http://jpp.mums.ac.ir

Case Report (Pages: 19532-19539)

Recurrent Hematuria Unveiling Class V Lupus Nephritis in A Child: A Diagnostic Challenge

Neda Ghorbani-khosroshahi [1], Vadood Javadi [2], Fatemeh Nili [3], Hananeh Gholamali-Majdabadi [4], Masoumeh Mohkam [1], * Ghazal Azad [4]

[1] Pediatric Nephrology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[2] Pediatric Rheumatologist, Pediatric Pathology Research Center, Mofid Children's Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[3] Department of Pathology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

[4] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Background: Lupus nephritis (LN) is a serious renal complication of systemic lupus erythematosus (SLE), particularly in the pediatric population. It often presents with persistent hematuria and proteinuria, which can overlap with other glomerular disorders. This case report highlights the diagnostic challenges associated with LN in the presence of nonspecific clinical features.

Case presentation: A 4-year-old boy was admitted for evaluation of persistent recurrent gross hematuria, which continued despite previous surgery for suspected urethral stricture. Initial laboratory tests showed significant hematuria, proteinuria, and mildly elevated inflammatory markers, raising concerns for nephritis. The patient was initially diagnosed with post-streptococcal glomerulonephritis (PSGN), but this was later excluded. A renal biopsy revealed membranous glomerulonephritis (MGN) stage I-II, and further immunological testing, including antinuclear antibodies (ANA) and anti-dsDNA antibodies, led to the final diagnosis of lupus nephritis class V. The findings were consistent with systemic lupus erythematosus, confirming the diagnosis.

Conclusion: We report a pediatric patient diagnosed with Class V lupus nephritis based on renal biopsy, presenting with recurrent hematuria. This case emphasizes the importance of early nephrology consultation, serial testing, and renal biopsy for accurate diagnosis and appropriate management.

Key Words: Case report, Hematuria, Lupus nephritis, Systemic lupus erythematosus.

* Please cite this article as: Ghorbani-khosroshahi N, Javadi V, Nili F, Gholamali-Majdabadi H, Mohkam M, Azad G. Recurrent Hematuria Unveiling Class V Lupus Nephritis in A Child: A Diagnostic Challenge. J Ped Perspect 2025; 13 (6):19532-19539. **DOI: 10.22038/jpp.2025.88440.5558**

Corresponding Author:

Ghazal Azad, Mofid children's hospital, Shariati St, Tehran, Iran. Tel: +98 9120518431; Email: ghazalazad79@gmail.com

1- INTRODUCTION

Hematuria, an alarming and common sign in pediatrics, can indicate various underlying pathogenic conditions (1). Therefore, a thorough medical history, physical examination, and necessary lab tests can help in reaching an appropriate diagnosis. Tea-colored hematuria suggests the oxidation of urinary heme pigments (2). When accompanied by dysmorphic RBCs and proteinuria, it may imply glomerular bleeding. Membranous nephropathy (MN) or membranous glomerulonephritis (MGN), an immune-complex-mediated disease (3) usually presents as nephrotic syndrome or asymptomatic proteinuria (4). It is a rare histologic entity in children and is associated with microscopic hematuria (4). It is histologically defined by a consistent thickening of the glomerular capillary wall linked to the presence of subepithelial immune complex deposits, appearing as granular immunoglobulin (Ig) G deposits under immunofluorescence and as electron-dense deposits under electron microscopy (5). This disease can be either primary or secondary, with the secondary type being more common in children (4). Conditions such as systemic lupus erythematosus (SLE), hepatitis B or C infection, secondary and congenital syphilis, malaria, and Epstein-Barr virus (EBV) infection are some examples of common secondary causes (3).

Renal involvement occurs in 50-75% of pediatric patients with SLE (6), resulting from the deposition of circulating immune complexes (IC) in renal tissue or the formation of IC in situ (7). Lupus nephritis (LN), one of the most severe clinical manifestations of SLE, is more frequent and severe in pediatric patients and has been linked to higher morbidity and mortality rates. As the glomerulus is the most affected structure in individuals with LN, proteinuria of varying degrees, glomerular hematuria, and decreased glomerular filtration with different progressive rates are the main clinical manifestations (8). According to the guidelines established by the Systemic Lupus International Collaborating Clinics (SLICC), renal involvement in patients with SLE is characterized by a 24-hour urinary protein level of ≥ 500 mg (or a urine protein-to-creatinine ratio of ≥ 0.5) or the presence of red blood cell casts in the urine (9). An ideal additional criterion is renal biopsy demonstrating immune-complex-mediated nephritis with complement deposition, along with varying levels of cell damage (10) and high levels of antinuclear antibodies (ANA) and/or increased circulating levels of anti-double- stranded DNA (anti-dsDNA) antibodies (9). Therefore, kidney biopsy is crucial for evaluating tissue involvement, classifying LN, and determining the appropriate treatment plan (8, 11).

In this case, we aim to highlight the clinical manifestations and disease progression, emphasizing the diagnostic challenges and stressing the importance of proper patient follow-up in reaching a final diagnosis. We also discuss the role of kidney biopsy in the diagnosis and management of the patient.

2- CASE PRESENTATION

A 4-year-old boy was admitted to our hospital with complaints of cola-colored urine, along with pain and swelling in the left knee, left wrist, and left elbow. The patient reported intermittent gross hematuria starting five months ago, which was painless, occurred throughout urination, and was not associated with dysuria. The hematuria initially appeared following an episode of fever and upper respiratory tract infection (URI). At that time, due to the presence of parotitis and fever, the patient was diagnosed with mumps, and treatment led to a partial recovery. However, two months later, due to the presence of proteinuria and

persistent hematuria, he was referred to an adult urologist. Despite the presence of proteinuria and hematuria in the urine test, which pointed towards a diagnosis of nephritis, the urologists subjected the patient to surgery for urethral stricture. One month after the surgery, as proteinuria and hematuria did not improve, the patient was referred to the nephrology department of our hospital for further investigation. Four days before admission, the patient developed pain in the left knee, which gradually became accompanied by swelling and effusion that led to limping and an inability to bear weight on the affected joint; one week ago, he also had an episode of fever and URI.

The patient is the third child of consanguineous parents. Family history is significant for psoriasis in his sister and rheumatoid arthritis in his maternal grandmother. The antenatal and perinatal history was unremarkable. On admission, the patient appeared mildly ill and pale, with stable vital signs (blood pressure: 100/80 mmHg). The physical examination was unremarkable except for swelling and effusion in the left knee, wrist, and elbow joints, accompanied by tenderness on palpation and significantly limited range of motion without erythema.

The initial laboratory evaluations showed in table-1. Renal ultrasound revealed a right kidney measuring 57x 30 mm and a left kidney measuring 57x 32 mm with mild fullness.

Since the patient's nephritis symptoms, including hematuria, occurred one week after developing a URI and fever, the initial diagnosis of post-streptococcal glomerulonephritis (PSGN) was made. Based on the history and presence of recurrent hematuria, negative throat culture, low titers of anti-streptococcal antibodies (ASO titer<200), and the patient's serum C3 levels, the diagnosis of PSGN was excluded. Due to the presence of arthritis, ongoing hematuria, and a positive family history of autoimmune diseases, the patient was referred to a pediatric rheumatologist for further evaluation. Based on the aforementioned clinical and laboratory manifestations, he considered the possibility of SLE or acute rheumatic fever (ARF) for the patient. Additional investigations revealed borderline levels of autoantibodies (Table1). These findings raised suspicion of SLE.

Table-1. Initial labratory evaluations.

Urinalysis		**CBC**		**Serology**	
appearance	turbid	**WBC**	9600/mL	**CRP**	7
SG	1.010	**Hb**	9.4 g/dL	**C3**	368(75-135)
color	red	**plt**	285000/mL	**C4**	36(9-36)
protein	3+	**BC**		**CH50**	130(51-150)
Blood	3+	**Alb**	2.7	**viral markers**	negative
WBC	6-8/HPF	**Cr**	0.5	**ANA**	1/40
RBC	many	**Na**	137	**anti-dsDNA**	23.7
24-hour urine test		**K**	4.5	**anti- smith**	7
volume	600ml			**cardiolipin IgG**	2.3
protein	2730mg			**β2 glycoprotein IgG**	3
creatinine	308mg/day				
Dysmorphic RBC	30%				

Table-2. Pre-Biopsy Laboratory Test Results.

Urinalysis		**CBC**		**BC**	
SG	1.032	**WBC**	8.5	**Alb**	2.4
PH	6.7	**Hb**	9.9 g/dL	**total Protein**	4.6
protein	2+	**Plt**	394000	**Ca**	8.9
blood	4+	**ESR**	107	**BUN**	11.2
WBC	2-3/HPF	**Serology**		**Cr**	0/4
RBC	many	**CRP**	1+	**P**	4.9
				Chol	199
				TG	347

Given the chronic history of hematuria (about 5-6months) and persistent proteinuria, a kidney biopsy was performed. Before performing the biopsy, a series of laboratory tests were requested for the patient (Table2). Pathology revealed segmental thickening of glomerular basement membrane (GBM), subepithelial spikes along the GBM, microvillous transformation of visceral foot processes and vacuolization of podocytes consistent with MGN stage I-II (Figures 1(A)-1(F)).

To rule out secondary causes of MGN, further immunology, hematology, and rheumatology evaluations were requested. During this period, while awaiting the consultation results and a final diagnosis, nephrologists prescribed prednisolone 25 mg in the morning and12.5 mg in the evening, Enalapril 2.5 mg daily and pantoprazole 20mg daily to manage the patient's symptoms. The hematologist, in order to rule out malignancy as a common cause of MGN in children, ordered an abdominopelvic CT scan, along with α-fetoprotein, β-HCG, ferritin, TIBC, LDH, Hb electrophoresis, and PBS tests, all of which returned normal results. The rheumatologists, considering the involvement of the upper respiratory tract and kidneys, proposed a diagnosis of ANCA-associated vasculitis for the patient and ordered relevant tests ; (Table3): Immunologists, considering the low IgG and normal IgA and IgM levels, evaluated the titer of iso-hemagglutinins, anti-diphtheria, and anti-tetanus to rule out primary and secondary causes of hypogammaglobulinemia. Based on the laboratory findings (especially progressive elevation of the levels of ANA and Anti-dsDNA antibodies over time), persistent proteinuria, hematuria, and the exclusion of other etiologies, the diagnosis of LN class V was established. Therefore, the patient was referred to the rheumatology department and the treatment regimen changed to hydroxychloroquine 100 mg daily, aspirin80 mg daily, and mycophenolate mofetil (MMF) 750mg daily following the standard protocol for lupus nephritis. The patient is currently under close follow-up with the rheumatology service for monitoring and further management.

Table-3. Laboratory Test Results Related to Rheumatology Consultation.

Serology		**C4**	18	**IgM**	271(24-210)
pANCA	1	**CH50**	87.5	**IgA**	96
cANCA	2.5	**PTT-LA**	41.4	**IgG**	300 (504-1464)
RF	negative	**dRVTTs-PT**	40.4	**IgE**	117(>52)
C3	207	**dRVVTc-PT**	38.2		

Abnormal data have been underlined.

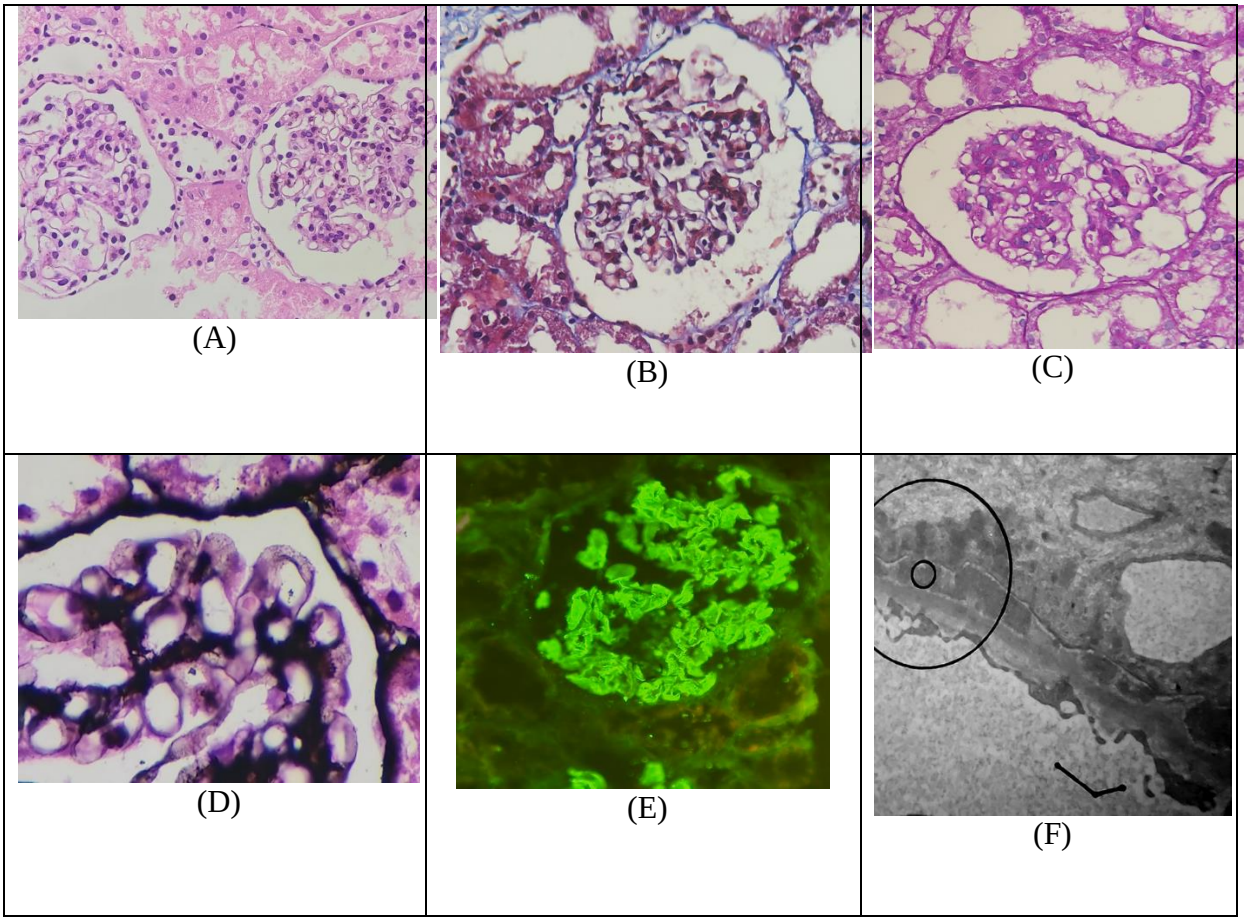

Figure-1: A) Microscopic examination of H&E slides show cortical kidney tissue with mesangial hypercellularity and mild GBM thickening (400X). **B, C)** On Trichrome and PAS stains, mesangial hypercellularity and mild segmental GBM thickening are also noted (400X). **D)** Methemanine Jone's stain revealed subepithelial holes along the GBM (arrow) (1000X). **E)** On immunofluorescence study, 2+ fine granular deposition of IgG is seen. **F)** Electron microscopy shows subepithelial electron dense immune deposits (arrows)(11000X).

3- DISCUSSION

This case involves a 4-year-old boy with recurrent gross hematuria, nephrotic-range proteinuria, and arthritis, who was eventually diagnosed with class V LN. The incorrect surgical intervention for suspected urethral stricture and the initial diagnosis of PSGN delayed the correct diagnosis. A renal biopsy revealed MGN, confirming class V LN, which was later confirmed by progressive serological markers for SLE. The patient responded well to treatment with prednisolone, mycophenolate mofetil, hydroxychloroquine, and aspirin, following standard protocols for lupus nephritis.

A key challenge was the initial misdiagnosis of a urethral stricture as the cause of hematuria. While urethral pathology can explain hematuria, it does not account for concurrent proteinuria, which is a hallmark of glomerular disease. The continued presence of proteinuria, hematuria, and the excretion of dysmorphic red blood cells post-surgery suggest an underlying glomerular pathology rather than a structural issue.

PSGN is a leading cause of glomerulonephritis in children, often developing after infections (12). The persistent hematuria and proteinuria following an URI initially raised concerns for post-infectious glomerulonephritis,

with PSGN as a likely cause, as it is a common etiology of nephritic symptoms in children (12). However, PSGN typically presents with transient proteinuria, low C3 levels, and positive ASO titers (12). Persistent proteinuria, normal C3 levels, and negative ASO titers suggest an alternative diagnosis.

Since MGN can be primary or secondary, determining the underlying etiology was essential. In pediatric patients, secondary MGN is commonly linked to SLE but can also result from infections such as hepatitis B and C, congenital and secondary syphilis, malaria, and EBV infection (13).

While new-onset arthritis and a family history of autoimmune disease raised concern for an autoimmune etiology, the diagnosis was complicated by the absence of early features of SLE. As immunological markers indicating SLE, ANA is a highly sensitive but nonspecific marker for SLE, while anti-dsDNA antibodies exhibit greater specificity and are closely linked to disease activity and lupus nephritis (14). In our case, initial lab tests showed borderline ANA and anti-dsDNA levels, making the diagnosis uncertain; but serial testing later revealed rising autoantibody titers, indicating an evolving autoimmune process. This demonstrates the importance of serial evaluation of the patient, even with primary negative results. Additionally, the variability of ANA and anti-dsDNA antibody levels, particularly in early stages, may contribute to diagnostic challenges in pediatric lupus nephritis, as serological markers are not always definitive (15).

The SLICC criteria allow for the classification of SLE in patients who present with biopsy-confirmed LN accompanied by positive ANA or anti-dsDNA antibodies, a provision that is especially significant in pediatric cases with primary renal involvement (9). Ultimately, the combination of LN class V on renal biopsy and serological autoantibodies confirmed SLE. Delayed diagnosis is a well-documented challenge in pediatric LN, reinforcing the need for early biopsy when hematuria and proteinuria persist beyond three months.

LN is a prevalent manifestation of SLE, associated with considerable morbidity and mortality, frequently presenting in the early stages of the disease (16). According to the ISN/RPS classification, lupus nephritis is histologically categorized based on the location of immune complex deposition: mesangial in Classes I and II, subendothelial in Classes III and IV, subepithelial in Class V, and glomerulosclerosis in Class VI (17). Class V LN is relatively uncommon in pediatric SLE, accounting for approximately 13.9% of cases (16). Membranous lupus nephritis (MLN), also known as Class V LN, is characterized by the extensive deposition of immune complexes within the glomerular subepithelial space (18). Immune complexes either pass through the glomerular basement membrane or form locally against podocyte antigens, activating the complement system, which leads to basement membrane thickening and podocyte destabilization (19). In this patient, the renal biopsy revealed segmental thickening of the GBM and subepithelial spikes, consistent with membranous glomerulonephritis, which further supported the diagnosis of Class V LN. This pathology leads to proteinuria, which can also occasionally present in children as microscopic and, in rare cases, macroscopic hematuria, nephrotic syndrome, hypertension, and renal dysfunction (13).

The standard treatment for SLE includes the use of corticosteroids, antimalarials, and disease-modifying anti-rheumatic drugs (DMARDS) and/or immunosuppressants (20). Mycophenolate mofetil is also incorporated due to its proven efficacy as an immunosuppressive

agent, particularly in managing nephrotic-range proteinuria (19). To reduce the likelihood of treatment failure and control disease progression in lupus nephritis, hydroxychloroquine is included due to its immunomodulatory effects (18). The patient underwent the same treatment regimen, which effectively managed symptoms and achieved disease stabilization.

A limitation of this case was the delay in diagnosis due to PSGN and urethral stricture, which underscores the diagnostic challenges associated with pediatric lupus nephritis with atypical presentations. Variability in early serological markers also complicated the diagnosis, reflecting a challenge in the early identification of autoimmune diseases. Furthermore, genetic and biomarker analyses were not performed, which could have provided additional insights into disease predisposition. Future studies are necessary to improve early recognition and management strategies for pediatric lupus nephritis.

4- CONCLUSION

In conclusion, we are reporting a case of Class V lupus nephritis, that emphasizes the diagnostic challenge in a pediatric patient with nonspecific early findings and negative autoimmune markers. The progression of serological markers over time highlights the importance of serial testing in suspected cases. Early nephrology consultation is crucial to prevent diagnostic delays and ensure appropriate management, as renal biopsy plays a key role in confirming the diagnosis, reinforcing its value in unclear nephropathies.

5- AKNOWLEDGMENTS

The authors thank all patients who participated in the study. They would also like to express their gratitude to the staff of the Pediatric Nephrology Research Center at Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

6-ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Shahid Beheshti University of Medical Sciences.

7-CONFLICTS OF INTEREST

The authors have declared that no conflict of interest exists.

8- INFORMED CONSENT

Informed consent was obtained from the patient described in this case report.

9- REFERENCES

1. Bignall OR, Dixon BP. Management of hematuria in children. Current treatment options in pediatrics. 2018 Sep;4(3):333-49.

2. Viteri B, Reid-Adam J. Hematuria and proteinuria in children. Pediatrics in review. 2018 Dec 1;39(12):573-87.

3. Ponticelli C. Membranous nephropathy. Journal of nephrology. 2007 May 1;20(3):268-87.

4. Valentini RP, Mattoo TK, Kapur G, Imam A. Membranous glomerulonephritis: treatment response and outcome in children. Pediatric Nephrology. 2009 Feb;24(2):301-8.

5. Kleinknecht C, Levy M, Gagnadoux MF, Habib R. Membranous glomerulonephritis with extra-renal disorders in children. Medicine (Baltimore). 1979;58(3):219-28.

6. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. Pediatric Clinics of North America. 2012 Apr;59(2):345.

7. Anders HJ, Fogo AB. Immunopathology of lupus nephritis. InSeminars in immunopathology 2014 Jul (Vol. 36, No.

4, pp. 443-459). Berlin/Heidelberg: Springer Berlin Heidelberg.

8. Bennett M, Brunner HI. Biomarkers and updates on pediatrics lupus nephritis. Rheumatic diseases clinics of North America. 2013 Jul 16;39(4):833.

9. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis & Rheumatism. 2012 Aug;64(8):2677-86.

10. Hahn BH, Mcmahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis care & research. 2012 Jun;64(6):797-808.

11. Sinha R, Raut S. Pediatric lupus nephritis: Management update. World journal of nephrology. 2014 May 6;3(2):16.

12. Kambham N. Postinfectious glomerulonephritis. Advances in anatomic pathology. 2012 Sep 1;19(5):338-47.

13. Menon S, Valentini RP. Membranous nephropathy in children: clinical presentation and therapeutic approach. Pediatric Nephrology. 2010 Aug;25(8):1419-28.

14. Ostrov BE. Reliability and reproducibility of antinuclear antibody testing in pediatric rheumatology practice. Frontiers in medicine. 2023 Jan 9;9:1071115.

15. Alsharif AA, Almutairi AM, Basahl EB, Alshathri AA, Kari JA, Shalaby MA, et al. Juvenile lupus-like with negative serology: a clinical dilemma and diagnostic challenge. Journal of Rheumatic Diseases. 2025 Jan 1;32(1):57-62.

16. Vazzana KM, Daga A, Goilav B, Ogbu EA, Okamura DM, Park C, et al. Principles of pediatric lupus nephritis in a prospective contemporary multi-center cohort. Lupus. 2021 Sep;30(10):1660-70.

17. Pennesi M, Benvenuto S. Lupus nephritis in children: novel perspectives. Medicina. 2023 Oct 16;59(10):1841.

18. Almaani S, Parikh SV. Membranous lupus nephritis: a clinical review. Advances in Chronic Kidney Disease. 2019 Sep 1;26(5):393-403.

19. Pinheiro SV, Dias RF, Fabiano RC, Araujo SD, Silva AC. Pediatric lupus nephritis. Brazilian Journal of Nephrology. 2018 Nov 14;41(2):252-65.

20. Tunnicliffe DJ, Singh-Grewal D, Kim S, Craig JC, Tong A. Diagnosis, monitoring, and treatment of systemic lupus erythematosus: a systematic review of clinical practice guidelines. Arthritis care & research. 2015 Oct;67(10):1440-52.