Case report

Biopsy-Confirmed Lupus Nephritis with Advanced Sclerosing Disease Managed with Overlap Treatment

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Abstract

Background: Lupus nephritis, complicating systemic lupus erythematosus, can progress to end-stage kidney disease, with a poor prognosis. Histological diagnosis is essential in formulating an effective treatment regimen particularly with symptom overlap.
Method: We highlighted the role of a histological diagnosis in the management of Lupus nephritis with complex overlapping symptoms according to approved treatment protocol.
Result: She was anemic and the histological diagnosis was class VI lupus nephritis. She was managed using an overlapping treatment spanning classes IV – VI, with haemodialysis (HD), mycophenolate mofetil, methylprednisolone and diuretics based on heightened disease activity and extrarenal manifestations. Using the WHO and the International Society of Nephrology/Renal Pathology Society revised guidelines, KDIGO recommended haemodialysis for classes III, IV, and V with nephrotic syndrome, in addition to high dose corticosteroids, cyclophosphamide/MMF (induction therapy), and low dose corticosteroid/MMF for maintenance therapy. The disease went into remission, and she continued outpatient HD.
Conclusion: The case highlights the place of histological diagnosis in managing LN associated with complexities of staging and symptoms-overlap to achieve optimal results.

Keywords: Case report, lupus nephritis, systemic lupus erythematosus, histology, kidney biopsy, remission, relapse, haemodialysis.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune, multisystemic clinically heterogeneous disease characterized by circulating autoantibodies directed against nuclear antigens.[1] The disease is more prevalent in women, Africans and in the reproductive age group, with more than 85% of victims being younger than 55 years. Males, children and the young tend to have more severe forms of the disease.[1] The incidence and prevalence of SLE range from 0.3-8.7 per 100,000 persons and 3.2 to 159 per 100,000 persons, respectively.[2] Genetic predisposition is anchored on high concordance rates in monozygotic twins, high percentage (17%) of affected relatives, higher frequency of HLA genotypes particularly, B8, DR_2, DR_3 and DQW_1, and the higher frequency of the disease in populations with deficiency of complements factors C1q, C_2 and C_4.[3] Hormonal and environmental factors have been implicated in the aetiology.[1-3]

Lupus nephritis (LN) often develop concurrently or shortly following the onset of SLE, and results from glomerular immune complexes deposition. It often runs a protracted course with periods of remission and exacerbations, clinical renal manifestations often correlate with the degree of glomerular involvement.[4] Progression to end-stage kidney disease (ESKD) requiring renal replacement therapy (RRT) is common.[2,3] We present the case management of a 45-year-old woman with LN who successfully had class and symptom overlap treatment.

Case Summary

A 45-year-old woman presented at the emergency department with a 4-month history of recurrent dyspnea, 2 months of leg swelling and skin excoriation. Dyspnea was progressive, with orthopnoea and paroxysmal nocturnal dyspnea (PND). Cough was productive of frothy sputum, without haemoptysis nor night sweats. She had right hypochondrial pain with progressively worsening vomiting, anorexia and body weakness. She had had non-pruritic skin excoriations at 30 years, then scalding, and patchy hair loss. The facial rashes were worse and peppery outdoor. She had recurrent episodes of low grade fever, non-swelling arthralgia. She was diagnosed hypertensive at 35 years and had been on amlodipine 10mg, frusemide 40mg and spironolactone 25mg. She had a recent diagnosis of SLE during work up for pericardial and pleural effusion, for which she had chest tube drainage and pericardiocentesis.

She was pale, acyanosed, febrile (37.9^0c) and oedematous. She had a dark scaly rash over the bridge of the nose (sparing the nasolabial folds), scarring alopecia with discoid patches, and hyperpigmented papular rashes on the limbs and trunk. Her blood pressure 119/82mmHg, respiratory rate was 24/min, and oxygen saturation was 96% in room air. The breath sound were reduced in both lung bases.

Assessment – Lupus nephritis, complicated by pleural effusion, with resolving serositis

Bedside urinalysis showed protein 3+, nitrites 1+, and leucocytes 1+. 24-hour urine protein was 3.8g. Electrocardiogram (ECG) showed low voltage complexes. Echocardiogram showed pericardial effusion with severe concentric left ventricular hypertrophy (LVH). Chest x-ray showed cardiomegaly with bi-atrial enlargement. Urine culture yielded growth of E. coli sensitive to ceftriaxone, gentamycin and ceftazidime. Blood culture yielded growth of staphylococcus aureus sensitive to amoxicillin, clindamycin and erythromycin.

The serum biochemistry at presentation showed: total protein (90 g/dL), albumin (12 g/dL), aspartate transaminase (43 IU), alanine transaminase (142 IU) and alkaline phosphatase (102 IU), The fasting lipid showed: total cholesterol (121 mg/dL), high density lipoprotein (27 mg/dL), low density lipoprotein (75 mg/dL) and triglyceride (94 mg/dL). The fasting blood glucose was 104 mg/dL. The complement factor C3 and C4 were 0.85 g/L and 0.26 g/L respectively.

Serological screening were negative for HIV, hepatitis B, and C viruses. Antinuclear antibodies (ANA) were positive, with speckled pattern, and double stranded DNA (dsDNA) was negative. Antinuclear neutrophil cytoplasmic antibodies (ANCA) were both negative (cytoplasmic and perinuclear). Kidney scan showed right kidney (9.81 x 4.13), and left kidney (9.3 x 4.51), both showed poor cortico-medullary differentiation. The glomerular filtration rate (eGFR) at presentation was 11.7 mL/min. She had her first haemodialysis session via a central venous catheter, and was commenced on:
Methylprednisolone succinate 500 mg daily for 3 days, Prednisolone 60mg daily (from 4DOA), Mycophenolate mofetil 1g 12hly, Hydroxychloroquine 400 mg daily, Ceftriaxone 1g 12hly, Frusemide 80 mg 12hly, Amlodipine 10mg daily, and Lisinopril 10mg daily.

The pericardial effusion was mild and did not require pericardiocentesis. Her condition improved and an arterovenous fistula (AVF) was created. She was discharged and commenced on subcutaneous

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Erythropoietin 75ug monthly. She is being followed up on twice weekly haemodialysis and has remained stable.

Histology of the kidney biopsy specimen showed:
1. Advanced global glomerulosclerosis, with diffuse glomerulosclerosis (>90% global sclerosis) representing healing of previously inflamed tissues.
2. Advanced tubulointerstitial disease with interstitial fibrosis, tubular atrophy with PAS-positive hyaline casts, some small atrophic tubules without prominent lumen and marked interstitial inflammatory cellular infiltration.

Definitive diagnosis: Stage VI Lupus nephritis with resolving serositis.

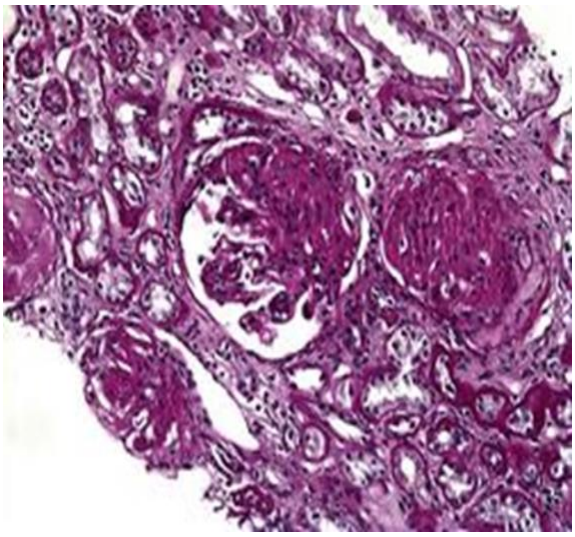

Figure 1: Photomicrograph showing lupus nephritis class VI with advanced sclerosing glomerular disease and tubular atrophy. (x300)

Table 1: Serum laboratory results all through admission

Variables	Range	Admission	3DOA	8DOA	14DOA	21DOA	27DOA
Sodium, mmol/L	135-145	148	147	135	130	143	144
Potassium	3.5-5.0	3.2	3.1	3.9	4.0	3.7	3.6
Urea, mmol/L	3-7	19.7	22.4	66.4	47.3	33.1	18.8
Creatinine, µmol/L	50-110	429	452	1652	1032	620	394
Hemoglobin, g/dL	13.0-16.0	6.5	12.4			8.6	10.2
Hematocrit, %	36-48	21	40	38.5	33	26.6	31
Leucocytes, 10^9/L	4-11	8.1		15	13.3	4.0	5.2
Platelets, 10^9/L	150-400	247	385		385		221

Discussion

SLE is a multisystemic, autoimmune, clinically heterogeneous disease typified by circulating autoantibodies directed against nuclear antigens [1,2]. LN is a frequent and potentially serious complication of SLE that is more prevalent in women Africans and in the reproductive age group.[1] LN tend to be more severe in young adults than the elderly, as seen in the index case.[1] Adelowo et al[5] reported a prevalence of 5.28% with females constituting 95.5%, with a mean age of 33 years (17-55 years). The authors also reported a 25-50% of LN among the SLE population.[5]

Typical of SLE are abnormal immune regulations, loss of self-tolerance, reduced circulating cytotoxic and suppressor cells, increased helper T-Cells, polyclonal activating B cells, defective B-cell tolerance, dysfunctional T-cell signaling and abnormal Th1 and Th2 cytokine production[2,4].

Renal involvement often develops within 3-5 years onset of onset of SLE and may follow a protracted course characterized by remission and exacerbations.[4] Clinical renal involvement correlates well with the degree of glomerular involvement.[6] Lupus nephritis exhibit a pleomorphic histopathologic pattern, and can transform between patterns spontaneously or with treatment.[6]. The World health Organisation (WHO) and the International Society of Nephrology/Renal Pathology Society (ISN/RPS), in the revised form, classified LN into six stages: Class I (minimal mesangial immune complex deposition); class II (mesangial proliferative disease); class III (focal proliferative LN with <50% of glomerular affectation); class IV (diffuse proliferative LN with >50% of glomerular affectation; class) V (membranous LN), and class VI as (advanced sclerosing LN).[7]

Considering the acute flare and the clinical state of the index patient, the possibility of an active disease was envisaged, hence she was managed empirically with methylprednisolone, mycophenolate mofetil (MMF) and haemodialysis prior to tissue diagnosis. The possibility of using non-steroidal anti-inflammatory drugs

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(NSAIDs) in this early flare could worsen kidney function or delay the optimal response to treatment.[8] The Kidney Disease Improving Global Outcome (KDIGO) guideline for glomerulonephritis recommended aggressive treatment for the active disease (classes III and IV), with high dose corticosteroids and cyclophosphamide or MMF for induction therapy, and low dose corticosteroid with azathioprine or MMF for maintenance therapy.[9] KDIGO recommended the same regimen for Class V disease persisting with nephrotic syndrome, but with an option of a calcineurin inhibitor (CNI).[10] For classes I and II, KDIGO recommended conservative management, or with steroids or an immunosuppressant, as determined by extra renal manifestations. Its recommendation that class VI disease should be managed as an ESKD explains why the long term management plan for the index patient was by haemodialysis and a possible kidney transplant.[10]

The patient presentation with nephrotic range proteinuria and ESKD (eGFR 11.7 mL/min/ 1.73m^2) placed her in KDIGO stage V or VI of the clinical practice guidelines for glomerulonephritis.[10,11] We felt she had class V (membranous glomerulonephritis) on account of the anarsaca, with pericardial effusion that is more likely to be seen in this stage. Moreover, urinalysis showed nephrotic range proteinuria. Her GFR of 11.7 mL/min with obvious uremic symptoms typifies her condition as class VI lupus (advanced sclerosis), hence in keeping with KDIGO guidelines, we commenced her on prednisolone 60mg daily (high dose) and MMF 1g twice daily (induction phase), even though immunosuppressive drugs are commonly not used in stage VI lupus nephritis except with situations such as declining kidney function, presence of extra renal manifestations such as pericardial effusion(both present in index patient), or a histology-confirmed proliferative disease.[10,11] Hydroxychloroquine, as used in this case, is documented to reduce flare rates, as reported from a prospective controlled trial where those who continued hydroxychloroquine had lower flare rates compared with those switched to placebo.[5]

Conclusion

LN represents a major burden, and it is associated with significant morbidity and mortality in patients with SLE. A high index of suspicion is required to make an early diagnosis. This entails periodic screening for proteinuria and blood pressure measurement. Prompt treatment with corticosteroids or other immunosuppressive agents can be cost effective, achieve remission, and retard progression to ESKD. Though the biopsy showed advanced sclerosis, of which haemodialysis is the main stay of treatment, the presence of proteinuria, strengthened our use of corticosteroids and immunosuppressants to which our patient showed favorable clinical response. The case highlights the place of kidney biopsy in the optimal management of LN as it specified the disease class, and highlighted possible complexities that could arise in disease staging, and overlap of symptoms, signs and treatment.

Declarations

Ethical Consideration: Ethical clearance was not needed. However, the authors certify that they have obtained all appropriate patient consent forms, and the patient gave her consent for her clinical information to be reported in the journal. The patient understand that her name and initials will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Authors' Contribution: All authors contributed equally to the study.

Conflict of interest: None declared

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