IU/mL (normal <5 IU/mL).

The patient was treated with intravenous methylprednisolone (1000 mg daily for three days) followed by oral prednisolone 50 mg once daily as well as re-started on mycophenolate mofetil 1000 mg twice daily and hydroxychloroquine 200 mg twice daily.

Despite this re-induction, she progressed to have a fulminant flare of her lupus involving many organs. She had acute kidney injury with oliguria requiring dialysis, she developed heart failure from cardiac involvement and she had an extensive pulmonary embolism with subsequent respiratory failure requiring ventilation in intensive care. She then developed a disseminated intravascular coagulation with profound thrombocytopenia and a reduced conscious state probably from a mixed issue of cerebral lupus and a cerebral infarct (shown on CT).

Aggressive treatment was commenced with a combination of plasma exchange, intravenous cyclophosphamide and continued high-dose intravenous methylprednisolone. This successfully, over a week, reversed the severe disease flare and the patient was able to go into partial remission. She was subsequently transferred to the medical ward and eventually undertook rehabilitation a month later.

Discussion

Noncompliance is unfortunately common in patients with SLE because of both chronic disease issues leading to depression and huge tablet burdens.[1] Patients who suddenly stop taking their medication for SLE can have fulminant flares that require very intensive therapy, and morbidity and mortality is high for many months after such aggressive therapy.

Conclusion

Renal hypertension, haematuria, heavy proteinuria and acute kidney injury may signal lupus nephritis. These four cases demonstrate both initial diagnostic presentations and different types of lupus nephritis. Early diagnosis and screening for SLE nephritis is warranted to try and prevent the marked morbidity in such an aggressive and potentially treatable disease. Early treatment with the combination of corticosteroids (high-dose), hydroxychloroquine and either cyclophosphamide or mycophenolate mofetil is appropriate but the ability to induce remission is variable. Although often presenting nonspecifically, the detection of urinary abnormalities is essential in patients with SLE so that an early referral to a nephrologist can be made to reduce the risk of adverse renal outcomes. MT

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