Case Report: Coexistence of acute post-streptococcal glomerulonephritis and rheumatic heart disease in a 9 years old girl

Yudit Angelia Sumarno * and Novita Tjiang

Department Of Child Health, Waikabubak General Hospital, West Sumba, East Nusa Tenggara, Indonesia.

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Abstract

Background: Group A-haemolytic streptococcus (GAS), one of the most frequent pathogens in pediatric group causing various diseases, from acute pharyngitis (AP) to severe complication such as acute rheumatic fever (ARF) and acute post-streptococcal glomerulonephritis (APSGN). GAS, round gram positive bacteria typically form pairs or chains, was reported causing 1.78 million cases with 500.000 death due to its severe complication in 2005.

Case Illustration: A 9-year-old female patient came to emergency unit (ER) complained swollen face and legs since 5 days ago, accompanied by tea color urine and reduced frequency and volume of micturition. Patient also complained shortness of breath which getting worse since yesterday, easily fatigue and dizziness. Moreover her mother also admitted that her daughter had history of migratory joints pain 3 weeks before admission, with sore throat a month ago. Blood pressure was 110/70 mmHg, Ross score was 8. Physical examination showed puffy face, pretibial edema, heart auscultation we heard pansystolic murmur. Chest radiography showed cardiomegaly and congestive pulmonum while laboratory exam showed ASTO 200, urinalysis showed red color, cloudy clarity, protein 1+, erythrocyte 3+, leukocytes 1+, urinary microscopic examination: 30-40 erythrocytes, 8-12 leukocytes, electrocardiography showed sinus tachycardia, prolonged PR interval, right atrial enlargement, right ventricle hypertrophy with right axis deviation. Patient was diagnosed with APSGN, hypertension grade II and heart failure due to rheumatic heart disease.

Summary: APSGN and ARF rarely occur together, the coincidence might be due to streptococci with nephritogenic and rheumatogenic same strains. Early detection and treatment of GAS are crucial to prevent complications.

Keywords: Streptococcus; Edema; Glomerulonephritis; Hypertension; Rheumatic Fever

1. Introduction

Group A Streptococcus (GAS), round gram positive bacteria that typically form pairs or chains during their growth period. It can cause variety of diseases ranging from superficial minor infections in throat or skin infection such as cellulitis, erysipelas, bacteremia and necrotizing fasciitis to post Streptococcal complications such as rheumatic heart disease (RHD) and post streptococcal acute glomerulonephritis (APSGN). The World Health Organization (WHO) reported 1.78 million new cases in 2005 with 500.000 death anually [1-2].

Acute post streptococcal glomerulonephritis (APSGN) is characterized by proliferation and inflammation of glomeruli, preceded by group α β-Hemolytic Streptococci infection with nephritic symptoms. About 10-15% GAS patients with nephritogenic strains develop into APSGN. APSGN affects all age group especially those aged 2.5-15 years with peak age of 8.4 years being the most common age group [3-6].
The clinical symptoms of GNAPS vary widely from asymptomatic to characteristic symptoms. Classic or typical cases begin with an upper respiratory tract infection with sore throat two weeks preceding the onset of swelling. The latency period is 10 or 21 days on average after infection of the throat or skin [3-6].

Acute rheumatic fever (ARF) is an inflammatory condition affecting heart, joints, central nervous system and subcutaneous tissues. It is a delayed sequel from an infection secondary to group a streptococcus (GAS). The first symptoms of the disease classically present two to three weeks after an infection with GAS which presents as sore throat. Symptoms manifest as fever, polyarthralgia, polyarthritis, chorea and erythema marginatum. In severe case when there is a cross-reaction between carbohydrate cell wall of the bacterial and the valve tissue (antigenic mimicry), it will cause chronic damage to valve tissue, which is termed as Rheumatic Heart disease (RHD)[7]. Hereby we report a rare case of patient with coincidence of APSGN and RHD, which both are complication of GAS infection.

2. Case Illustration

A 9-year-old female patient came to the Waikabubak Hospital emergency unit with complaint swelling face and legs since 5 days ago and getting worse since yesterday. At first swelling was noticed on eyelids and feet every morning while waking up and continues to entire face. The patient did not complain swelling of stomach or genitals but had reddish urine like tea color and reduced micturition, in a day only 3/4 cup with frequency 1-2 times a day. Patient also felt nauseous and dizziness since morning without headaches, blurred vision, vomit or seizure. The patient did not have history of kidney disease nor does her family.

Patient also complained shortness of breath since a week ago, especially when walking and laying which did not related to weather. Shortness of breath did not improve with sitting position and got worsen since yesterday. The patient admitted had cough, intermittent fever and sore throat four weeks before being admitted to the hospital. The body temperature was high and recovered with fever medicine. The patient was said had history of migratory joints pain. Initially, it involved her right knee joint, but then sequentially her right ankle, left knee, left ankle and elbow joints were also involved. The joints were said swollen, red and very painful, even with mild movement since two weeks ago. History of trauma, pain in the lumbar region, pain while micturition or significant weight loss were denied.

Patient was the fourth child of 5 siblings, born spontaneously full term at the public health center, assisted by midwife, with birth weight 2800 grams, birth length 50 cm. The patient cried immediately at birth, there was no history of cyanosis or hyperbilirubinemia. During pregnancy, patient’s mother routinely performed antenatal care at midwife. History of basic immunization seems complete. The patient currently attending grade 4 in local Primary School. The patient lives in village area, in a permanent house with 2 bedrooms, both of her parents work as farmers. Health issues was covered by using the National Health Insurance facility.

On physical examination, the patient condition generally appeared to be moderately ill, alert, body weight (BW) 30.2 kg, body height (BH) 132 cm, based on the CDC curve body weight for age (BW/A) below P5, BH according to age (BH/A) P50, blood pressure 110/70 mmHg, pulse rate 114 beats / minute, respiratory rate 58 times / minute, body temperature 37.4° C, Ross score 8. On the eyelids and face looked puffy, ears, nose, and mouth impression within normal limits. On neck examination, the JVP did not increase, the impression was within normal limits. Lungs, chest motion and tactile fremitus were symmetrical, rhonchi and wheezing were absent, impressions were within normal limits. On heart auscultation we heard pansystolic murmur of grade 5/VI with thrill at mitral area, radiating to axilla and scapula area. The impression abdomen is within normal limits. Extremity, no parese obtained, pitting edema (+). Laboratory tests showed hemoglobin 11.5 gr/dL, white blood cell 17,400 /µl, platelets 465,000 /dL, albumin 2.7 g/dL, urea 35 mg/dL, creatinine 1.3 mg/dL, SGOT 10.3, SGPT 13.5, blood sugar 80mg/dl. ASTO 200, erythrocyte sedimentation rate (ESR) 80 mm/hour.

The urinalysis results showed red color like tea color, cloudy clarity, protein 1+, erythrocyte 3+, leukocytes 1+, urinary microscopic examination: 30-40 erythrocytes, 8-12 leukocytes. Chest X-ray showed cardiomegaly with congestive pulmonum (figure 1), meanwhile electrocardiography (ECG) showed sinus tachycardia with prolonged PR interval, right atrial enlargement, right ventricle hypertrophy with right axis deviation (figure 2). Patient was diagnosed with APSGN, hypertension grade II and heart failure due to rheumatic heart disease. Patients was hospitalized with non-medical management in the form of bed rest, limiting salt intake, fluid diet that was adjusted to input and output, as well as medical management in the form of dopamine drip 10 mcg/kg/minute, furosemide injection 30 mg/12 hours, captopril tablet 12.5 mg/12 hours, spironolactone tablet 12.5 mg/12 hours, erythromycin tablet 250 mg/12 hours, aspilet tablet 750mg/6 hours for 14 days and oxygen according to clinical condition.
On day 6th of treatment heart failure improved with Ross score declined to 5, shortness of breath and swelling were reduced, thus dopamine drip was gradually reduced. On day-11 erythromycin was switched to secondary prevention dosage (250mg/12 hours) and the patient was discharged after 14 days of treatment with aspilet and anti hypertensive drugs. When patient controlled at the pediatric outpatient clinic, patient complained cough with phlegm meanwhile shortness of breath has recovered while other complaints such as cold sweat and tea color urine were not found (figure 2). Ross Score decline into 4. Urine analysis showed Blood (-), Protein (+1), Leukocytes: 4-8, erythrocytes: 3-6. The patient was prescribed ambroxol tablet 15mg tid, aspilet tablet 480mg qid (for 6 weeks), erythromycin 250mg bid, furosemide 30mg bid, captopril 12.5mg bid and spironolactone 12.5mg bid and plan for echocardiography in Sanglah hospital.
3. Discussion

Group A-haemolytic streptococcus (GAS) or *Streptococcus pyogenes*, is one of the most frequent pathogens in the pediatric age group. It produces diseases of varying severity, from acute pharyngitis (AP) and its severe complications to forms associated with high mortality, including post-infection complications (rheumatic fever [RF], acute post-streptococcal glomerulonephritis [APSGN] and other invasive diseases[1-2].

3.1. Acute poststreptococcal glomerulonephritis (APSGN)

Acute poststreptococcal glomerulonephritis (APSGN) is the prototype of post-infectious glomerulonephritis and is associated with previous skin or throat infection by group A streptococcus (*Streptococcus pyogenes*), or occasionally groups C or G streptococcus [3-6]. APSGN may occur in epidemic outbreaks or in clusters of cases, and it may occur in isolated patients. APSGN was considered to be caused by an antigen present in group A streptococci. *Streptococcus pyogenes* of M types 1, 2, 4 and 12 were associated with epidemic nephritis resulting from upper respiratory infections and M types 47, 49 and 55 were associated with epidemic nephritis following pyoderma [3-8]. It remains as important non-suppurative complication of group A streptococcal infection worldwide. The estimated worldwide burden of APSGN is 472,000 cases yearly; approximately 404,000 of those cases occur in children, male:female ratio is 2:1 in Indonesia between the ages 2.5-15 with median ages 8.46. The latent period between upper respiratory infection and nephritis is 7-10 days and 2-4 weeks in cases that follow skin infection [4-7]. This is in accordance with our patient whom was 9 years old with history of pharyngitis 4 weeks before admitted to hospital although we couldn’t perform culture to find the serotype.

Three phases of APSGN can be identified: the latent phase, the acute phase and the recovery phase. The latent phase is the phase between the occurrences of streptococcal infection to the appearance of clinical symptoms. The clinical manifestation usually appear 7-14 days after upper respiratory tract infection or 3-6 weeks after pyoderma. The acute phase is the phase which the patient begins to develop symptoms of nephritic syndrome in the form of proteinuria, hematuria, azotemia, oliguria and hypertension. Lastly the recovery phase is characterized by improvement of clinical and laboratory symptoms. Thus point out our patient came to ER in acute phase [7-8].

The typical clinical presentation of APSGN is acute nephritic syndrome such as hematuria, edema, hypertension and oliguria while in minority, APSGN may also be manifested by nephrotic syndrome; and in rare cases, by rapid progressive (crescentic glomerulonephritis) clinical course[3-8]. Our patient came to ER with complain of periorbital edema, hematuria, oliguria and hypertension grade II which are nephritic syndrome moreover it align with Eison et al whom stated Children with APSGN most often seek medical attention due to edema or gross hematuria[7].

The clinical manifestation of APSGN may vary from asymptomatic to severe symptoms. Thus the definite diagnosis of APSGN is nephritic syndrome and positive culture of GAS, however the culture examination often shows negative result (sterile) so investigation such as microscopic hematuria, erythrocyte thorax, proteinuria in urinanalysis, increased antistreptolysin O titer and decreased of C3 complement are useful in diagnosing APSGN. Antistreptolysin O titers and anti-DNase B titer is the most frequently elevated in upper respiratory infections and pyodermitis, respectively. A streptozyme test that includes 4 major antigens (DNase B, Streptolysin O, hyaluronidase and streptokinase) is reported to be positive in more than 80% of the cases [3-7]. In this case the ASO titer result was increased to 200 which was align with study from Suarta et al whom stated increased of ASO titer and decrease of C3 in APSGN [5].

Streptococcal infection in APSGN triggers the formation of antigen-antibody complex that circulate into glomerulus and mechanically trapped in basement membrane which will attract polymorphonuclear cell and platelets to the lesion site. The phagocytosis and lysosomal enzymes then damage endothelial and glomerular basement membrane resulting in increased basement membrane permeability. The glomerular filtration rate will decrease due to occlusion of the glomerular capillaries and ventroile vasospasm, causing water and sodium retention which results in clinical appearance of edema and hypertension, as well as glomerular capillary leak that allows erythrocytes and protein to pass out into urine. Macroscopic hematuria, edema and hypertension are clinical manifestations that are often found in patients with APSGN. Hypertension is one of the triad of clinical manifestations in APSGN that often occurs [3-8]. A study stated that hypertension as the majority of cases with 61% of them being hypertension grade 2[4]. Another study showed similar results that the most common clinical manifestation of APSGN was severe hypertension [6]. The same clinical manifestations were found in the case above which the patient suffered edema, hematuria, proteinuria and hypertension grade II.

Patients with an acute nephritic syndrome require restriction of sodium and fluid intake. For more than three decades, loop diuretics have been known to accelerate the resolution of edema and improve hypertension. Thiazide diuretics are
ineffective and aldosterone antagonists carry the risk of hyperkalemia. In cases with severe hypertension, nifedipine may be useful. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers carry the risk of hyperkalemia. Nitroprusside may be needed to treat hypertensive encephalopathy, but only in exceptional cases. Pulmonary edema may complicate the clinical course and should be treated with oxygen, loop diuretics and rotating tourniquets. Our patient was treated with diuretics and ace inhibitor as the anti-hypertensive which also acted as anti-failure medication [6].

In a typical case of post-streptococcal nephritis, improvement is observed after 2–7 days when the urine volume increases, followed by rapid resolution of edema and return of the blood pressure to normal levels. Meanwhile asymptomatic disease may be manifested as microscopic hematuria and fall of serum complement levels, and is 4-5 times more common than clinical disease in non-epidemic conditions [6]. Our patient showed progression on the tenth day of treatment, proven by resolved edema and shortness of breath, but the delayed recovery could be caused by coexistence of heart failure due to RHD.

### 3.2. Rheumatic heart disease (RHD)

Rheumatic heart disease (RHD) has a worldwide prevalence of 33 million cases and 270,000 deaths annually, making it the most common acquired heart disease in the world. Rheumatic heart disease (RHD) remains as significant issue affecting children and adults especially in middle-income and low-income countries. Rheumatic heart disease or valvular damage is the result of acute rheumatic fever (ARF). The incidence of acute rheumatic fever and rheumatic heart disease is high in children between 5 and 14 years of age [9-15]. Children with ARF present with one or more of the following features: fever, carditis, polyarthritis, chorea, erythema marginatum and subcutaneous nodules [9-15]. The "Jones Criteria" currently the basis of clinical guidelines for diagnosing ARF. The revised Jones criteria 2015 for the diagnosis of rheumatic fever and rheumatic heart disease are divided into major and minor criteria. The major criteria include carditis, arthritis, polyarthralgia, Sydenham's chorea, erythema marginatum and subcutaneous nodule. The minor criteria include hyperpyrexia (≥ 38.0°C), monoarthritis, erythrocyte sedimentation rate ≥ 30 mm/hour and/or C-reactive protein ≥ 3.0 mg/dl and prolonged PR interval. The diagnosis is made with evidence of a preceding GAS infection (positive throat culture for group A beta-hemolytic Streptococci, positive rapid Streptococcal antigen test, or an elevated or rising anti-Streptococcal antibody titer and the presence of two major or one major and two minor criteria [16-17]).

In this case, we found history of fever, arthritis, carditis, prolonged PR interval, elevated ESR which fulfilled 3 major criteria (arthritis, carditis, polyarthralgia) and 3 minor criteria (fever, ESR ≥30mm/hour) with ASO titer 200 as evidence of GAS infection.

Mitral regurgitation is the predominant cardiac valvular lesion in children with RHD. Inadequate secondary prevention was identified as one of the main causes of development and progression of the disease, leading in adults to mitral stenosis, combined valvular lesions, arrhythmic and infective complications. In this case we suspect the patient with mitral regurgitation due to pansystolic murmur we heard during auscultation of the heart [9, 15].

The treatment plan of ARF includes antibiotic therapy, anti-inflammatory treatment and management of cardiac symptoms. The goals should include symptomatic relief, eradication of the group a streptococcal infection, prophylaxis against future infection and proper education to prevent future episodes. The most convenient way to treat GAS pharyngitis is with the use of long acting penicillin G. Symptomatic relief or arthritis symptoms can be provided with nonsteroidal anti-inflammatory drugs such as aspirin or naproxen. Other options also include using low dose glucocorticoids for patients who are allergic to aspilet or naproxen. Carditis can be prevented with early echocardiography and prevention of complications [9,15]. In this case, the patient was treated with erythromycin since penicillin G was unavailable that moment, aspilet as the anti-inflammation and bed rest for 4 weeks. Patient was planned to be referred to Bali for echocardiography.

Education of patients and their parents is very important for improving compliance with long-term prophylaxis especially in low educated patients. Special attention should be given to patients from rural areas and those with difficulties in adhering to antibiotic prevention regimes.

### 4. Conclusion

Although APSGN and ARF rarely occur together, the coincidence may be due to streptococci with nephritogenic and rheumatogenic strains. Early detection and treatment of GAS are crucial to prevent the risk of complications.
Compliance with ethical standards

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Statement of informed consent
Informed consent was obtained from parents.

References