

# NEPHROTIC SYNDROME AS AN INITIAL CLINICAL MANIFESTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

*Jisieike-Onuigbo NN<sup>1</sup>, Onuigbo PC<sup>1</sup>, Unuigbo EI<sup>2</sup>*

1. NAUTH,Nnewi
2. Department of Medicine, University of Benin Teaching Hospital, Benin

## ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology characterized by multi-systemic affectation. Glomerulonephritis is a frequent and important complication of SLE and the presence and extent of kidney involvement greatly influences the long term outcome of this disease. The clinical presentation and course of SLE are variable. Variability is also a feature of renal involvement in SLE. Renal involvement may occur in 25-50% of patients during the early course of their disease and may affect 60-80% of patients followed long term [1, 2].

Thus the evaluation, treatment and prognosis for each patient need to be individualized. We report a case that highlights the fact that renal involvement or lupus nephritis (LN) can be a first presentation in SLE patients and a high index of suspicion is needed in evaluating patients with clinical diagnosis of nephrotic syndrome as seen in this 54-years old female Nigerian.

## CASE REPORT

Mrs. OD, a 54-years old female Nigerian trader, had been diagnosed to have nephrotic syndrome with a histological diagnosis of membranous glomerulopathy. She had been on treatment for nephrotic syndrome for 2 years until presentation to us, when she noticed joint pains, skin rashes and vomiting. Joint pain was generalized involving all the joints of the body and was associated with fever and skin rashes. Skin

rashes were photosensitive and located on the malar regions, the upper and lower limbs. She also had oral ulcers and low grade fever. About the same time she started vomiting and this was initially postprandial, was associated with anorexia, abdominal discomfort and vomitus consisted of freshly eaten food; there was no change in bowel habit or jaundice. She had facial swelling, increased frothiness of urine but no change in urine output, no gross hematuria and no flank pain. She also complained of bilateral leg swelling but had no dyspnea, chest pain or cough. There was no history of non-steroidal anti-inflammatory drugs (NSAID) abuse, use of mercury-containing soaps or creams. She was diagnosed hypertensive a year prior to current illness but she is not a known diabetic patient, had no past history of jaundice, blood transfusion, insect or snake bites. She had been on tablets lisinopril, frusemide, prednisolone, soluble aspirin and hematonic. She denied history of use of traditional medications or herbal preparations. She was 4 years post-menopausal. There was no family history of hypertension, diabetes mellitus or renal disease. She neither smoked nor drank alcohol. Clinical examination revealed an acutely ill looking middle aged woman with fluffy hair, puffy face, afebrile to touch, mildly pale, anicteric with hyperpigmented malar rash, oral ulcers, no finger clubbing hyperpigmented upper and lower limb rashes with bilateral pitting pedal oedema.

She had a pulse rate of 92 beats per minute, blood pressure of 100/60mmHg supine, jugular venous pressure was not elevated; there was no

cardiomegaly or left ventricular hypertrophy, heart sounds 1 and 2 only were heard with no murmur. Chest was clinically clear. Abdominal examination was unremarkable except for ascites. Central nervous system examination was essentially normal. Bedside urinalysis revealed hematuria and 3+ proteinuria.

A clinical diagnosis of SLE with lupus nephritis was made.

Significant results of the investigations done in the patient included a 24-hours urinary protein of 5.3gms/24hours, serum urea and creatinine of 76mg/dL and 1.4mg/dL respectively with an estimated glomerular filtration rate (eGFR) of 47.5ml/min/1.73m<sup>2</sup> using MDRD formula, haematocrit of 28%, erythrocyte sedimentation rate (ESR) of 144 (Westergreen). She had a dyslipidaemia with total cholesterol of 493mg/dl, triglyceride of 228mg/dl, high density lipoprotein-C of 75mg/dl and low density lipoprotein-C of 373mg/dl. Total serum protein was 3.9g/dl, albumin 1.6g/dl, globulin 2.3g/dl with an albumin/globulin ratio of 0.7. Urine microscopy revealed red cell casts. Abdomino-pelvic ultrasound scan showed renal sizes of 10.7cm × 5.5cm for the left and 10.9 × 5.1 for the right with both kidneys showing normal echogenicity and no loss of cortico-medullary differentiation. Viral screening were negative for hepatitis B, C and retrovirus. Antinuclear antibody (ANA) titter and double stranded DNA (dsDNA) assay were not done because of financial constraints

She was commenced on a 3-days course of intravenous methylprednisolone 500mg daily and continued on oral prednisolone 30mg daily, intravenous frusemide 80mg daily, tablets azathioprine 100mg daily, tablets lisinopril 5mg daily, tablets ferrous sulphate 200mg thrice daily for the anaemia and oraldene mouth wash thrice daily. Her protein intake was 1gram /kg/day. Patient improved with above treatment with alleviation of presenting symptoms and improvement in renal function. She was discharged home on her drugs after 3 weeks of in-patient care and is being followed up monthly as an out-patient.

## **DISCUSSION**

SLE is a multi-systemic disease with variable presentations, affecting mostly females with a female to male ratio of 8-13:1. Despite this gender difference in prevalence, incidence of renal disease is the same for both males and females [3-4]. Although young

adults are more affected and 85% of cases are younger than 53 years when diagnosed, there have been reports of older age groups been affected [5]. The index case, a 54-years old lady falls into the latter category. Oduola et al reported a mean age of 26.5 years amongst lupus nephritis patients seen in Ile-Ife Nigeria [6]. SLE is more likely to be associated with severe nephritis in children and less likely so in the elderly [5].

Certain genetic, hormonal and environmental factors have been postulated to influence the course and severity of disease expression but the exact etiology of SLE is unknown.

The features of SLE are variable affecting multiple systems and most of the features are as a result of vasculitis. In 1997, the American Rheumatology Association established certain clinical and laboratory features for diagnosis of SLE and development of 4 out of 11 features over a life time is 96% sensitive and specific for SLE [7]. These features include malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, pleuro-pericarditis, renal disease (proteinuria and/or granular casts), neurologic disorder (epilepsy, psychosis), hematological disorder (hemolytic anemia, leucopenia, thrombocytopenia raised ESR), positive LE cell, anti-ds DNA, ANA. The diagnosis of SLE in this index patient was based on the clinical findings of malar rash, photosensitive skin rashes, oral ulcers, non-erosive arthritis, raised ESR and evidence of renal disease. This patient possibly had other features to support the diagnosis but these could not be ascertained because of lack of facilities in our Centre and the huge finances to do more composite investigations. Antinuclear antibody titre and double-stranded DNA assay could not be done because there were no facilities for these in our Centre and the plan to refer patient out for these serological tests was refused by patient and her family who admitted that such a plan would place an extra unbearable financial burden on them.

Lupus nephritis (LN) is a common presentation of SLE. Renal involvement could present as proteinuria, glomerulonephritis, nephrotic syndrome, interstitial nephritis, tubular disease, thrombotic microangiopathy, vasculitis and patients may present in end-stage renal disease needing renal replacement therapy. Lupus nephritis is commoner in blacks, although the precise roles of biologic,

genetic and socioeconomic factors have not been clearly defined [8].

Cases of renal involvement preceding the clinical manifestation of SLE have not been commonly reported but in a report of more than 50 cases, overt SLE developed months or even decades after the diagnosis of membranous nephropathy. Patients with lupus membranous glomerulopathy can have only renal disease at presentation before other systemic features of SLE develop and at this point they may show no serologic markers of SLE [9-13]. This assertion is supported by Adelowo et al. who have reported that none of the patients in their series fulfilled the ACR criteria for the diagnosis of SLE at initial presentation [14]. In another review, about half of the patients reported had proteinuria and hence renal involvement at diagnosis of SLE [15]. Similar reports have emanated from other parts of Africa. Retrospective studies from South Africa and Abidjan have reported cases of LN at initial diagnosis of SLE while some had LN diagnosed during follow-up of SLE cases [16-19]. Reports are the same in a cohort of European lupus nephritis patients where renal involvement was present in 16% of the cohort with renal involvement increasing to 50% during subsequent follow-up [20]. For this index patient overt SLE features presented 2 years after being followed up as a case of nephrotic syndrome with a histologic diagnosis of membranous nephropathy. The ACR criteria for definition of LN requires interpretation in the context of established or background SLE thus it is possible that an earlier diagnosis of LN was not made in this case because there were no overt clinical signs of SLE and histological techniques involved only light microscopy; if facilities for immunofluorescence and electron microscopy were available, possibly there could have been detection of the diffuse granular deposits of IgG, C3 and sub-epithelial immune deposits typically found in lupus nephritis revised WHO Class V disease [21].

Indeed a high index of suspicion of lupus nephritis must be entertained in adults with nephrotic syndrome especially females although this limitation has been circumvented by the proposed criteria of the Systemic Lupus International Collaborating Clinics whereby biopsy proven LN in the presence of positive serological markers of ANA and anti-dsDNA is diagnostic of SLE even in the absence of other features [22]. From a clinical point of view,

membranous nephropathy in SLE patients is invariably associated with proteinuria. At presentation some 50% have nephrotic syndrome but eventually about 66% may become nephritic. Microscopic haematuria, arterial hypertension and or mild renal insufficiency may be present at onset [23]. The initial clinical picture in our patient was that of nephrotic syndrome which characterizes stage V lupus nephritis disease [21]; it is not surprising that extra-renal manifestations of SLE appeared later. The presenting urinalysis findings of proteinuria, haematuria and urinary casts in this patient clearly define an active case of lupus nephritis. Active lupus nephritis can be defined clinically or pathologically. Clinically, the disease is evaluated by urinalysis, 24-hours urine protein and creatinine excretion, serum creatinine, anti-DNA titers and serum complements. Additionally serum albumin and cholesterol can be used to help characterize nature of lupus nephritis. The index patient had haematuria, proteinuria, red cell casts, low total protein and albumin and deranged lipid levels.

This case report highlights lupus nephritis presenting long before features of SLE became evident. The diagnosis of lupus nephritis was made two years after managing this patient for membranous nephropathy and the diagnosis was mainly based on clinical presentation. A high index of suspicion is required in order to pick up cases of SLE in patients (like the index patient) who present with features of glomerulopathy. Also in spite of poor resources and financial burdens on families who have to pay out of pocket for medical care, all attempts should be made to fully evaluate and manage such patients. This is even more essential in a resource poor health environment so that cases can be diagnosed before they enter advanced stages of chronic kidney disease whose treatment is capital intensive.

## REFERENCES

1. Contreras G, Roth D, Pardo V *et al*: Lupus nephritis: A clinical review for the practicing nephrologists: *ClinNephrol* 2002; 57: 95-107.
2. Cameron JS. Lupus nephritis: *J.Am. Soc. Nephrol* 1999;10: 413-424.
3. Cervera R, Khamashia MA, Font J *et al*. SLE: Clinical and immunologic patterns of disease expression in a cohort of 1000 patients: *Medicine (Baltimore)* 1993; 72: 113.

4. Kaufman LD, Gopez-Reino JJ, Heinicke MK and Gorevic PD. Male lupus. Retrospective analysis of clinical and laboratory Features of 52 patients with a review of literature. *Seminars in Arthritis and Rheumatism*. 1989; 18:189.
5. Schaller J. Lupus in childhood. *Clinical Rheumatism* 1982; 8: 219.
6. Oduola T, Uchegbo OO, Arogundade FA, Bello IS, Akinjole OO and Awioro OG. Prevalence and pattern of lupus erythematosus cell positivity in disease in Ile-Ife, Nigeria. *African journal of biomedical research*. 2005; (vol 8): 135-137.
7. Hochberg MC. Updating the American college of Rheumatology revised criteria for the classification of SLE. *Arthritis and Rheumatism* 1997; 40: 1725.
8. Ballou SP, Khan MA and Kushner I: Clinical features of systemic lupus erythematosus, Difference related to race and age of onset :*Arthritis Rheumatism*. 1982; 25 :55..
9. Shean MA, Hopper J, Biava CG. Membranous lupus nephropathy initially seen as idiopathic membranous nephropathy. Possible diagnostic value of reticular structures. *Archives of Internal Medicine* 1980; 140: 1521-1523.
10. Agnello V. The immunopathogenesis of lupus nephritis. *Advances in Nephrology*. 1976; 6: 119-136.
11. Cameron JS. Pathogenesis and treatment of membranous nephropathy. *Kidney International* 1979; 15: 88-103.
12. Kallen RJ, Lee SK, Aronson AJ and Spargo BH. Idiopathic membranous glomerulopathy preceding the emergence of systemic lupus erythematosus in two children. *Pediatrics* 1977; 90: 72-76.
13. Libit SA, Burke B, Michel AF and Venier RL. Extramembranous glomerulonephritis in childhood: relationship to systemic lupus erythematosus. *Pediatrics* 1976; 88: 394-402
14. Adelowo OO, Umezudike T, Olaosebikan H and Awobusuyi JO. Nephritis as an initial diagnosis of lupus in Nigerian patients. *African Journal of Medicine*. 2014; 43: 99-105.
15. Adelowo OO and Oguntona SA. Pattern of systemic lupus erythematosus among Nigerians. *Clinical Rheumatology*. 2009 June 28 (6): 699-703.
16. Okpechi IG, Ayodele OE, Jones ES *et al.* Outcomes of patients with membranous lupus nephritis in Cape Town South Africa *Nephrology and Dialysis Transplantation* 2012 sept; 29(9): 3509-3515
17. Okpechi IG, Swanepoel CR, Tiffin N, et al. Clinicopathological insights into lupus nephritis I South Africans; A Study of 251 patients. *Lupus* 2012 Aug 21( 9): 1017-1024
18. Olugbenga EA and Okpechi IG, Swanepoel CR. Predictors of poor renal outcomes in patients with biopsy-proven lupus nephritis. *Nephrology* 2010 June 15 (4 ):482-490..
19. Diallo AD, Nochy D, Niamkey E, Yao Beda B, Etiologic aspects of nephrotic syndrome in black African adults in a hospital in Abidjan. *Bulletin of Societe Pathologique Exotique*. 1997; 90(5): 342-345.
20. Cervera R, Khamashia MA, Font J, Sebastiani GD *et al.* Systemic lupus erythematosus, clinical and immunologic patterns of disease expression in a cohort of 1000 patients. The European working party on Systemic lupus erythematosus. *Medicine (Baltimore)* 1993; 72 :113-124.
21. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE and Appel GB. The classification of glomerulonephritis in systemic lupus erythematosus revised. *Journal of American Society of Nephrology* .2004 ;Feb.15 (2): 241-250.
22. Petri M, Orbai AM, Alarcon GS, Gordon C *et al.* Derivation and validation of SLE Collaborating Clinics classification (SLICC) criteria for SLE. *Arthritis Rheumatism*, 2012 Aug 64( 8 ):2677-2688
23. Ponticelli C, Banfi G and Moroni G. Systemic lupus erythematosus (clinical). In: Davison AM, Cameron JS, Grynfeldt JP, Kerr DN, Ritz E, Winearls CG eds. *Oxford Textbook of Clinical Nephrology* (2nd Ed.) Oxford , Oxford University Press 1998; 935-959.