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A Case Report

Case Based Discussion: Lupus Nephritis Atypical Case Presentation in A 12 Years Old Female

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Abstract-

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can cause multi-organ involvement. Lupus nephritis is one of the most serious complications of SLE, affecting up to 60% of patients with SLE. While lupus nephritis is well known to clinicians, some pediatric cases may present with atypical symptoms, which can make it challenging to diagnose and manage. Hera we report a case a 12-year-old girl with an atypical presentation of lupus nephritis. She presented with fever, cough, vomiting, foamy urine, and swelling around her eyes. Lab results showed grade 3 renal impairment and positive ANA and anti-histone antibodies. A renal biopsy confirmed lupus nephritis. The patient was managed with hemodialysis and pulse steroids and cyclophosphamide, leading to significant improvement in her condition. We present a case report of a pediatric patient who presented with atypical symptoms of lupus nephritis, highlighting the diagnostic challenges and management strategies of this condition.

Conclusion: In atypical Lupus nephritis the need for prompt diagnosis and appropriate management is essential to improve patient outcomes and prevent complications.

Keywords: Systemic Lupus Erythematous (SLE), Lupus Nephritis (LN), Pediatrics.Inflammation. Hemodialysis.Autoimmne Disease

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Introduction:

Lupus nephritis is an inflammatory disease of the kidneys caused by an autoimmune disease known as systemic lupus erythematosus[3] It is one type of glomerulonephritis in which glomeruli are inflamed and is secondary to SLE and has a different pattern and outcome from conditions with a primary cause originating in the kidney.[4][2] The diagnosis of lupus nephritis done by blood tests, urinalysis, X-rays, ultrasound scans and a kidney biopsy. On urinalysis, a nephritic picture is seen and red blood cell casts, red blood cells and proteinuria is present.

Classification : The World Health Organization in 1982

has classified lupus nephritis into five stages based on the biopsy and revised it in 1995.[5][6]. Class IV disease (Diffuse proliferative nephritis) is the most severe, and the most common subtype. Class VI (advanced sclerosing lupus nephritis) is a final class which is thought to be due to the chronic interferon exposure.[7] :

Class I Minimal mesangial glomerulonephritis 5% Normal appearance Mesangial deposits are visible under an electron microscope Kidney failure is very rare in this form.[8] Normal urinalysis.[9]

Class ii: Mesangial proliferative glomerulonephritis 20% Mesangial hypercellularity and matrix expansion. Microscopic haematuria with or without proteinuria may be seen. Hypertension, nephrotic syndrome, and acute kidney injury are very rare at this stage.[9] Responds to high doses of corticosteroids

Class III : Focal glomerulonephritis 25% Sclerotic lesions involving less than 50% of the glomeruli, which can be segmental or global, and active or chronic, with endocapillary or extracapillary proliferative lesions.

Subendothelial deposits are noted, and some mesangial changes may be present Immunofluorescence reveals positively for IgG, IgA, IgM, C3, and C1q. Clinically, haematuria and proteinuria are present, with or without nephrotic syndrome, hypertension, and elevated serum creatinine.[9] successfully responds to high doses of corticosteroids.

Class IV : Diffuse proliferative nephritis 40% More than 50% of glomeruli are involved. Lesions can be segmental or global, and active or chronic, with endocapillary or extracapillary proliferative lesions. Under electron microscopy, subendothelial deposits are noted, and some mesangial changes may be present. Clinically, haematuria and proteinuria are present, frequently with nephrotic syndrome, hypertension, hypocomplementemia, elevated anti-dsDNA titres and elevated serum creatinine.[9] Kidney failure is common.[8] Corticosteroids and immunosuppressant drugs.

Class V: Membranous glomerulonephritis 10%.Diffuse thickening of the glomerular capillary wall (segmentally or globally), with diffuse membrane thickening, and subepithelial deposits seen under the electron microscope. Signs of nephrotic syndrome. Microscopic haematuria and hypertension may also be seen. Can also lead to thrombotic complications such as renal vein thromboses or pulmonary emboli.[9] Kidney failure is uncommon.[8]

Class VI: Advanced sclerosing lupus nephritis.[10] Global sclerosis involving more than 90% of glomeruli, and represents healing of prior inflammatory injury. Active glomerulonephritis is not usually present. This stage is characterised by slowly progressive kidney dysfunction, with relatively bland urine sediment. Response to immunotherapy is usually poor.

A tubuloreticular inclusion within capillary endothelial cells is also characteristic of lupus nephritis and can be seen under an electron microscope in all stages. It is not diagnostic however, as it exists in other conditions such as HIV infection.[11]

Signs and symptoms: General symptoms of lupus nephritis include[2][12]:Fever,Edema, High blood pressure,Joint pain, Muscle pain, Malar rash, Foamy urine.

The cause of lupus nephritis, a genetic predisposition, plays a significant role in lupus nephritis. Multiple genes, many of which are not yet identified, mediate this genetic predisposition.[10][13]

The immune system protects the human body from infection, and with immune system problems it cannot distinguish between harmful and healthy substances. Lupus nephritis affects approximately 3 out of 10,000 people.[3]

Pathophysiology: of lupus nephritis has autoimmunity contributing significantly. Autoantibodies direct themselves against nuclear elements. The characteristics of nephritogenic autoantibodies (lupus nephritis) are antigen specificity directed at nucleosome, high affinity autoantibodies form intravascular immune complexes,

and autoantibodies of certain isotypes activate complement.[10] **HISTORY :**Patients with active lupus nephritis often have other symptoms of active systemic lupus erythematosus (SLE), including fatigue, fever, rash, arthritis, serositis, or central nervous system (CNS) disease. These are more common with focal and diffuse lupus nephritis. [29].Some patients have asymptomatic lupus nephritis; however, during regular follow-up, laboratory abnormalities such as elevated serum creatinine levels, low albumin levels, or urinary protein or sediment suggests active lupus nephritis. This is more typical of mesangial or membranous lupus nephritis.Symptoms related to active nephritis may include peripheral edema secondary to hypertension or hypoalbuminemia. Extreme peripheral edema is more common in persons with diffuse or membranous lupus nephritis, as these renal lesions are commonly associated with heavy proteinuria. [24]. Other symptoms directly related to hypertension that are commonly associated with diffuse lupus nephritis include headache, dizziness, visual disturbances, and signs of cardiac decompensation.

Physical Examination: WIith focal and diffuse lupus nephritis, the physical examination may reveal evidence of generalized active SLE with the presence of a rash, oral or nasal ulcers, synovitis, or serositis. Signs of active nephritis are also common. With active lupus nephritis, patients have hypertension, peripheral edema, and, occasionally, cardiac decompensation.With membranous lupus nephritis, signs of an isolated nephrotic syndrome are common. These include peripheral edema, ascites, and pleural and pericardial effusions without hypertension.

Diagnostic Concideration: Lupus nephritis usually arises within 5 years of diagnosis of systemic lupus erythematosus (SLE); however, renal failure rarely occurs before American College of Rheumatology criteria for classification are met. Besides the conditions listed in the differential diagnosis, other problems to be considered include Mesangial glomerulonephritis, Glomerulosclerosis.

Diffential Diagnosis: Chronic Glomerulonephritis, Diffuse Proliferative Glomerulonephritis Granulomatosis with Polyangiitis (GPA, formerly Wegener Granulomatosis), Membranous Glomerulonephritis, Polyarteritis Nodosa, Rapidly Progressive Glomerulonephritis

Approach: Evaluating kidney function in patients with systemic lupus erythematosus (SLE) to detect any kidney involvement early is important because early detection and treatment can significantly improve renal outcome. [24] Kidney biopsy should be considered in any patient with SLE who has clinical or laboratory evidence of active nephritis, especially upon the first episode of nephritis. [24, 30]. Lupus nephritis is staged according to the classification revised by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2013. This classification is based on light microscopy, immunofluorescence, and electron microscopy findings from kidney biopsy specimens.

Laboratory tests to evaluate kidney function in SLE patients includes: Blood urea nitrogen (BUN) testing: Serum creatinine, Urinalysis (to check for protein, red blood cells [RBCs], and cellular casts). A spot urine test for creatinine and protein concentration (normal creatinine excretion is 1000 mg/24 h/1.75 m2; normal protein excretion is 150-200 mg/24 h/1.75 m2; normal urinary protein-to-creatinine ratio is < 0.2) A 24-hour urine test for creatinine clearance and protein excretION. In an international study, Smith and colleagues reported that a panel of novel urinary biomarkers can accurately identify active lupus nephritis in children. [31] These authors concluded that the optimal biomarker panel would include: Alpha-1-acid glycoprotein (AGP), Ceruloplasmin, Lipocalin-like prostaglandin D synthase (LPGDS). Transferrin (area under the curve [AUC] 0.920)**.Laboratory Tests** for SLE Disease Activity: SLE disease activity can be evaluated by assessing antibodies to double-stranded DNA (dsDNA), complement (C3, C4, and CH50), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels.The CRP level is

generally not elevated in patients with SLE, even with active disease, unless the patient has significant arthritis or infection. [24] Generally, elevated ESR and anti-dsDNA and depressed C3 and C4 levels are associated with active nephritis, especially focal and diffuse lupus nephritis. Clinically relevant lupus nephritis is associated with a 30% decrease in creatinine clearance, proteinuria of greater than 1000 mg/d, and/or renal biopsy findings indicating active lupus nephritis. Anti-nucleosome antibodies appear early in the course of the autoimmune response in SLE, they have high sensitivity and specificity for a diagnosis of SLE, and the titers correlate with disease activity. [32, 33, 34] Anti-C1q antibodies are associated with lupus nephritis; higher titers correlate with active renal disease. [35, 36]. Anti-C1q antibodies have a sensitivity of 44-100% and a specificity of 70-92% in active renal disease (SLE); in combination with low C3 and C4 levels, these may be the predictors of renal flares in patients with SLE. [37] Although anti-DNA antibodies were more sensitive than anti-C1q antibodies for active lupus nephritis (75% vs 53%, respectively), anti-C1q antibodies were more specific (84% vs 49%, respectively); the negative predictive value of negative anti-DNA and anti-C1q antibodies for active lupus nephritis was 91%. [38

Kidney Biopsy: Kidney biopsy may be useful in patients with recurrent episodes of nephritis, depending on the clinical circumstances. By revealing the histologic pattern and stage of disease (activity and chronicity), kidney biopsy is useful in determining prognosis and treatment. Findings from a thorough clinical and laboratory evaluation can be used to predict the histologic type of lupus nephritis in approximately 70-80% of patients; however, this is not accurate enough, in view of the toxicity of some of the treatment protocols. A good rule is to perform a kidney biopsy if the findings will potentially alter patient management. If a particular patient has other manifestations of SLE (eg, severe central nervous system [CNS] or hematologic involvement) and will be treated with cyclophosphamide, biopsy may not be necessary but should still be considered because it may help predict renal outcome. Sampling error can occur during a kidney biopsy. Thus, the results of the biopsy should always be evaluated for consistency with the clinical and laboratory presentation of the patient.

In addition to the pathologic classification, activity and chronicity indices are scored pathologically and predict the renal prognosis—that is, the progression of renal disease (see Table 3 below). The activity index reflects the state of active inflammation observed at biopsy, which may be reversible with medical therapy. The chronicity index reflects the amount of fibrosis and scarring, which are unlikely to respond to therapy. Renal lesions with a high activity index are more likely to respond to aggressive therapy, whereas renal lesions with high chronicity are not.

Activity Index

Chronicity Index

• Endocapillary hypercellularity with or without leukocyte infiltration; luminal reduction

• Karyorrhexis

• Fibrinoid necrosis

• Rupture of glomerular basement membrane

• Cellular or fibrocellular crescents

• Subendothelial deposits on light microscopy

• Intraluminal immune aggregates

• Glomerular sclerosis; segmental, global

• Fibrous adhesion

• Fibrous crescents

Treatment: The principal goal of therapy in lupus nephritis is to normalize kidney function or, at least, to prevent the progressive loss of kidney function. Therapy differs depending on the pathologic lesion. [24, 42] It is important to treat extrarenal manifestations and other variables that may affect the kidneys. Patients should be

on hydroxychloroquine if possible, as data suggest that this improves outcomes in patients who have lupus nephritis, in addition to reducing lupus-related flares and disease damage accrual. [43]

Corticosteroid therapy should be instituted if the patient has clinically significant renal disease. Use immunosuppressive agents, particularly cyclophosphamide, azathioprine, or mycophenolate mofetil, if the patient has aggressive proliferative renal lesions, as they improve the renal outcome. Immunosuppressives can also be used if the patient has an inadequate response or excessive sensitivity to corticosteroids. [42, 44, 45, 39]

Calcineurin inhibitors, especially tacrolimus, have demonstrated benefit in lupus nephritis. However, most studies have been limited to Asian patients, and further research is required on long-term benefits and disadvantages. [46, 47, 48, 39] The calcineurin inhibitor voclosporin is the first oral therapy approved by the US Food and Drug Administration (FDA) for lupus nephritis in conjunction with immunosuppressive treatment. [49]

Leflunomide, a pyrimidine synthesis inhibitor that is approved by the FDA for use in rheumatoid arthritis, has shown efficacy in proliferative lupus nephritis in Chinese patients. [50, 51] More recent evidence indicates that leflunomide may also have some efficacy in lupus nephritis in patients of other ethnic groups.

Treat hypertension aggressively. On the basis of beneficial effects in other nephropathies, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been routinely used to treat proteinuria in lupus nephritis.

Alter the diet according to the presence of hypertension, hyperlipidemia, and renal insufficiency. Restrict fat intake or use lipid-lowering therapy such as statins for hyperlipidemia secondary to nephrotic syndrome. Restrict protein intake if renal function is significantly impaired.

Administer calcium supplementation to prevent osteoporosis if the patient is on long-term corticosteroid therapy, and consider adding a bisphosphonate (depending on renal function).

Avoid drugs that affect renal function, including nonsteroidal anti-inflammatory drugs (NSAIDs), especially in patients with elevated creatinine levels. Nonacetylated salicylates can be used to safely treat inflammatory symptoms in patients with renal disease.

Patients with active lupus nephritis should avoid pregnancy, because it may worsen their renal disease and because certain medications used in the treatment may be teratogenic. [52] In women who desire pregnancy, the following approach is advised [53] :

A preconception evaluation to establish and inform the patient about pregnancy risks

Plan for pregnancy during inactive lupus nephritis

Keep the lupus nephritis inactive with the lowest possible dosage of allowed drugs

Treat known risk factors (hypertension, antiphospholipid and antibodies)

Monitor closely during and after pregnancy to rapidly identify and treat SLE flares and obstetric complications

Patients with end-stage renal disease (ESRD), sclerosis, and a high chronicity index based on renal biopsy findings are unlikely to respond to aggressive therapy. In these cases, focus therapy on extrarenal manifestations of systemic lupus erythematosus (SLE) and on possible kidney transplantation.

Pharmacotherapy for Lupus Nephritis Based on Stage

Classes I and II

Minimal mesangial (class I) lupus nephritis requires no specific therapy. [24]

Mesangial proliferative (class II) lupus nephritis may require treatment if proteinuria is greater than 1000 mg/day. Consider prednisone in low-to-moderate doses (ie, 20-40 mg/day) for 1-3 months, with subsequent

taper.

Classes III and IV

Patients with either focal (class III) or diffuse (class IV) lupus nephritis are at high risk of progressing to ESRD and thus require aggressive therapy.

Administer prednisone 1 mg/kg/day for at least 4 weeks, depending on clinical response. Then, taper it gradually to a daily maintenance dose of 5-10 mg/day for approximately 2 years. In acutely ill patients, intravenous (IV) methylprednisolone at a dosage of up to 1000 mg/day for 3 days may be used to initiate corticosteroid therapy.

In patients who do not respond to corticosteroids alone, who have unacceptable toxicity to corticosteroids, who have worsening renal function, who have severe proliferative lesions, or who have evidence of sclerosis on renal biopsy specimens, use immunosuppressive drugs in addition to corticosteroids.

Both cyclophosphamide and azathioprine are effective in proliferative lupus nephritis, although cyclophosphamide is apparently more effective in preventing progression to ESRD. Mycophenolate mofetil has been shown to be at least as effective as intravenous (IV) cyclophosphamide, with less toxicity, in patients with focal or diffuse lupus nephritis who have stable renal function. [54, 55] It may be used alone [54, 55] or sequentially after a 6-month course of IV cyclophosphamide. [56]

Administer IV cyclophosphamide monthly for 6 months and every 2-3 months thereafter, depending on clinical response. The usual duration of therapy is 2-2.5 years. Reduce the dose if the creatinine clearance is less than 30 mL/min. Adjust the dose depending on the hematologic response. [57, 58] The gonadotropin-releasing hormone analog leuprolide acetate has been shown to protect against ovarian failure. [59]

Shorter courses and lower doses of IV cyclophosphamide are used currently, which reduces the overall toxicity of cyclophosphamide. Sequential therapy with monthly IV cyclophosphamide for 6 months followed by mycophenolate mofetil [56] or Euro-Lupus dosing, which is 500 mg of IV cyclophosphamide every 2 weeks for 3 months followed by azathioprine. [60] Both of those regimens have been shown to be effective in proliferative lupus nephritis.

Appel et al studied 370 patients with lupus nephritis in a randomized open-label study and found no significant difference in clinical improvement was observed with mycophenolate mofetil compared with IV cyclophosphamide. [61] The study included induction and maintenance therapy, and both study groups received prednisone.

Azathioprine can also be used as a second-line agent, with dose adjustments depending on hematologic response.

Mycophenolate mofetil was found to be superior to azathioprine in maintaining control and preventing relapses of lupus nephritis in patients who have responded to induction therapy. [62]

In a 10-year follow-up of the MAINTAIN Nephritis Trial, which compared azathioprine and mycophenolate mofetil as maintenance therapy of proliferative lupus nephritis, Tamirou and colleagues found that the two treatments resulted in similar outcomes. Two deaths and one case of end-stage renal disease developed in the azathioprine group, versus three deaths and three cases of end-stage renal disease in the mycophenolate mofetil group. [63]

Class V: Patients with membranous lupus nephritis are generally treated with prednisone for 1-3 months, followed by tapering for 1-2 years if a response occurs. If no response occurs, the drug is discontinued. Immunosuppressive drugs are generally not used unless renal function worsens or a proliferative component is present on kidney biopsy specimens. Some clinical evidence indicates that azathioprine, cyclophosphamide, cyclosporine, and chlorambucil are effective in reducing

proteinuria. Mycophenolate mofetil may also be effective. European guidelines recommend mycophenolate mofetil as first choice for class V disease, with calcineurin inhibitors (especially tacrolimus) as alternative options. [64]

In a study of membranous lupus nephritis, 38 patients were treated with corticosteroids and azathioprine; after 12 months of treatment, 67% of patients had a complete remission and 22% had a partial remission, with only 11% resistant to treatment. [65] Long-term follow-up of 12 years showed 19 episodes of renal flares. Retreatment with corticosteroids and azathioprine showed similar responses.

New Therapies

Belimumab (Benlysta) is an anti–B-lymphocyte stimulator [BLyS] monoclonal antibody). [66] It is approved by the US Food and Drug Administration (FDA) to treat adults with active lupus nephritis who are receiving standard therapy.

Efficacy was based on a phase III, BLISS-LN trial that randomized patients (n=448) with lupus nephritis—including patients with focal (class III), diffuse (class IV), and membranous (class V) lupus nephritis—to receive either belimumab or placebo with standard therapy. The Primary Efficacy Renal Response (PERR) was significantly higher in the belimumab arm than the placebo arm at Week 52 (47% versus 35%, respectively) and Week 104 (43% versus 32%, respectively). Patients in the belimumab group also had improved outcomes, including complete renal response (CRR) over a 2-year period. [67]

Voclosporin (Lupkynis), a calcineurin inhibitor, is the first FDA-approved oral therapy used in combination with immunosuppressive therapy for lupus nephritis. Approval was based on data from 2 clinical trials, the phase III AURORA trial and the phase II AURA-LV trial. Both studies enrolled patients with lupus nephritis of Class III or IV (alone or in combination with Class V) or pure Class V.

The AURA-LV study randomized patients to placebo or an induction regimen that combined voclosporin with mycophenolate mofetil and low-dose oral corticosteroids. CRR at week 24 was achieved by 32.6% in the low-dose voclosporin group, 27.3% in the high-dose voclosporin group, and 19.3% in the placebo group. The CRR rate in the low-dose and high-dose voclosporin groups was higher compared with placebo at 48 weeks. [68]

The phase III AURORA trial compared the efficacy and safety of voclosporin (23.7 mg twice daily) with placebo in combination with mycophenolate and low-dose oral corticosteroids. At 1 year, the renal response rate was higher in the voclosporin group than in the placebo group (40.8% vs 22.5%; odds ratio, 2.65; $P < 0.001$). In addition, the median time to the achievement of a urine protein-to-creatinine ratio below 0.5 mg/mg was significantly and clinically better with voclosporin than with placebo (169 vs 372 days; log rank $P < 0.001$). [69]

Investigational Therapies for Lupus Nephritis and SLE:**Rituximab:** B-lymphocytes play a pivotal role in the pathogenesis of SLE, which makes rituximab, a B-lymphocyte–depleting therapy, an attractive therapeutic option in SLE and lupus nephritis. [70] In meta-analyses, rituximab has proved effective, especially in lupus nephritis that is refractory to standard therapy. [71] Most of the studies have been retrospective, but one prospective observational single-center cohort study demonstrated the efficacy of a steroid-sparing regimen of rituximab and mycophenolate mofetil for lupus nephritis. For the study, Condon et al treated 50 consecutive patients 2 doses of rituximab (1 g) and methylprednisolone (500 mg) on days 1 and 15, and mycophenolate mofetil for maintenance therapy. By 52 weeks, 52% of patients had achieved complete biochemical remission and 34% had achieved partial remission. [72].However, despite wide clinical use, rituximab remains a controversial choice for lupus nephritis, due to the lack of robust supporting evidence and some negative results. For example, a randomized, double-blind, phase II/III trial of rituximab in moderately-to-severely active SLE (EXPLORER) failed

to show differences compared with placebo, although a beneficial effect of rituximab was noted in the African-American and Hispanic subgroups. [73] A randomized, double-blind, phase III trial of rituximab in active proliferative lupus nephritis (LUNAR) showed that rituximab therapy resulted in more responders and greater reductions in anti-DNA antibodies in increases in C3 and C4 levels, but it did not improve clinical outcomes after 1 year of treatment. [74]

Other anti-CD20 monoclonal antibodies: Other anti-CD20 monoclonal antibodies have been used experimentally for lupus nephritis; for example, in patients who respond to rituximab but develop intolerable adverse effects. Case series have described benefit with ofatumumab. [75, 76] In a phase III trial of ocrelizumab for class III/IV lupus nephritis, overall renal response rates with ocrelizumab were numerically but not statistically significantly superior to those with placebo, and the trial was terminated early because of higher rates of serious infections in patients receiving ocrelizumab and background mycophenolate mofetil. [77]

Atacicept: Atacicept is a TACI-Ig fusion protein that inhibits BLyS and a proliferation-inducing ligand [APRIL]). [66] In early phase studies, atacicept was demonstrated to have biologic effects in patients with SLE, resulting in a dose-dependent reduction in B cells and immunoglobulin levels. [78]

Abetimus: is a B-lymphocyte tolerogen that was found to be ineffective in preventing flares of lupus nephritis in a large controlled trial, although it did reduce levels of anti-DNA antibodies. [79]

Anticytokine therapies:Various anticytokine therapies have been proposed, including monoclonal antibodies directed against the following [66] :

Interferon-α

Interleukin (IL)-1

IL-6

IL-10

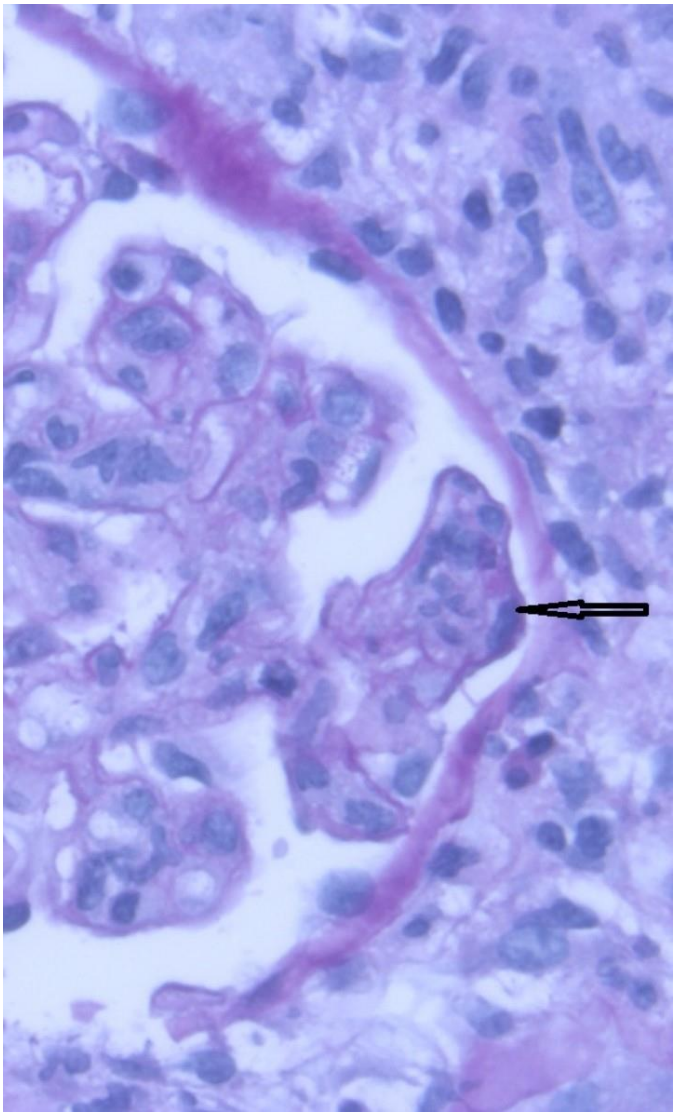
Tumor necrosis factor alpha (TNF-α)

Management of End-Stage Renal Disease: Patients with ESRD require dialysis and are good candidates for kidney transplantation (see Kidney Transplantation). Patients with ESRD secondary to SLE represent 1.5% of all patients on dialysis in the United States. The survival rate among patients on dialysis is fair (5-year survival rate, 60-70%) and is comparable with that among patients on dialysis who do not have SLE. Hemodialysis is preferred to peritoneal dialysis; several studies have documented higher levels of antibodies to double-stranded DNS (dsDNA), more thrombocytopenia, and higher steroid requirements in patients with SLE and ESRD who are on peritoneal dialysis. Hemodialysis also has anti-inflammatory effects with decreased T-helper lymphocyte levels. SLE is generally quiescent in patients on hemodialysis, although flares, including rash, arthritis, serositis, fever, and leukopenia may occur, necessitating specific treatment.

Treatment: Drug regimens prescribed for lupus nephritis include mycophenolate mofetil (MMF), intravenous cyclophosphamide with corticosteroids, and the immune suppressant azathioprine with corticosteroids.[14] MMF and cyclophosphamide with corticosteroids are equally effective in achieving remission of the disease, however the results of a recent systematic review found that immunosuppressive drugs were better than corticosteroids for renal outcomes.[15] MMF is safercyclophosphamide with corticosteroids, with less chance of causing ovarian failure, immune problems or hair loss. It also works better than azathioprine with corticosteroids for maintenance therapy.[16][17] A 2016 network meta-analysis, which included 32 RCTs of lupus nephritis, demonstrated that tacrolimus and MMF followed by azathioprine maintenance were associated with a lower risk of serious infection when compared to other immunosuppressants or glucocorticoids.[18][19] Individuals with lupus nephritis have a high risk for B-cell lymphoma (which begins in the immune system cells).[2]

Prognosis: In those who have SLE, concomitant lupus nephritis is associated with a worse overall prognosis.[20] 10-30% of people with lupus nephritis progress to kidney failure requiring dialysis, with the 5 year mortality rate of 5-25%.[20] The proliferative forms of lupus nephritis are associated with a higher risk of progression to end stage kidney disease.[20] Black and Hispanic people with lupus nephritis are more likely to present with severe disease at initial presentation (with more proteinuria and more extensive histopathologic changes) and progress to end stage kidney disease. This is thought to be due to socioeconomic factors but auto-antibodies strongly associated with lupus nephritis such as anti-Sm, anti-Ro and anti-ribonucleoprotein are also more commonly seen in Black and Hispanic people.[20] Men with SLE tend to have more aggressive forms of lupus nephritis as well with a higher risk of progression to end stage kidney disease and higher risk of concurrent cardiovascular disease.[20]

Case Report: A 12-year-old female patient presented with fever and chills, reduced urine output, vomiting, foamy urine, cold and cough, and swelling around the eyes. Laboratory results revealed high creatinine, hyponatremia, hypo-albuminemia, hypocalcemia, raised LDH, severe anemia, thrombocytopenia, high retic count, weakly positive Coombs test, ANA, and anti-histone antibodies. ANCA (c/p) and anti-GBM antibodies were negative, while the C3 level was low and the C4 level was normal. The urine routine suggested high albumin, high RBCs, and high protein creatinine ratio. Ultrasound of the abdomen and pelvis showed both kidneys to be bulky with no obstruction. The patient underwent multiple episodes of hemodialysis for fluid overload and uremic symptoms, and blood transfusion was given during dialysis. A renal biopsy was planned, but the patient had an episode of convulsion in ward and was shifted to the ICU, intubated, and ventilated because of respiratory failure. The patient later developed ET bleeding and diffuse non-blanching purpuric spots. Fundoscopy revealed grade 2 hypertensive retinopathy, while an MRI showed posterior reversible encephalopathy syndrome. HRCT thorax showed diffuse pulmonary hemorrhage. The patient was diagnosed with acute glomerulonephritis with a possible autoimmune etiology, and pulse steroids and Inj Cyclophosphamide were given to her after explaining the side effects under antibiotic cover. The patient showed dramatic improvement, with increase in hemoglobin and platelet counts, lung infiltrates cleared, vitals stabilized, and the patient was extubated. Dialysis was stopped as urine output improved. A biopsy performed later once the patient stabilized showed lupus nephritis (ISN/RPS Grade 3). The patient was shifted to the ward and was given Inj Cyclophosphamide, after 14 days, and oral steroids. She was discharged with no symptoms, edema-free, and with normal creatinine levels.



Discussion: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organs and systems, and lupus nephritis is a severe complication of SLE. Lupus nephritis is a well-known manifestation of SLE in both adults and children, and its diagnosis and management have been extensively studied.[1] However, some pediatric cases of lupus nephritis present atypically, which can make it challenging to diagnose and manage. Atypical presentations of lupus nephritis in pediatric cases can include diverse clinical features such as fever, cough, vomiting, purpuric spots, seizures, and respiratory failure. These symptoms may not immediately suggest the presence of lupus nephritis and may lead to misdiagnosis or delayed diagnosis. As a result, some patients may experience significant morbidity and mortality before receiving appropriate treatment.[2]**Lupus nephritis is clinically evident in 50-60% of patients with systemic lupus erythematosus (SLE), and it is histologically** evident in most SLE patients, even those without clinical manifestations of kidney disease. Evaluating kidney function in SLE patients is important because early detection and treatment of kidney involvement can significantly improve renal outcome. Advanced sclerosis lupus nephritis. International Society of Nephrology/Renal Pathology Society 2003 class VI (×100, hematoxylin-eosin).Signs and symptoms: Patients with lupus nephritis may report other symptoms of active SLE (eg, fatigue, fever, rash, arthritis, serositis, or central nervous system [CNS] disease); these are more common with focal (proliferative) and diffuse (proliferative) lupus nephritis. Asymptomatic lupus nephritis : During regular follow-up, laboratory abnormalities suggesting active lupus nephritis include hematuria or proteinuria; this is more typical of mesangial or membranous lupus nephritis.Nephritic symptoms related to hypertension and poor kidney function (typical of diffuse lupus nephritis):Peripheral edema, Headache and dizziness, Nausea and vomiting. Nephrotic symptoms related to proteinuria (ypical of membranous lupus nephritis):Peripheral or periorbital edema Coagulopathy. The index case treated successfully with international treatment guidelines improved drastically so discharged.

Physical finding: Focal and diffuse lupus nephritis – Generalized active SLE with the presence of a rash, oral or nasal ulcers, synovitis, or serositis; signs of active nephritis Active lupus nephritis – Hypertension; peripheral edema; and, occasionally, cardiac decompensation. Membranous lupus nephritis – Peripheral edema, ascites, and pleural and pericardial effusions without hypertension

Diagnosis Laboratory tests to evaluate kidney function in SLE patients include: Blood urea nitrogen (BUN) testing

Serum creatinine assessment. Urinalysis (to check for protein, red blood cells [RBCs], and cellular casts) .Spot urine test for creatinine and protein concentration. 24-hour urine test for creatinine clearance and protein excretion

Laboratory tests for SLE disease activity include the following:

Antibodies to double-stranded DNA (dsDNA)

Complement (C3, C4, and CH50)

Erythrocyte sedimentation rate (ESR)

C-reactive protein (CRP)

Kidney biopsy should be considered in any patient with SLE who has clinical or laboratory evidence of active nephritis, especially upon the first episode of nephritis.

Lupus nephritis is staged according to the classification revised by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003, as follows:

Class I – Minimal mesangial lupus nephritis

Class II – Mesangial proliferative lupus nephritis

Class III – Focal lupus nephritis (active and chronic; proliferative and sclerosing)

Class IV – Diffuse lupus nephritis (active and chronic;

proliferative and sclerosing; segmental and global)

Class V – Membranous lupus nephritis

Class VI – Advanced sclerosis lupus nephritis

Management: The principal goal of therapy in lupus nephritis is to normalize kidney function or, at least, to prevent the progressive loss of kidney function. Therapy differs, depending on the pathologic lesion.. As per American College of Rheumatology guidelines for managing lupus nephritis are as follows:

Patients with clinical evidence of active, previously untreated lupus nephritis should have a kidney biopsy to classify the disease according to ISN/RPS criteria . All patients with lupus nephritis should receive hydroxychloroquine, unless contraindicated. Glucocorticoids plus either cyclophosphamide intravenously or mycophenolate mofetil orally should be administered to patients with class III/IV disease; patients with class I/II nephritis do not require immunosuppressive therapy. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers should be administered if proteinuria reaches or exceeds 0.5 g/day. Blood pressure should be maintained at or below 130/80 mm Hg. Patients with class V lupus nephritis are generally treated with prednisone for 1-3 months, followed by tapering for 1-2 years if a response occurs. If no response occurs, the drug is discontinued. Immunosuppressive drugs are generally not used unless kidney function worsens or a proliferative component is present on kidney biopsy samples.

Newer therapies for lupus nephritis include the following:: The oral calcineurin inhibitor voclosporin, which is approved for use in conjunction with immunosuppressive treatment. Belimumab, an anti–B-lymphocyte stimulator [BLyS] monoclonal antibody, which is approved for treatment of adults with active lupus nephritis who are receiving standard therapy

Investigational therapies for lupus nephritis and SLE include Rituximab, Other anti-CD20 monoclonal antibodies (eg, ocrelizumab, ofatumumab, epratuzumab, and TRU-015),Atacicept, Abetimus, Anticytokine therapies (eg, monoclonal antibodies directed against interferon alfa, interleukin [IL]-1, IL-6, IL-10, and tumor necrosis factor alpha [TNF-α]),Patients with end-stage renal disease require dialysis and are good candidates for kidney transplantation.

Conclussion: Patients with active lupus nephritis often have other symptoms of active systemic lupus erythematosus (SLE), including fatigue, fever, rash, arthritis, serositis, or central nervous system (CNS) disease. These are more common with focal and diffuse lupus nephritis. [29].Some patients have asymptomatic lupus nephritis; however, during regular follow-up, laboratory abnormalities such as elevated serum creatinine levels, low albumin levels, or urinary protein or sediment suggests active lupus nephritis. This is more typical of mesangial or membranous lupus nephritis.Symptoms related to active nephritis may include peripheral edema secondary to hypertension or hypoalbuminemia. Extreme peripheral edema is more common in persons with diffuse or membranous lupus nephritis, as these renal lesions are commonly associated with heavy proteinuria. [24]. Other symptoms directly related to hypertension that are commonly associated with diffuse lupus nephritis include headache, dizziness, visual disturbances, and signs of cardiac decompensation.The index case diagnosed to have Lupus nephritis with presslar syndrome treated successfully and discharged.

Conflict of interest: None to declare.

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