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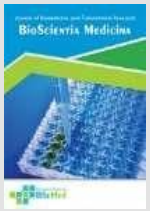

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IgA Nephropathy and Lupus Nephritis in a 17-Year-Old Female: A Case Report

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A B S T R A C T

Background: Acute nephritic syndrome is classically presented with proteinuria, haematuria, azotemia, red blood casts, oliguria, and hypertension (PHARAOH) occurring acutely. Extensive inflammation of the glomeruli causes a decrease in the glomerular filtration rate so that it will produce uremic symptoms such as water and salt retention which will give a clinical picture of edema and hypertension, positive protein in the urine, the presence of erythrocytes or the appearance of dysmorphic erythrocytes in the urine. **Case presentation:** A 17 year old female with nephritic syndrome is reported to have nephritic lupus and IgA nephropathy. He has been treated with corticosteroids, immunosuppressants, antihypertensives, and also diuretics followed by progress of clinical and laboratory conditions. Biopsy has been performed to provide a definitive diagnosis in the patient and determine the type of nephritic syndrome experienced. The biopsy showed features of IgA nephropathy (IgAN) and lupus nephritis. **Conclusion:** Nephritic syndrome has been suspected due to the presence of haematuria, proteinuria, eyelid swelling, and hypertension. The management given to patients is supportive and symptomatic. Long-term administration of corticosteroids is needed in the treatment of nephritic syndrome as a maintenance therapy. Observation during treatment is needed to assess improvement or worsening of the disease experienced.

1. Introduction

The nephritic syndrome provides evidence of inflammation within the glomeruli, which leads to a reduction in the glomerular filtration rate, proteinuria, edema, hypertension (secondary to sodium retention), and hematuria with the presence of red blood cell casts. Nephritic syndrome represents a common presentation across almost all forms of proliferative glomerulonephritides (GN).[1,2] This incidence can be attributed to acute proliferative glomerulonephritis (associated with post-infectious states and infections), crescentic glomerulonephritis, and proliferative lupus nephritis.[3] Unlike nephritic syndrome, nephrotic syndrome is caused by injury to the glomeruli, leading to increased permeability of the capillary walls to proteins, resulting in more massive proteinuria in patients with nephrotic syndrome. The differences between nephritic and nephrotic syndromes can be distinguished clinically and through laboratory examination results.[4] In developing countries, the incidence of nephritic syndrome remains high due to factors such as large populations, poor hygiene conditions, low socioeconomic levels, and limited access to medical treatment.[1,3]

2. Case Presentation

A 17-year-old female adolescent was admitted to K.R.M.T Wongsonegoro Regional General Hospital Semarang on January 3rd, 2023, presenting with primary complaints of swelling around both eyelids, face, and feet. The patient also reported reddish urine accompanied by froth, without fever or pain during

urination, and these symptoms had been intermittent. The patient mentioned these symptoms first appeared in December 2022. A week prior to admission, she experienced fever and sore throat, and she reported frequent episodes of flu since 2022.

During the physical examination, the patient was alert and oriented, with a blood pressure of 120/67 mmHg, pulse rate of 90 beats per minute, temperature of 36.2°C, weight of 56 kilograms, height of 160 cm, and a normal body mass index (BMI). There was no edema observed around the eyelids, no anemic conjunctiva or icteric sclera. The head, nose, and ears showed no deformities. The oral examination revealed no pharyngeal erythema, tonsillar enlargement, or other deformities. No cervical lymphadenopathy was noted. The extremities were warm to touch, with no edema, a capillary refill time of less than 2 seconds on both sides, and equal radial pulse strength bilaterally. Chest examination revealed a normal chest shape, symmetric wall movement, abdominal-thoracic type respiration, no intercostal retractions, equal tactile fremitus on both sides, sonorous percussion over all lung fields, and vesicular breath sounds with coarse rales at the base of both lungs, without wheezing. Cardiac examination showed no visible or palpable ictus cordis at the apex, normal heart borders, and normal first and second heart sounds without murmurs or gallops. The abdomen was soft without distension, striae, normal bowel sounds, no tenderness, negative shifting dullness, and a tympanic sound across all quadrants.

Laboratory tests revealed a random blood glucose level of 78 mg/dL, calcium 1.25 mmol/L, sodium 135.0 mmol/L, potassium 4.50 mmol/L, creatinine 1.2 mg/dL, urea 59.4 mg/dL, hemoglobin 11.9 g/dL, hematocrit 36.3%, platelet count 443 /µL, red blood cell count 4.32/µL, white blood cell count 14.4/µL, globulin 3.1 g/dL, albumin 2.8 g/dL, SGPT 19 U/L, SGOT 33 U/L, total protein 5.9 g/dL, total cholesterol 385 mg/dL, HDL cholesterol 82 mg/dL, indirect LDL cholesterol 286 mg/dL, triglycerides 85 mg/dL, uric acid 8.1 mg/dL. Urinalysis showed negative bilirubin, 5-8 epithelial cells per high-power field (HPF), 7-10 red blood cells per high-power field, pH 6.0, negative ketones, negative nitrites, positive protein (+1), negative glucose, specific gravity 1.020, negative urobilinogen, negative amorphous materials, positive bacteria (+1), negative casts, light yellow color, negative crystals, negative fungi, 10-15 white blood cells per high-power field, and no other significant findings. Chest X-ray in anteroposterior projection showed mild cardiomegaly and signs of bronchopneumonia. Ultrasound examination indicated the presence of free fluid in the Douglas pouch. Echocardiography results were normal.

Pharmacological treatments administered during hospitalization included intravenous Ceftriaxone 1 gram twice daily, Ranitidine injection twice daily, Methyl Prednisolone 125 mg for 3 days, Captopril 12.5 mg three times daily, Nocid three times daily, Bic Nat three times daily, Simvastatin 20 mg once daily, Salbutamol 4 mg three times daily, and Furosemide 40 mg twice daily. Non-pharmacological treatment included a kidney biopsy. Post-biopsy care involved the patient resting in a supine position for 6 hours, with monitoring for hematuria. Post-biopsy pharmacological treatments included Tranexamic Acid injection twice daily, Ceftriaxone 2 grams once daily, Ketorolac drip for pain management, and Paracetamol 3x500 mg for pain. Outpatient management included Methyl Prednisolone 16 mg, two tablets in the morning and 1.5 tablets at noon, Nocid three times daily, Bic Nat three times daily, Omeprazole 20 mg three.

3. Discussion

There are several types of diseases classified under nephritic syndrome. Nephrotic syndrome is often considered a differential diagnosis for nephritic syndrome due to the similarities in signs and symptoms. The differences between nephritic syndrome and nephrotic syndrome can be observed in Table 1.[2,5]

Table 1. Differences between nephrotic syndrome and nephritic syndrome.

Distinctive characteristics	Nephrotic syndrome	Nephritic syndrome
Onset	Gradual	Sudden
Edema	++++	++
Blood pressure	Normal	Elevated
Jugular venous pressure	Normal/Low	Elevated
Proteinuria	++++	++
Hematuria	May or may not be present	+++
Red blood cell cast	Absent	Present
Serum albumin	Low	Normal/slightly decreased

Based on clinical signs/symptoms and laboratory examinations, a diagnosis of either nephritic syndrome or nephrotic syndrome can be established. However, this alone is insufficient for determining an appropriate therapeutic plan for both short-term and long-term management, necessitating histopathological examination through biopsy. IgA Nephropathy is the most common pattern of primary glomerular disease worldwide and is a leading cause of chronic kidney disease (CKD) and end-stage renal failure.[6,7] IgA Nephropathy is often asymptomatic and follows a slowly progressive course, with about 25-30% of cases progressing to renal failure within 20-25 years. The management of IgA Nephropathy differs from that of most other glomerular diseases, focusing on a non-immunosuppressive strategy known as supportive care to slow disease progression. This includes controlling blood pressure, optimal renin-angiotensin system (RAS) inhibition, and lifestyle modifications, including weight reduction, regular exercise, smoking cessation, and dietary sodium restriction.[8,9]

IgA Nephropathy (IgAN) is an autoimmune kidney disease that arises due to elevated levels of circulating IgA1 with O-glycans in the hinge region lacking galactose. However, glycosylation aberrations alone are insufficient to cause nephritis. For the clinical manifestation of kidney injury, several additional insults are required, including the synthesis of circulating antibodies directed against abnormally glycosylated O-linked hinge region glycans to form immune complexes, accumulation of these complexes in the mesangium, and activation of mesangial cells. Genetic factors appear to influence the expression of these attack mechanisms.[2,10] The pathogenesis of IgAN provides opportunities for the development of disease-specific therapies, which are currently unavailable. The pathogenesis of IgA Nephropathy is not fully understood. In recent years, laboratory and clinical investigations have led to the development of several theories supporting IgA as an autoimmune disease with a complex, multi-step pathogenic process. In the first step of IgAN, autoantibody isotypes IgG and IgA recognize circulating galactose-deficient IgA1 (Gd-IgA1). Following this, IgA1-IgG and IgA1-immune complexes are formed, which include complement system components. These immune complexes are then formed and trapped in the glomerular mesangial layer, leading to dysregulated mesangial cells and renal tissue damage. A second theory suggests that deposits of aberrantly glycosylated IgA1 in the mesangium act as lanthanide deposits that strongly bind to newly formed autoantibodies, resulting in the in situ synthesis of immune complexes. These immune deposits cause mesangial cells to proliferate and produce excessive amounts of extracellular matrix, cytokines, and chemokines, damaging podocytes and leading to proteinuria. The activation of the classical complement pathway plays a role in the formation and activity of circulating complexes, contributing to glomerulosclerosis and tubulointerstitial fibrosis in the kidneys.[11,12]

The diagnosis of IgA nephropathy (IgAN) can only be definitively made through an invasive kidney biopsy. To determine the severity of IgAN in a patient,

the biopsy findings can be evaluated using the MEST-C score, which includes Mesangial [M] proliferation, Endocapillary [E] hypercellularity, Segmental [S] sclerosis, Tubular atrophy/Interstitial [T] fibrosis, and Crescents [C], in accordance with the revised Oxford Classification.[10,13] Currently, there are no validated serum or urine biomarker tests available for diagnosing IgAN. Furthermore, it's crucial to identify secondary causes in patients with IgAN, such as IgA vasculitis, viral infections (HIV, hepatitis), inflammatory bowel disease (IBD), autoimmune diseases, liver cirrhosis, and IgA-dominant infections associated with glomerulonephritis.[11,14] In this particular case, the patient had experienced fever and sore throat a week before hospitalization, which might be linked to an IgA-dominant infection related to glomerulonephritis, one of the potential causes of IgA Nephropathy. Moreover, the patient reported frequent flu-like symptoms over the past year, which could indicate the presence of an ongoing IgA-dominant infection correlating with the onset of swollen eyes and frothy reddish urine. However, other factors must also be considered as potential risk contributors to the development of IgA Nephropathy in this patient.

Lupus nephritis (LN) is a type of glomerulonephritis caused by immune complexes and is a common and serious condition in patients with systemic lupus erythematosus (SLE). According to the 2012 American College of Rheumatology Guidelines (ACRG) for LN, a kidney biopsy is indicated for patients with deteriorating renal function, proteinuria exceeding 1 g/day, or more than 0.5 g/day with additional urinary sediment abnormalities.[2,12] Similarly, the recommendations for LN management by the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) and the updated 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for glomerular disease management retain the threshold of 500 mg/day proteinuria (with or without abnormal urinary sediment) and reduced kidney function as indications for a kidney biopsy in SLE patients. The Systemic Lupus International Collaborating Clinics (SLICC) criteria include nephritis proven by biopsy compatible with LN, with the presence of either antinuclear antibodies (ANA) or anti-double stranded (ds) DNA antibodies being sufficient evidence for diagnosing systemic lupus erythematosus.[2,15]

In LN, autoantibodies against dsDNA, Sm antigen, C1q, nucleosomes, and other antigens are found. dsDNA antibodies can directly bind to the glomerular basement membrane (GBM), and there is cross-linking between positively charged nucleosome components like chromatin, autoantibodies, and the GBM. In proliferative LN, immune complexes are found in the subendothelial space, activating pro-inflammatory mechanisms, including the complement pathway, leukocyte Fc receptors, cytokines regulating proliferation and matrix formation, and procoagulant factors. Nucleosomes activate dendritic cells through binding to TLR 2 and 9.[2,10] These activated pathways lead to kidney damage through complement system activity, intraglomerular hypertension, coagulation, and leukocyte infiltration via Fc receptors, releasing proteolytic enzymes. In Membranous LN, immune complexes are found in subepithelial areas, associated with less inflammation but increased GBM component production and more significant podocyte injury. Neutrophils undergo a cell death process called NETosis, where chromatin networks (or NETs) are released. NETs (visible on biopsy) are a source of autoantigens and are not well degraded in lupus patients, who have an increased number of low-density granulocytes, making them more prone to NETosis. NETs induce IFN-alpha production by plasmacytoid dendritic cells found in LN kidneys. LN can be classified into several classes based on biopsy results, and the management of LN is based on the class diagnosed.[4,16]

Based on the clinical findings, this case report presents signs and symptoms such as edema of the face, eyelids, lower limbs, and foamy urine that have been present for one month. Laboratory test results indicating elevated creatinine and urea levels suggest renal dysfunction, while decreased serum albumin

and total protein levels, coupled with the presence of mild proteinuria evidenced by protein leakage into the urine, contribute to the patient's edematous signs.[2] These signs and symptoms, supported by diagnostic tests, indicate the presence of nephritic syndrome, warranting a renal biopsy for definitive diagnosis. The renal biopsy confirmed the presence of class II lupus nephritis and IgA nephropathy in the patient.[12,17]

The patient was prescribed methyl prednisolone at a dosage of 16 mg with two tablets in the morning and 1.5 tablets in the afternoon, serving as an anti-inflammatory and immunosuppressive agent. This is a typical initial management strategy for glomerular diseases, particularly for class I/II IgA nephropathy.[2,10] Hypertension is a symptom experienced by patients with nephritic syndrome due to intravascular protein leakage leading to reduced renal perfusion, which activates the renin-angiotensin system (RAS), subsequently increasing blood pressure. In this case, the patient did not exhibit hypertension, yet was administered captopril 12.5 mg, an ACE-Inhibitor antihypertensive medication. The primary aim of this medication is to reduce proteinuria in the patient. Apart from ACE-inhibitors, angiotensin II receptor blockers (ARBs) are also considered first-line treatments for proteinuria.[8,17]

Bic Nat, which contains sodium bicarbonate, is commonly prescribed to address metabolic acidosis in patients with chronic kidney disease (CKD). In this patient's case, the administration of Bic Nat aims to slow down the progression of renal function decline and potentially enhance endothelial vascular function significantly.[1,17] A low-protein diet is crucial in both acute and chronic kidney diseases; however, it is often more effective when supplemented with ketoanalogs or Ketocid. The administration of ketoanalogs, such as Nocid in this patient, is expected to result in reduced plasma urea, urea synthesis, urea excretion, and enhanced nitrogen retention in kidney disease. This approach aims to alleviate the burden on the kidneys by reducing the amount of nitrogenous waste they need to filter and excrete, thus helping to preserve kidney function.[18]

The administration of glucocorticoids necessitates that the patient continues to follow up with their doctor for up to 6 months to monitor the progression of their condition and potentially taper down the steroid dosage. Additionally, the patient is prescribed mycophenolate mofetil (MMF) at a dosage of 1 gram twice daily, with a minimum treatment duration of 6 months, requiring regular follow-up visits. MMF has emerged as a first-line treatment option among immunosuppressive agents for the induction therapy of lupus nephritis. The long-term administration of MMF as maintenance therapy has proven to be effective and safe. Besides pharmacological treatment, supportive therapies are also crucial, including blood pressure monitoring, lifestyle modifications, and weight monitoring to facilitate the tapering of steroids.[3,17]

4. Conclusion

Our case presented a 17-year-old female patient diagnosed with class II lupus nephritis and IgA Nephropathy, manifested through clinical signs such as edema of the face, eyelids, lower limbs, and foamy urine, alongside laboratory findings indicative of renal dysfunction and mild proteinuria. The treatment regimen includes methyl prednisolone for its anti-inflammatory and immunosuppressive properties, captopril to address proteinuria, and Bic Nat (Sodium Bicarbonate) to manage metabolic acidosis associated with chronic kidney disease (CKD). Additionally, the patient was prescribed mycophenolate mofetil (MMF) as a first-line immunosuppressive agent for lupus nephritis, highlighting its role in induction therapy and its safety and efficacy as a long-term maintenance therapy. The management plan also underscores the importance of a low-protein diet supplemented with ketoanalogs like Nocid to reduce the renal burden of nitrogenous waste processing. The case underscores the necessity of a renal biopsy for an accurate diagnosis and to ascertain the specific type of nephritic syndrome, as this significantly impacts the management and therapeutic approach. It also emphasizes the importance of continuous monitoring,

including follow-ups for up to 6 months to assess disease progression and adjust treatment plans accordingly, particularly concerning the tapering down of steroid dosage. This comprehensive approach, combining pharmacological treatments with dietary management and lifestyle modifications, aims to manage symptoms, slow disease progression, and maintain the patient's quality of life.

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