Treatment of lupus nephritis

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Abstract

This case demonstrates a classical presentation of newly diagnosed systemic lupus erythematosus (SLE) in a previously fit and healthy 23 year old woman. A significant feature of Ms EX's presentation is the renal involvement of her SLE, classified as Class III A Lupus Nephritis. There are two main treatment options considered for Ms EX's active lupus nephritis: a combination of 1) cyclophosphamide or 2) mycophenolate mofetil with methylprednisone (given in pulses), followed by prednisone (tapering course). The discussion below summarises the current literature on short- and long-term treatment of lupus nephritis.

Case Report

Ms EX, a 23 year old Samoan woman, presented with a one month history of headaches, fevers and night sweats.

The headaches were bi-frontal in location with no radiation. They occurred intermittently almost every day, with each episode lasting three to four hours. They were described as a dull, heavy ache. There were no associated speech or visual changes, weakness, or numbness.

During this time Ms EX was suffering from fevers and night sweats. She also reported generalised myalgia, fatigue and anorexia. There was no history of weight loss. A non-itchy, red rash had also developed on both her arms over the past month. Three days prior to admission, a new red rash had appeared on Ms EX's face in the butterfly distribution. She denied any photosensitivity. Review of systems revealed no further symptoms.

Ms EX had no relevant past medical history and was not using any regular medications. She reported no recent overseas travel and family history was unremarkable.

Ms EX was living at home with her parents. She was enrolled in a hospitality course but had missed a month of this due to her current illness. She was a non-smoker and did not drink alcohol.

On examination, Ms EX was febrile at 38.3°C. Her arms revealed a widespread blanching vasculitic rash bilaterally. There was a malar rash present on her face and her lips and oral mucosa were ulcerated. There were no other positive findings.

Several investigations were carried out on Ms EX. Below are the relevant results (the extractable nuclear antigen antibodies [ENA] screen results are presented in Table 1):

- Erythrocyte sedimentation rate 136 mm/hr (1 – 19 mm/hr);
- C-reactive protein 74 mg/L (0 – 5 mg/L);
- Creatinine 102 µmol/L (45 – 90 µmol/L) ;
- Mid-stream urine: protein-creatinine ratio 128 mg/mmol (< 23 mg/mmol), 3 hyaline casts;
- Antinuclear antibodies: Positive;
- Complement C3 0.2 g/L (0.8 – 1.8 g/L), C4 <0.1 g/L (0.2 – 0.6 g/L);
- Kidney biopsy: Class III A (proliferative) lupus nephritis.

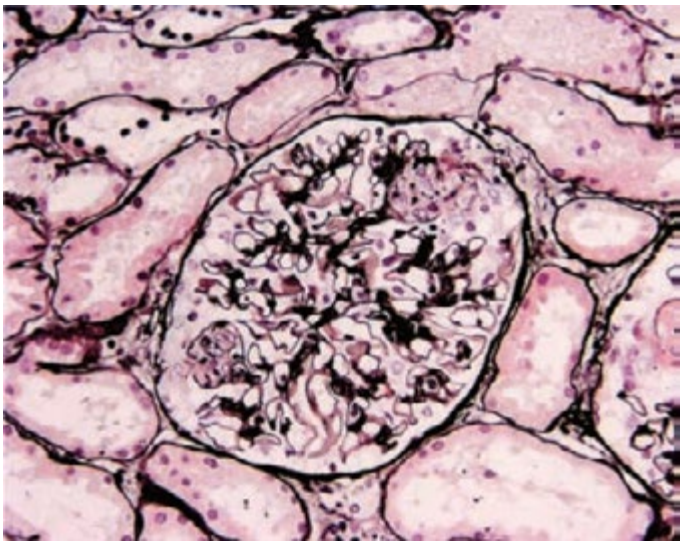

Figure 1. Light micrography demonstrating a glomerulus with segmental capillary necrosis however sparing of the remainder of the capillary tuft, a vasculitis-like lesions (methanamine silver)[1]

Table 1. ENA screen results for Ms EX in ELISA Units (EU); positive results ≥ 20

ENA Screen for Ms EX in ELISA Units (EU)	
Anti-SS-A	133 EU
Anti-SS-B	17 EU
Anti-Sm	>200 EU
Anti-Sm/RNP	171
Anti-Scl-70	51
Anti-Jo-1	22
Anti-DsDNA	>200
Anti-Centromere	7

Table 2. 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of SLE.[1] A patient must meet four or more of the above 11 criteria for them to be classified as having SLE.

The Diagnostic Criteria for SLE according to the American College of Rheumatology	
Malar Rash	Fixed erythematous rash either flat or raised over the malar eminences
Discoid Rash	Raised erythematous patch with keratotic scaling, follicular plugging or atrophic scaring
Photosensitivity	Skin rash caused by an unusual reaction to sunlight
Oral ulcers	Ulcers in the mouth or nasopharynx, usually painful
Arthritis	Non-erosive joint inflammation involving ≥ 2 peripheral joints
Serositis	Pleurisy or pericarditis
Renal disorder	Persistent proteinuria or presence of cellular casts
Neurological disorder	Seizures or psychosis not explained by other causes
Haematological disorder	Haemolytic anaemia with reticulocytes, leukopenia, lymphopenia or thrombocytopenia
Immunological disorder	Presence of Anti-double stranded DNA, Anti-Smith or positive findings of antiphospholipid antibodies (anticardiolipin antibody, lupus anticoagulant, or false positive venereal reference laboratory test)
Anti-nuclear antibody	Abnormal ANA titre at any point in time in the absence of drugs known to be associated with drug-induced lupus syndrome

Together, Ms EX's clinical presentation and investigation results indicated a new diagnosis of systemic lupus erythematosus, with Class III A lupus nephritis and possible CNS lupus.

Discussion

Background

Systemic Lupus Erythematosus (SLE) is a chronic, multi-systemic autoimmune disease. In European populations it is more common in women than men, with a female to male ratio of 9:1.[3] Although SLE can affect any age group, it typically manifests during the reproductive age in women.[3] In New Zealand the prevalence of SLE is significantly higher in Pacific Islanders and Māori.[4]

Approximately 50% of all SLE cases will develop renal involvement, termed lupus nephritis.[5] This is one of the more serious and common manifestations of SLE. Lupus nephritis occurs through a complex inflammatory process following the deposition of immune complexes in the glomerulus, ultimately leading to glomerulonephritis and in severe cases necrotising crescentic GH (Class IV). Long term, lupus nephritis may progress to ESKD.

A retrospective New Zealand study conducted in 2007 demonstrated that Pacific Island and Māori people were at a three times and eight times higher risk respectively of developing lupus nephritis compared to European populations.[4] In Ms EX's case, a high index of suspicion for lupus nephritis was maintained due to the elevated serum creatinine, increased protein-creatinine ratio, and presence of hyaline casts in the urine. These laboratory-based indicators of a decline in kidney function warranted a kidney biopsy. A kidney biopsy is the gold standard for the diagnosis of lupus nephritis.[6] It enables lupus nephritis to be classified on the basis of histopathology. This classification further guides therapeutic options and indicates likely prognosis.[7] According to the ISN/RPS lupus nephritis 2003 classification, Ms EX's lupus nephritis was classified as Stage III A.[7]

Treatment of Lupus Nephritis

Proliferative lupus nephritis, such as Class III lupus nephritis, is treated using immunosuppressive agents. Treatment can be divided into two forms: induction and maintenance therapy.

Induction

Induction therapy aims to delay disease progression and achieve remission. The first agents used for the treatment of lupus nephritis were corticosteroids, such as methylprednisone. However, in the 1970s, several clinical trials, including those carried out at the National Institutes of Health, showed that the combination of cyclophosphamide (CYC), a cytotoxic agent, and corticosteroids was more superior in producing remission than corticosteroids alone.[5] Since then, this combination became the first-line regimen for induction therapy of lupus nephritis.[5,8] Nevertheless, despite its high efficacy, CYC has numerous adverse effects, including bone marrow suppression, increased risk of infection, haemorrhagic cystitis, bladder cancer, and gonadal failure.[5]

Over the past decade, mycophenolate mofetil (MMF), a drug used for preventing transplant rejection, has emerged as another agent to pair with corticosteroids for induction therapy. A Cochrane review comparing various regimens of MMF and CYC in 10 randomised controlled trials (RCT) demonstrated that MMF was as effective at achieving remission in lupus nephritis as CYC, but was associated with fewer adverse effects of premature ovarian failure, alopecia, and leukopenia.[8] However, one disadvantage of MMF was that it caused more gastrointestinal side effects such as diarrhoea than CYC. It should also be noted that a major contraindication to both MMF and CYC is pregnancy, as both these drugs are teratogenic.[5]

There are fewer studies conducted on the use of azathioprine (AZA), a purine antimetabolite, as an agent in induction therapy. However, two randomised control trials have both showed that long-term AZA used in induction therapy was associated with higher relapse rates than CYC.[9, 10]

More recently, calcineurin inhibitors, such as cyclosporine and tacrolimus, have been investigated as induction agents. A small RCT comparing cyclosporine and CYC in 40 patients found no difference between the two treatments after 40 months of treatment.[11] Another small pilot study with a study population of 60 patients, compared tacrolimus to MMF and concluded that there was potentially faster resolution of proteinuria and hypoalbuminemia with tacrolimus than the other two agents.[12]

Biological agents such as rituximab have also been considered for use of induction therapy in lupus nephritis. The LUNAR study, a RCT with 114 participants, found that rituximab therapy resulted in a greater reduction in serum anti-dsDNA and C3/4 than CYC. However, after a one year treatment period, this did not lead to any improvement in clinical outcomes.[13]

Meaningful conclusions into the efficacy of tacrolimus, cyclosporine and rituximab as induction agents cannot be drawn due to the limited number of RCTs and the small sample sizes in the studies completed.

Since Ms EX is a young woman of childbearing age, the most appropriate induction therapy for her lupus nephritis would be MMF with methylprednisone, as it has a more favourable side effect profile compared to CYC and achieves similar efficacy.

Maintenance

After remission is achieved, maintenance therapy is given to prevent relapse and reduce the risk of developing end-stage renal disease. This is usually achieved with either MMF or AZA.

In the past decade, the National Institutes of Health trials have demonstrated that maintenance therapy with MMF or AZA is more efficacious and is associated with fewer adverse effects than long-term treatment with CYC.[5] Furthermore, a systematic review carried out by the Cochrane collaboration group on two RCTs also concluded that MMF was superior to AZA in preventing renal flares, but was equal to AZA in doubling creatinine, mortality, risk of infection, gastrointestinal effects and leukopenia.[8] However, another meta-analysis that compared MMF and AZA in four RCTs found that MFF was safer and a better tolerated form of maintenance therapy.[14]

Limited studies have been conducted investigating the use of rituximab as a form of maintenance therapy for lupus nephritis, but it appears to be a promising area of development.[8]

MMF would be a suitable treatment for maintenance therapy in Ms EX's case. However, if Ms EX wished to become pregnant, then AZA could be used as the next best form of maintenance therapy.

Follow up and complications

The degree of renal disease in lupus nephritis is typically monitoring with both clinical examination such as blood pressure recording, as well as biochemical markers: urinalysis, protein/creatinine ratio, serum creatinine, C3/C4 levels and anti-DNA.[15] The frequency of testing is determined by whether the patient has active nephritis at commencement of treatment, previous active nephritis, current nephritis and their current pregnancy status.[15]

In the long run, morbidity in lupus nephritis is linked with the progression of renal disease as well as the adverse effects of therapy. Worsening renal function can lead to hypertension, anaemia, uraemia, electrolyte and acid-base disturbances. Early onset lupus nephritis is also associated with an increased risk of ischaemic heart disease.[16] In cases with nephrotic syndrome there is an added risk of developing coronary artery disease and thrombosis.[17] The major complications from therapy include immunosuppression, and those directly associated with long-term steroid uses: hypercholesterolemia, hypertension, diabetes mellitus, bone thinning, osteoporosis and fractures.[17]

Conclusion

Lupus nephritis is a common manifestation of SLE that is associated with serious mortality and morbidity. For this reason, clinicians must have a low threshold for suspecting lupus nephritis in asymptomatic patients like Ms EX and urinalysis must be undertaken in all patients presenting with evidence suggestive of SLE. In Ms EX's case, laboratory findings pointed towards renal involvement of SLE. This was promptly followed up with a kidney biopsy and the ISN/RPS classification was used to classify Ms EX's lupus nephritis as Class III A. The current literature suggests that the best treatment for Ms EX's lupus nephritis would be with methylprednisone and MFF in the induction phase, followed by MFF and prednisone in the maintenance phase. Suitable alternatives (if MFF was contraindicated) would be CYC and methylprednisone in the induction phase, and AZA in the maintenance phase. More research into newer therapies such as calcineurin inhibitors and biological agents is needed to determine their role in the treatment of lupus nephritis.

Conflict of interest: None

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References

1. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney international 2004;65(2):521-30.
2. Hochberg M. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis & Rheumatism 1997;40:1725-1725.
3. D'Cruz DP. Systemic lupus erythematosus. BMJ 2006;332(7546):890-4.
4. Burling F, Ng J, Thein H, et al. Ethnic, clinical and immunological factors in systemic lupus erythematosus and the development of lupus nephritis: results from a multi-ethnic New Zealand cohort. Lupus 2007;16(10):830-7.
5. Schober FP, Dooley MA. Management of Lupus Nephritis. Curr Treatm Opt Rheumatol 2016;2(3):225-38.
6. Schwartz N, Goilav B, Putterman C. The pathogenesis, diagnosis and treatment of lupus nephritis. Current Opinion in Rheumatology 2014;26:502-509.
7. Weening J. The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited. Journal of the American Society of Nephrology 2004;15:241-250.
8. Henderson L, Masson P, Craig JC, et al. Treatment for lupus nephritis. Cochrane Database Syst Rev 2012;12:Cd002922.
9. Arends S, Grootscholten C, Derksen RH, et al. Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus cyclophosphamide in patients with proliferative lupus nephritis. Annals of the Rheumatic Diseases 2012;71(6):966-73.
10. Grootscholten C, Ligtenberg G, Hagen EC, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney international 2006;70(4):732-42.
11. Zavada J, Pesickova S, Rysava R, et al. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study. Lupus 2010;19(11):1281-9.
12. Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrology Dialysis Transplant. 2012;27(4):1467-72.
13. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis and rheumatism 2012;64(4):1215-26.
14. Feng L, Deng J, Huo DM, et al. Mycophenolate mofetil versus azathioprine as maintenance therapy for lupus nephritis: a meta-analysis. Nephrology (Carlton) 2013;18(2):104-10.
15. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care & Research 2012;64(6):797-808.
16. Faurschou M, Mellemkjaer L, Starlinkt H et al. High Risk of Ischemic Heart Disease in Patients with Lupus Nephritis. The Journal of Rheumatology 2011;38:2400-2405.
17. Bono L. The very long-term prognosis and complications of lupus nephritis and its treatment. QJM 1999;92:211-218.