Egyptian Pediatric Association Gazette

CASE REPORT

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Unusual presentation of systemic lupus erythematosus in a male child: a case presentation

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Abstract

Background Systemic lupus erythematosus is an autoimmune connective tissue disorder that is common among women of age group 15–40 years. The novelty in our case is owed to the deceptive demographic characteristics, not only the sex (F > > M) but also of the age profile (common in 15–44 years age group) along with deviation from typical disease presentation of skin rash/arthritis/nephritic syndrome. We aim to emphasize the importance of having a high index of suspicion in any child presenting with nephrotic range proteinuria in order to prevent delay in diagnosis.

Case presentation Eight-year-old boy presented with generalized swelling, proteinuria, hypoalbuminemia and hypertriglyceridemia and was found to be unresponsive to systemic steroid therapy. Further testing revealed low complement levels(C3/C4) along with ANA positive, homogenous pattern (titre ≥ 1:80) and anti-dsDNA positive (titre 229:24) pointing towards the diagnosis of childhood SLE, which was made based on EULAR/ACR criteria. Subsequent renal biopsy was done in order to stage the disease and for initiation of appropriate treatment protocol.

Conclusions SLE is a highly heterogenous disorder in terms of clinical presentation. All patients with steroid resistant nephrotic syndrome should undergo renal biopsy as a part of their workup. This case is a learning opportunity which demonstrates that even in absence of typical disease manifestations and demographic profile, a high index of suspicion will help in rapid diagnosis and prevention of complications. Knowledge about the varied presentations of renal lupus is of utmost importance for the same.

Keywords Systemic lupus erythematosus, Nephrotic syndrome, Steroid resistance, Membranous glomerulonephritis, Focal segmental glomerulosclerosis, Antinuclear antibody

Background

Systemic lupus erythematosus is a clinically heterogenous, remitting and relapsing, autoimmune connective tissue disorder of unknown etiology. Seventy-eight percent of all autoimmune disorders occur in females, including SLE which is generally prevalent in females of childbearing age and is rare in men. Childhood-onset SLE (cSLE) is a rare disease with an incidence of 0.3–0.9 per 100,000 children-years and a prevalence of 3.3–8.8 per 100.000 children. A higher frequency of cSLE is reported in Asians, African American, Hispanics and native Americans. The reported female to male ratio for SLE is 8–15:1; pre-pubertal and post-menopausal ratios are much lower at 2–6:1 and 3–8:1, respectively, suggesting hormonal influences in its pathogenesis [1]. Indian patients have significantly less skin manifestations compared to Chinese and Malaysian patients but have the

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poorest survival rates of 70% compared to 82% of the latter groups [2].

Organ damage is primarily because of immune complex deposition and formation of tissue antibodies against self-antigens. Deficiency of early complement proteins (C1q, C4, C2) leading to decreased clearance of immune complexes has also been attributed.

More complex clinical course of the disease in males can be owed partly to the delayed diagnosis resulting is a greater burden of inflammation and subsequent organ damage over time. The diagnosis of SLE is based on both clinical and immunologic criteria, and antinuclear antibodies (ANA) (90.9%) are the most common serological markers identified.

We report a case of an 8-year-old boy who presented with steroid-resistant nephrotic syndrome with no other alerting manifestations like rash or arthritis pointing towards SLE. Atypical features and high index of suspicion lead to early diagnosis, which was finally clinched upon autoimmune antibody panel screening and renal biopsy.

Case presentation

An 8-year-old boy born of non-consanguineous marriage and second birth by order presented with swelling over face for 15 days. Swelling was first noticed in periorbital region and aggravated on waking up followed by abdominal distention, pedal, and scrotal edema. There was no history of breathlessness, jaundice, headache, blurring of vision, rash, arthritis, photosensitivity, or oliguria. Weight on admission was 25 kg compared to 20 kg baseline and BP was normal. Urine analysis showed urine albumin 4+, urine protein-creatinine ratio 6.9 (normal < 0.2), 2–3 RBC/hpf was normal. Bloodwork showed serum albumin 1.6 g/dl (normal 3.4–5.4 g/dl) and serum triglycerides 293 mg/dl (normal < 150 mg/dl). Diagnosis of nephrotic syndrome was established and patient was started on Tab Prednisolone (60 mg/m^2/day) along with strict monitoring urine albumin, daily weight monitoring and BP monitoring. Child showed a response with decreased oedema, improved urine output and serial monitoring showed an improving trend if urine albumin with a value of 2+ after which child was discharged.

However, within 20 days of discharge, patient yet again came in with complaints of generalised body swelling. Urine albumin was 3+, serum albumin 1.8 g/dl and BP was 134/80 mm Hg, that is in the 95th percentile. In lieu of non-response to steroids and hypertension, investigations were done to rule out secondary causes of nephrotic syndrome. CBC showed normocytic normochromic anaemia, thrombocytopenia, ESR-91, BUN 15 mg/dl, serum creatinine 0.8 mg/dl and urine routine microscopy revealed urine albumin 3+, urine protein-creatinine ratio 6.0 and 25–30 RBC/hpf. C3 and C4 levels were reduced (41/7), and USG abdomen was suggestive of gross ascites. HIV, HBsAg, HCV, malaria antigen, and dengue IgM screening were all negative. Autoimmune antibody panel was sent showing ANA positive, homogenous pattern 160-fold and nucleolar pattern 80-fold and anti-dsDNA positive (titre 229:24), thus confirming the diagnosis of SLE.

Renal biopsy was subsequently planned in order to stage renal lupus which showed membranous glomerulonephritis with secondary focal segmental glomerulosclerosis corresponding to stage V+III (ISPN stage). Modified activity index was 11 (endocapillary hypercellularity 3, neutrophils 1, fibrinoid necrosis 0, hyaline deposits 1, cellulae/fibrocellular crescents 4, interstitial inflammation 2) and modified chronicity index was 3 (total glomerulosclerosis score 1, fibrous crescents 1, tubular atrophy 1, interstitial fibrosis 0) [3]. Anti-phospholipase A2 receptor (PLA2R) antibody was found to be negative suggesting secondary cause of membranous nephropathy.

Figure 1 shows renal biopsy report depicting diffuse thickening of basement membranes and patent capillary

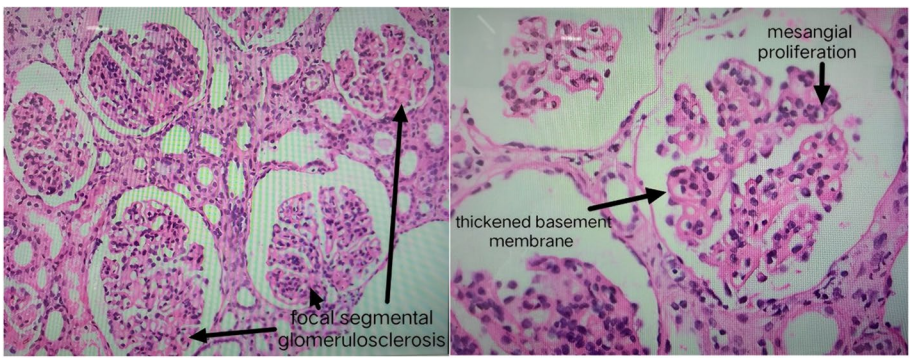

Fig. 1 Histopathology of Renal Biopsy

lumina. Few glomeruli show proliferation of mesangial cells (4–6 per region). One glomerulus reveals sclerosis of few of the loops present near the Bowman's capsule. The interstitium is oedematous and reveals occasional lymphocytes. The tubules show severe hydropic changes and rare tubules contain amorphous material. The vessels are unremarkable. Diagnosis is Membranous Glomerulonephritis with secondary focal segmental glomerulosclerosis.

Diagnosis of SLE was made based on EULAR/ACR criteria requiring positive ANA ≥ 1:80 and a score of 10 points or more (Fig. 2) [4].

According to this criterion, our patient had a score of 26 (fever 2, thrombocytopenia 4, renal biopsy class III or IV lupus nephritis 10, low C3, C4 4, and anti-dsDNA antibody 6).

Henceforth the patient was started on induction therapy for SLE according to American Journal of kidney diseases (AJKD) guidelines with hydroxychloroquine, kidney protective therapy in form of ACE inhibitor for proteinuria and mycophenolate moefitil and prednisolone as immunosuppressive therapy. Amlodipine, metoprolol and sublingual nifedipine were given additionally to control hypertension. Proper follow-up plan was

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

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If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Fig. 2 EULAR/ACR criteria for Diagnosis of SLE

advised every week for a month initially and then every month till 1 year. In each visit CBC, urine protein/creatinine ratio, serum creatinine, C3, C4 levels, and ophthalmologic evaluation (to check for hydroxychloroquine toxicity) was done. On follow-up 5 months after initiation of therapy urine protein-creatinine ratio was 2.8, serum creatinine was 0.5 mg/dl, serum albumin was 3.2 g/dl, C3/C4 were 52/7 mg/dl. Subsequent visit 10 months after initiation of therapy showed urine protein-creatinine ratio 0.8, serum creatinine was 0.4 mg/dl, serum albumin 4.0 g/dl, C3 level 100 mg/dl, C4 level 30 mg/dl. He did not progress to end-stage renal disease and did not require dialysis and is doing fine presently.

Conclusions

SLE is a complex multisystem disease with a multitude of clinical presentations since it affects many organs and systems like kidney, lungs, skin, nervous system, heart and musculoskeletal system. Patients with SLE also frequently experience haematological disparities such as anaemia (80% of SLE patients), leukopenia (50% of SLE patients), or thrombocytopenia (30 to 50% of SLE patients). This poses a challenge for arriving at the correct diagnosis promptly. The four main types of lupus are neonatal and paediatric lupus erythematosus (NLE); discoid lupus erythematosus (DLE); drug-induced lupus (DIL); and systemic lupus erythematosus (SLE).

Most widely accepted explanation for the disease mechanism is failure to uphold self-tolerance. Lupus patients also frequently have low complement levels during active phase of the disease which may revert to normal during remission [5]. Immune response is directed against nuclear material of dying cells which was not properly cleared. This results in upregulation of autoreactive T and B cells and subsequent production of high affinity autoantibodies directed against these nuclear antigens. They form immune complexes, aided in part by decreased clearance of such complexes due to complement deficiency, leading to organ damage.

The most striking part about our case is the deceptive demographic characterises, not only the sex (F > > M) but also of the age profile (common in 15–44 years age group) along with deviation from typical disease presentation of skin rash/arthritis/nephritic syndrome leading to a low index of suspicion. Potential causes of the female predilection for SLE included the effects of estrogen and its hydroxylation, decreased androgen levels, hyperprolactinemia and differences in gonadotropin-releasing hormone (GnRH) signalling mechanisms [6]. Men also tend to have fewer skin manifestations compared to women. However, there is no clear evidence explaining the rarity of the disease in men.

Of note in our patient is the steroid resistant nephrotic syndrome. Given the fact that minimal change disease is the most common cause of nephrotic syndrome in children accounting for nearly 90% cases, patient was reasonably started on steroid treatment. On top of that, only 10–15% patients with lupus develop nephrotic syndrome. Maximum number of lupus patients suffer from Diffuse proliferative glomerulonephritis (DPGN), which has a nephritic syndrome presentation. When renal biopsy was done after an unsuccessful steroid trail, our patient was found to have membranous glomerulonephritis with secondary FSGS suggesting advanced kidney disease. FSGS has a low rate of complete remission (22%) and a higher relapse rate (30–60%). Most patients with FSGS either have a partial remission (55%) or do not respond to therapy at all (22%), with a longer median time required to achieve remission [6]. Undoubtedly, patients with FSGS have worse outcomes, higher rates of hypertension, and acute kidney injury on clinical presentation, with more severe tubulointerstitial involvement on kidney biopsy compared to patients with MCD and mesangial proliferative lesions.

Hence, it is imperative to diagnose SLE in early stages and all patients with SLE should undergo renal biopsy even in absence of clinical abnormalities. Renal lupus itself is highly heterogenous with respect to clinical, laboratory, and biopsy manifestations. Different histopathological appearances on renal biopsy may be found in same patient over time [7].

SLE can present as steroid-resistant nephrotic syndrome without any other pointing disease manifestations. Hence, all patients with resistance to steroids should undergo renal biopsy as a part of their workup. This case is a learning opportunity which demonstrates that even in absence of typical disease manifestations and demographic profile, a high index of suspicion will help prevent delay in diagnosis and complications. Knowledge about the varied presentations of renal lupus is of utmost importance for the same.

Abbreviations

SLE	Systemic lupus erythematosus
cSLE	Childhood-onset Systemic lupus erythematosus
ANA	Antinuclear antibodies
BP	Blood pressure
CBC	Complete blood count
ESR	Erythrocyte sedimentation rate
USG	Ultrasonography
RBC	Red blood cell
BUN	Blood urea nitrogen
HIV	Human immunodeficiency virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
ISPN	Indian society of Pediatric Nephrology
PLA2R	Anti-phospholipase A2 receptor antibody

EULAR/ACR	European League Against Rheumatism/American College of Rheumatology
AJKD	American Journal of kidney diseases
ACE	Angiotensin converting enzyme
NLE	Neonatal and paediatric lupus erythematosus
DLE	Discoid lupus erythematosus
DIL	Drug-induced lupus
GnRH	Gonadotropin-releasing hormone
DPGN	Diffuse proliferative glomerulonephritis
FSGS	Focal segmental glomerulosclerosis
MCD	Minimal change disease

Acknowledgements
Not applicable.

Code availability
Not applicable.

Authors' contributions
KG: writing and conception of manuscript along with its substantive revisions. VDS: design of work and interpretation of data regarding examination findings and investigations of the patient. SS: analysis and revisions in manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission as well as agreed to be personally accountable for author's own contributions. The authors declare that all data were generated in-house and that no paper mill was used.

Funding
No funding was received from any source.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.
Written informed consent for participation including biomedical, clinical, and biometric data was obtained from patient's guardian.

Consent for publication
Written informed consent for publication of this case presentation was obtained from the patient's guardian.

Competing interests
The authors declare that they have no competing interests.

Received: 28 April 2023 Accepted: 13 August 2023
Published online: 04 December 2023

References

1. Baharudin R, Idris NS, Muhammad J, Abdullah WNHW (2022) A case report of male systemic lupus erythematous with antinuclear antibodies-negative: a challenging diagnosis. Korean J Fam Med 43(2):150–154. https://doi.org/10.4082/kjfm.20.0211. Epub 2022 Mar 17. PMID: 35320902; PMCID: PMC8943239
2. Wang F, Wang CL, Tan CT, Manivasagar M (1997) Systemic lupus erythematosus in Malaysia: a study of 539 patients and comparison of prevalence and disease expression in different racial and gender groups. Lupus 6(3):248–253. https://doi.org/10.1177/096120339700600306. PMID: 9104731
3. Choi SE, Fogo AB, Lim BJ (2023) Histologic evaluation of activity and chronicity of lupus nephritis and its clinical significance. Kidney Res Clin Pract 42(2):166–173. https://doi.org/10.23876/j.krcp.22.083. Epub 2023 Mar 15. PMID: 37037479; PMCID: PMC10085727
4. Aringer M, Costenbader K, Daikh D et al (2019) 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis 78:1151–1159
5. Birmingham DJ, Irshaid F, Nagaraja HN, Zou X, Tsao BP, Wu H, Yu CY, Hebert LA, Rovin BH (2010) The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. Lupus 19(11):1272–80. https://doi.org/10.1177/0961203310371154. Epub 2010 Jul 6. PMID: 20605879; PMCID: PMC3086056
6. Dey D, Ofori E, Hutton-Mensah KA, Akutek MLK, Okine R, Amoaba I, Agyemang-Duah K, Kwarko H (2019) Clinical characteristics of males with systemic lupus erythematosus (SLE) in an inception cohort of patients in Ghana. Ghana Med J 53(1):2–7. https://doi.org/10.4314/gmj.v53i1.1. PMID :31138937;PMCID:PMC6527833
7. Lionaki S, Liapis G, Vallianou K, Vergadis C, Boletis I (2020) The various forms of nephrotic syndrome in a patient with systemic lupus erythematosus. Case Rep Nephrol 13(2020):7869216. https://doi.org/10.1155/2020/7869216. PMID:32099705;PMCID:PMC7040396

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