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Case Study

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AN ASSORTED CASE SERIES OF LUPUS NEPHRITIS

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is an auto immune condition acquired due to the complicated processes underpinning the balance between immunological reactivity and immune tolerance. The disease progression varies in population across races and geographic distribution. An appalling complication is lupus nephritis (LN) with more than 40% prevalence. With time nearly 30% of patients progress to end-stage kidney disease (ESKD). We encountered three middle aged females with vivid presentation. First case was a mother of two kids presented with rashes and accelerated hypertension. Second case was a known case of cerebral venous thrombosis presented with frequent giddiness and blurring of vision. Third case presented with complaints of lower limb edema. On evaluation all three tested positive for ANA antibody and biopsy revealed stage IV lupus nephritis. They were treated with cyclophosphamide and immunomodulatory agents. However, one among them progressed to end stage renal disease requiring dialysis and succumbed. **Conclusion:** The disease per se presenting as LN is becoming more frequent. Hence, it is imperative for upcoming clinicians not to be oblivious as SLE manifestations are unusual. The disease progression is precipitous in few cases as in our study.

KEYWORDS: Lupus nephritis, SLE, immune tolerance, female.

INTRODUCTION

Lupus (Latin for 'wolf') was known ever since thirteenth century, it was Sir Rogerius a physician who described erosive facial lesions reminiscent of a wolf's bite. Sir William Osler was the first to describe nephritis as component of SLE. By mid-nineteenth century many dermatologists contributed for the features of lupus and discoid lupus was described in 1833 by Cazenave, butterfly distribution by Von Hebra in 1846.[1] Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that predominantly affects women of childbearing age. Lupus nephritis (LN) is one of the most common manifestations of SLE with aggressive disease course. Incidence of LN is higher in Asian population ranging from 33-55%.

Symptomatology of LN includes malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurological disorder, haematologic disorder, immunologic disorder. The pathophysiology of the disease vexes scientist because of its continuum in genetic, epigenetics and environmental factors. APOL1, PDGFRA and hyaluronan synthase 2 (HAS2) are considered as risk factor for developing LN. Autoantibodies against nuclear and cellular antigens results in immune complex formation and accumulation of immune complexes in glomeruli, increase the interaction of T and B cells, and activate complement to initiate intrarenal inflammation and injury.[2]

Clinical renal disease is marked by any or all of the following like Nephrotic-range proteinuria (protein excretion > 3.5 g/d), urinary protein creatinine ratio (UPCR) in a random spot specimen or a 24-hour urine collection >500-1000mg/day, Cellular casts, hematuria >5RBC/HPF, Pyuria >5 WBC/HPF in absence of infection and antibody positivity. The gold standard being Percutaneous Renal biopsy, and those with proliferative forms of LN (class III, IV, or III/IV + V) are at highest risk for requiring renal replacement therapy (RRT).[3]

Table 1: Current AJKD guidelines.[2]

Induction Steroid Regimen	IV methylprednisolone 0.25-1 g/d for 1-3 days, followed by Oral prednisone 0.5-1 mg/kg/d (max 80 mg/d) taper over several months
Induction Immunosuppression regime	a. Oral MMF 2-3 g/d in divided doses x 6 months
	b. IV cyclophosphamide (Euro-Lupus) 500 mg every 2 weeks for 3 months
	c. IV cyclophosphamide (NIH Regimen) 0.5-1 g/m2 monthly x 6 months
	d. PO cyclophosphamide 1-1.5 mg/kg/d (max 150 mg/d) for 3 months
	e. Hydroxychloroquine & Kidney Protective Measures
Unresponsive	Renal replacement therapy
Emerging therapies for proliferative LN	Rituximab, Oral mycophenolate mofetil, Tacrolimus, cyclosporine

Case 1: A 29-year-old female patient presented with complaints of headache, puffiness of face, swelling of limbs and rashes all over body since 10days. For the same complaints patient had been to dermatologist and was treated with antihistamines, ?steroids oral and topical preparation. She was a mother of two kids, with no significant history during or post-natal period. On examination patient looked swollen with lower limb edema, pale and polymorphic petechial rashes were noted. She had tachycardia and blood pressure of 250/140mmHg with retinopathy changes. Systemic examination revealed crepitations over the basal lung fields.

Patient was admitted to evaluate the cause of hypertension in young. Hb= 5.4gm/dL, Total count = 5200cells/mm3, ESR = 38, platelet count 3lak/mm^3, Urine routine showed albumin (1 +), creatinine = 1.4mg/dL with normal liver function tests and serum electrolytes. She was subjected for 24hr urine protein examination and result was 1200mg/day.

Serological examination showed ANA 3+, SSA 3+, Ro-52 3+, Histones 2+, ds DNA negative with normal Complement (102mg/dL).

On renal biopsy Diffuse Immune-complex mediated glomerulonephritis, with full house pattern of immune deposit were seen, LN Stage IV (According to ISN/RPS LN Histopathologic Classification).

Patient was treated with four different classes of antihypertensives and Steroids.

After nephrologist opinion patient was started on NIH protocol, IV cyclophosphamide 0.5-1 g/m2 monthly with IV methylprednisolone 0.25-1 g/d for 1-3 days. Currently completed 4 cycles with Oral prednisone 0.5-1 mg/kg/d (max 80 mg/d) was started and now in tapering doses.

Our definition of the primary end point (the primary efficacy renal response) was based on observations that a decrease in the urinary protein level to less than 0.5 to 0.8 g per day is the best predictor of long-term preservation of renal function in patients with kidney disease, whereas a decrease in the eGFR to less than 60 ml per minute per 1.73 m2 is an independent predictor of a poor prognosis. Case 1 achieved the primary end point and increased in eGFR.

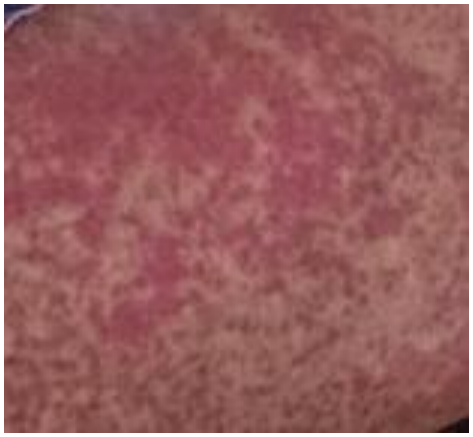

Figure 1: Polymorphous rash seen in case 1.

Case 2: A 21-year-old female patient presented with complaints of puffiness of face, rashes and small joint pain in the past 1 month. Patient had cerebral vein thrombosis during her first post-partum period 3 years ago and was medically managed. She was a mother of one kid, with frequent giddiness and blurring of vision. Patient was pale, facial puffiness was present and blood pressure was 180/114mmHg. On further evaluation, hemoglobin was 6.4gm/dL, Urine routine showing albumin (2+), 12 RBC's, creatinine = 2.4mg/dL, 24hr urine protein = 1800 mg/day. Renal biopsy showed features suggestive of LN Stage IV, Post biopsy she had fever and facial puffiness increased (?Flare). Serology suggestive of Homogenous ANA 3+ and low Complement. She was started on with Steroids and

Cyclophosphamide therapy completed 6 cycles now on maintenance steroids and hydroxychloroquine. She required one class of anti- hypertensives for hypertension management. She also attained the primary end point and showed improvement in eGFR.

Case 3: A 38-year-old female patient presented with complaints of loose stools and vomiting since 2 days. She also had puffiness of face, abdominal distension, reduced urine out-put, malar rash over nose bridge over 4 months period. On examination patient had Pallor, pitting edema was present also reduced breath sounds in the lower lung fields. Patient was febrile on admission with pulse = 120bpm, BP = 198/104mmHg and normal saturation.

In view of loose stools ciprofloxacin and metronidazole was started, she developed edema of lips, swelling of face. No H/o Atopy or allergy in past. Emergency iv hydrocortisone and pheniramine maleate was given. Blood investigation showed Hb= 6gm/dL, Urine routine showed albumin (2+), creatinine = 1.2mg/dL. She developed hematuria during the stay in hospital, urine RBC's were 15-20. Serum creatinine was serially monitored and was in raising trend (1.9mg/dL, 2.4mg/dL) with 24hr urine protein 3056 mg/day. Renal biopsy showed histological features crescents, glomerular lesions suggestive of LN Stage IV with ANA 3+ serology positivity and normal Complement. Patient was treated with Antihypertensives, induction Steroid regimen and completed first cycle of Cyclophosphamide therapy. Later patient had worsening of symptoms like reduced urine output, breathlessness, swelling of limbs and abdominal distension. Chest x ray showed features of pleural effusion and creatinine levels were snowballing. Later patient developed anuria, failed to achieve primary end point. Repeat biopsy was planned but patient denied and was taken for Hemodialysis. Patient was on twice weekly hemodialysis. After 1 month patient lost to follow up and expired.

DISCUSSION

Lupus nephritis (LN) is the commonest manifestation of kidney involvement in SLE. In spite of prompt diagnosis and treatment regimen, a substantial quantity of LN patients turns refractory. We combatted three cases, all of which were newly diagnosed lupus nephritis stage 4 affecting the child bearing age group. Black patients with lupus nephritis are more likely to have a worse prognosis,[4] in our study one out of three progressed to ESRD. At presentation two of three cases had high BP with lower limb edema and facial puffiness which correlates with study reports stating hypertension as the unexceptional presentation.[5] Hypertension has become a major concern because it is associated with early mortality related to the variable atherosclerotic events or renal damage associated with lupus nephritis.

Serology was tested positive for ANA with malignant hypertension at presentation which goes in line with a study conducted by Choe et al. On the other hand, a retrospective analysis of SLE patients by Kaplan et al demonstrated that hypertension developed less frequently in patients with rheumatoid-like arthritis than in patients without persistent arthritis.[6,7]

It is well known that different kidney pathological types of LN respond differentially to drug therapy. But in our study despite of all patients being diagnosed stage 4 and following same treatment regime, response was dissimilar. LN ending into ESRD ranges from 3-19% over 1-5 years. In our study it was as early as 2 months. The most commonly reported independent clinical laboratory predictor for ESRD in LN was high serum creatinine (>1.5 mg/dL) at disease onset, hypocomplementemia; class III, IV and VI LN; higher chronicity index; high systolic blood pressure; older age which was reflected in our study.[8]

Despite aggressive therapy, approximately 60% of patients with LN are refractory to treatment and have poor long-term outcomes. Furthermore, 27 to 66% of patients with lupus nephritis that is in remission have subsequent flares. Thus, reno-protective and anti-inflammatory therapy to prevent flares, and preserve kidney function are indispensable. [9, 10]

This study was conducted in a rural setting, restricting resources and exploring laboratory tests. It was challenging to convince the patient for repeat biopsy, following relapse. We did not assess the causal relationship of the same. This study is not an archetypal study of its own. As renal symptoms can be silent but have severe long-term consequences, the patient experience will be an important consideration in any future research in this area.

CONCLUSION

Despite the reasonable insights into the pathogenesis and molecular targets of disease has extended its spectrum, sizable fraction of population succumbs due to ESRD. Also, cynicism regarding the drug duration therapy, re-biopsy for the confirmation of treatment modification should have a meticulous attitude. India, country of rural population is divested of such emerging therapies and holistic individualized approach to progress with prudence.

Conflict of interest statement: nil.

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