**HENOCH SCHONLEIN PURPURA ASSOCIATED WITH ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS: A CASE REPORT**

**Deborah Melati, Ketut Dewi Kumara Wati, Gusti Ayu Putu Nilawati**

*Department of Child Health, Udayana University Medical School/ Sanglah Hospital Denpasar*

**ABSTRACT**

Acute post-streptococcal glomerulonephritis (APSGN) is one of the most common renal disease resulting from a prior infection with group A â-hemolytic streptococcus (GAS). Henoch Schonlein Purpura (HSP) is a systemic disease with frequent renal involvement, its etiology is still unknown but several infections have been described as trigger includingGAS infection. A 4 year 10 month old Balinese boy presented with full blown acute nephritic syndrome, an elevation in serum creatinine and four fold increase of anti streptolysin-O, also low serum levels of complement C3 with normal C4 confirmed the diagnosis of APSGN. During hospitalization he developed palpable purpura, gastrointestinal symptoms as well as leucytoclastic vasculitis in skin biopsy conclude HSP diagnosis.He was treated with anti-hypertensions and metylprednisolone intravenous. The prognosis of the patient was excellent, he showed normal physical examination with normal complete blood count and urinalysis after 3 months follow up. We conclude that both APSGN and HSP could appear concurrently after GAS infection. **[MEDICINA**

**2014;45:102-7]**

***Keywords:*** *APSGN, Henoch Schonlein purpura, children, anti streptolysin O*

**PURPURA HENOCH SCHONLEIN BERHUBUNGAN**

**DENGAN GLOMERULONEFRITIS AKUT PASCA INFEKSI STREPTOKOKUS**

**Deborah Melati, KetutDewi Kumara Wati, GustiAyuPutuNilawati** *Bagian Ilmu Kesehatan Anak, Fakultas Kedokteran Universitas Udayana/ Rumah Sakit Umum Pusat Sanglah Denpasar*

**ABSTRAK**

Glomerulonefritis akutpasca-infeksi streptokokus (GNAPS) adalah salah satu penyakit ginjal yang paling sering ditemukan pada anak, terjadi akibat infeksi streptokokus grup A (SGA). Purpura henoch shonlein (PHS) adalah penyakit sistemik disertai dengan keterlibatan ginjal dengan etiologi yang belum diketahui akan tetapi beberapa infeksi diketahui menjadi pemicu termasuk infeksi SGA. Kami mempresentasikan seorang anak laki-laki, suku Bali, berumur 4 tahun 10 bulan dengan gejala khas sindrom nefritik, penurunan kadar C3, dan kadar C4 normal serta peningkatan empat kali *anti- streptolysin O* (ASO) mendukung diagnosis GNAPS. Selama perawatan pasien mengalami palpable purpura, gejala nyeri perut, dan *leuko cytoclastic vasculitis* pada biopsi kulit mendukung diagnosis PHS. Pasien mendapat tatalaksana dengan terapi anti-hipertensi dan metilprednisolon intravena. Prognosis pasien sangat baik, setelah 3 bulan pemantauan didapatkan pemeriksaan fisik, laboratorium, dan urin lengkap dalam batas normal. Pada kasus ini didapatkan GNAPS dan PHS terjadi bersamaan setelah infeksi SGA. **[MEDICINA 2014;45:102-7]**

***Kata kunci:*** *GNAPS, purpura Henoch Schonlein, anak, anti streptolysin O*

**INTRODUCTION**

cute post-streptococcal glomerulonephritis (APSGN) caused by prior infection with specific nephritogenic strains

**A**

of group A beta-hemolytic streptococcus. The clinical presentation of APSGN varies from asymptomatic, microscopic hematuria to the full-blown acute nephritic syndrome, characterized

by red to brown urine, proteinuria (which can reach the nephrotic range), edema, hypertension, and acute kidney injury. Of the estimated 470,000 new annual cases of APSGN worldwide, 97 percent occur in developing countries, with an annual incidence that ranges from 9.5 to

28.5 per 100,000 individuals.1 The risk of APSGN is increased in older patients (greater than 60 years of

age) and in children between 5 and

12 years of age.2

Henoch Schonlein Purpura (HSP) is an IgA immune-complex mediated systemic leukocytoclastic vasculitis of small vessels and become the most common vasculitis in children occurs between the ages of 3 and 15 years. Henoch Schonlein Purpura is usually preceded by an upper respiratory infection (including

streptococcal infections) and may manifest with palpable purpura, arthralgia/arthritis, abdominal pain (due to vasculitis and intussusception in some), or renal disease.3,4 Both APSGN and HSP could appear after antigen exposure with similar clinical presentation such as hematuria, edema, and hypertension. The overall prognosis of HSP is favourable, but the long term outcome is dependent on the degree of renal involvement.2,3,5

The incidence of APSGN patients simultaneously presenting with HSP are rare and only five patients have been reported worldwide.6 We present one patient with APSGN then occurred HSP, the possibility of diagnosis and underlying mechanism of the two diseases.

**CASE ILLUSTRATION**

A 4 year 10 month old Balinese boy without previous renal diseases had an edema since three days before admission to the hospital, it was started in periorbital region especially noticed after wake up in the morning then extended to his abdomen and genitalia. He also complained having reddish urine since one day before hospitalized, without dysuria, polacysuria, nor pain in costo-vertebral angle. He had complained headache since three hours before admission to the hospital, constantly holding his head, without any symptoms of decrease consciousness, seizure nor vision loss. The physical exami- nation revealed a second grade hypertension, without shortness of breath, and tachycardia.

One month before he suffered two days fever, the fever was increase suddenly with the highest temperature was 39ºC, pain on swallowing, cough, and cold. The symptoms decreased after took an oral antibiotic and paracetamol. There was no history of hematuria, edema, hypertension, and joint pain in his family.

The urinalysis found proteinuria 500 mg/dl (+4) and

erythrocyturia 50/øl (+3) with erythrocyte dysmorphic. The laboratory result found four fold increase titer of anti- streptolysin O (ASO) 800, a normochromic normocytic anemia with hemoglobin level 10.0 g/dL, mean corpuscular volume (MCV) 77.4 fL and mean cell hematocrit concentration (MCHC) 34 g/dL. There was a decrease of glomerular filtration rate with increasing two fold of creatinine serum (2.22 mg/ dL) and throat swab found coccus gram positive and basil gram negative, decrease C3 complement level (37), and normal C4 complement level (17). He was diagnosed with APSGN with second grade hypertension and also overweight. He was treated with ACE inhibitor, furosemide, oral erythromycin, low salt diet, and maintenance protein diet as a nutritional therapy, and bed rest. The second grade hypertension still appeared until 5 days of hospitalization with the highest blood pressure was 140/100 mmHg.

On the third until fifth day of hospitalization he was complained for abdominal pain without any specific location accompanied with frequent nausea and vomiting, without blood, he was treated with an oral antiemetic but failed to reduce the symptoms. On the fifth day of hospitalization, there was a spontaneously appeared reddish palpable rash on his knee, elbow, and buttock, each diameter 0.5-2 centimetre, some of them confluences (**Figure 1**). Several hours after the rashes appeared, he suffered from pain and swollen joint on left knee and made it difficult to move. Second grade hypertension was still found, without edema nor macroscopic hematuria. Urinalysis examination found proteinuria 150 mg/dl (3+) and erythrocyturia 250/ øl (5+) with cast erythrocyte. The laboratory result showed leukocytosis of 11.20 K/uL, normochromic normocytic anemia with hemoglobin level 9.4 g/dL,

MCV 77.9 fL and MCHC 33.6 g/ dL, platelet count 400 K/uL, reticulocyte count 1.2, and slight increase creatinine serum (1,47 mg/dL). Blood smear result found normochromic normocytic anemia. There was an increased level of Immunoglobulin G (1562) and normal level of Immunoglobulin A (198). Skin biopsy found a mild lymphocytic vasculitis with busy dermis, conclude the leucocytoclastic vasculitis supporting the diagnosis of HSP ( **Figure 2** ). He was diagnosed with APSGN with second grade hypertension, HSP, and overweight. Intravenous methyl prednisolone was given for four days and the HSP symptoms gradually relieved.



**Figure 1**. Palpable purpura on the extremity.

He was discharge after 12 days of hospitalization, but first grade hypertension persisted. During follow up at pediatric outpatient clinic, oral anti- hypertensions gradually reduced with monitoring for blood pressure and hematuria.

On the third week after the symptoms of HSP, he returned and complained with reappeared gross hematuria, accompanied by first grade hypertension. The urinalysis found abundant erythrocytes with erythrocyte dismorphic, proteinuria of 500 mg/dL (+4), the complete blood count found

**Figure 2**. Leucocytoclastic vasculitis on skin biopsy.



nephritogenic strain serotype associated with post pharyngitis APSGN are M 1,4,12,25 and associated with pyoderma are M

2, 42, 49, 56, 57, 60.1,9,10

The clinical presentation of APSGN varies from asymptomatic, microscopic hematuria to the full blown acute nephritic syndrome, and an elevation in serum creatinine as a result of decrease glomerular

leucocytosis 14.4 K/uL,

hemoglobin level 11.1 g/dL, and platelet count 300 K/uL. There was a normal glomerular filtration rate with normal creatinine serum of

0.55 mg/dL and blood urea nitrogen 12.0 mg/dL. He was treated at home with oral ACE inhibitor, diuretic, and angiotensin receptor blocker, one week later he shown a normal urinalysis and normal complete blood count at pediatric outpatient clinic visit. The time line of the patient shown in **Figure 3.**

**DISCUSSION**

The case presented with full blown of APSGN accompanied with HSP during hospitalization. The case described both APSGN and HSP could occur concomitantly. The incidence APSGN spontaneously presen- ting HSP is rare and only five had

been reported worldwide since

1989.6

Acute glomerulonephritis is a clinical syndrome characterized with sudden decrease of glomerular filtration rate, found with edema, hematuria, hypertension, oligouria, and renal insufficiency. Acute post-streptococcal glomerulonephritis is a form of glomerulonephritis appears to induced by specific nephritogenic strains of group A beta-hemolytic streptococcus (GAS) causing a glomerular immune complex disease triggers complement activation and inflammation.1,2,8,9

Acute post-streptococcal glomerulonephritis found the most in children age three until eight years old, with boys and girls ratio

2:1, commonly at 2.5 until 15 years old.1,2,4 M protein component on GAS responsible for nephritogenic strain or cardiogenic strain, in

filtration rate.9 There is usually an antecedent history of a GAS skin or throat infection. The latent period between GAS infection and APSGN is dependent upon the site of infection: between one and three weeks following GAS pharyngitis and between three and six weeks following GAS skin infection.11

Generalized edema is present in about two-thirds of patients due to sodium and water retention, edema occurs in palpebral frequently after woke up in the morning. Gross hematuria is present in about 30 to 50 percent of patients, the urine looks smoky, and tea or coca cola-coloured. Hypertension is present in 50 to

90 percent of patients and varies from mild to severe, it is primarily caused by fluid retention.8,10 In this case there was an edema, headache, vomiting, epistaxis, gross hematuria, hypertension,



**Figure 3.**Time line of the patient.

and a history of pharyngitis one month prior to hospitalization.

The streptozyme test, which measures five different streptococcal antibodies including antistreptolysin O (ASO), is positive in more than 95 percent of patients due to pharyngitis and about 80 percent of those with skin infection.8,10 Prior data shown ASO have 70% sensitivity and 86-93% specificity. The evidence of GAS infection also find from throat swab culture or skin swab culture.11 In about 90 percent of patients with APSGN, C3 are significantly depressed in the first two weeks of the disease and return to normal within four to eight weeks after presentation.11,12 The combination of a low C3 level and a normal or only slightly decreased C4 level indicates activation of the alternative pathway of complement.10,19 In this case, the diagnosis of APSGN based upon clinical findings of acute nephritis and a laboratory findings of a recent GAS infection. Documentation of a recent GAS infection includes a fourfold increase ASO titer (800 IU/ml) confirmed with decrease of C3 level and normal C4 level, and increase of serum Immunoglobulin G(IgG) level**.**

APSGN resolves fairly slowly over many months, with hypertension resolves usually within 3 weeks, as does gross hematuria, but microscopic hematuria and proteinuria may persist for many months. Overall the prognosis of APSGN is excellent, with full recovery expected in more than 98% of affected children, only few children develop chronic renal failure.23

Recurrence of APSGN is a relatively rare phenomenon with an incidence of recurrent ranges from 0.7% to 7.0%.6,13 In our case, gross hematuria resolved early at the acute onset of the disease, in the other hand microscopic hematuria, proteinuria as well as hypertension persist within 3 weeks.

The case developed a palpable purpura localized in upper, lower extremities and buttocks on the fifth day of hospitalization.The rash appeared three days after others clinical manifestation of HSP such as abdominal pain and vomiting. The laboratory result found no thrombocytopenia, occult blood positive 2 and protenuria 150 mg/dl (3+) and erythrocyturia 250/ øl (5+) with cast erythrocyte. Henoch Schonlein Purpura is an immunoglobulin A (IgA) mediated small vessel vasculitis and is the most common vasculitis in children. The incidence is approximately 10-20/100,000.3 It is primarily a childhood disease that occurs between the ages of 3 and

15 years with a peak incidence at five to seven years of age. There is a male predominance with reported male-to-female ratios of

1.2:1 to 1.8:1.3,4 Gastrointestinal complaints precede the rash in about 15 to 35 percent of HSP cases and range from mild (nausea, vomiting, abdominal pain, and transient paralytic ileus) to more significant findings (gastrointestinal hemorrhage, bowel ischemia and necrosis, intussusception, and bowel perforation).3,14,15All HSP patients developed palpable purpura, but it is not always the initial presenting sign.3,14 The rash typically appears in crops, symmetrically distributed, and located primarily in gravity or pressure-dependent areas such as the lower extremities and buttocks.3

In 2008 European League Against Rheumatism (EULAR), Pediatric Rheumatology European Society (PRES), and Pediatric Rheumatology International Trials Organization (PRINTO) proposed new classification criteria for HSP classification includes purpura or petechiae not related to thrombocytopenia with lower limb predominance as a mandatory finding and at least one of the four following criteria: abdominal pain, histopathology, arthritis or arthralgia and renal

involvement. This criteria yields a sensitivity of 100% and a specificity of 87%.16 The characteristics finding of HSP are a leukocytoclastic vasculitis accompanied by IgA immune complexes within affected organs.3,15,16 On skin biopsy there was a leukocytoclastic vasculitis, therefore this case was fullfiling the diagnostic criteria of HSP.

Both APSGN and HSP could appear after antigen exposure with similar clinical presentation such as hematuria, edema, and hypertension.7 In our case there was two possible mechanisms of the diseases: 1) GAS infection predispose to APSGN, and APSGN exhibit atypical clinical manifestations including the co- occurrence of immune-mediated diseases, in this case is HSP. Recently has been identified the nephritis associated plasmin receptor (NAPlr) and a cationic cysteine proteinase known as streptococcal pyrogenic exotoxin B (SPEB) that is generated by proteolysis of a zymogen precursor (zSPEB). Both of these fractions are capable of activating the alternate pathway of the complement system and subsequent damage to the glomerular basement membrane (GBM) and podocytes in patients with APSGN. Both SPEB and NAPlr are capable of inducing chemotactic (monocyte chemoattractant protein 1) and IL-

6 moieties in mesangial cells, promoting enhanced expression of adhesion molecules. Recent investigations also demonstrated peripheral blood leukocytes respond with release of IL-6, TNF- á, IL-8, and TGF- â when reacted with SPEB. 2This mechanism option in our case is inflammatory response in APSGN contributing to the development of HSP by an immune complex-mediated mechanism triggered by GAS infection,62) The second possible mechanism is both APSGN and HSP developed after GAS infection, this happened when the

nephritogenic strain of GAS preceded before APSGN and GAS without specific strain contributing the development of HSP. It is also been found that NAPIr, which has been found in the glomeruli and in serum of many patients with APSGN,has been also found in renal glomeruli of patients with HSP and it is likely that NAPlr may have a role in the pathogenesis of HSP.17Although renal biopsy has important implications on early diagnosis and therapeutic interventions, children undergoing renal biopsy is not more than

10%.18 Renal biopsy is rare in APSGN children and found enlarged glomeruli, proliferating mesangial and endothelial cells, infiltration of polymorphonuclear leukocytes, monocytes, and eosinophils within the capillary lumina and mesangium on light microscopy.13 With the absence of electron microscopy and cost effectivity in our case therefore we did not perform a renal biopsy. We can speculate two possible mechanisms but further investigation is mandatory to prove which mechanism that may contributing of the development of APSGN and HSP concurrently.

Treatment of APSGN in our case include antibiotic, anti- hypertension, and nutritional supportive therapy. The resolution of APSGN in our case followed its natural history and HSP resolution after given methyl prednisolone injection for four days. The onset of HSP nephritis occurred 46% patients, at a mean of 14 days after HSP diagnosis, and within one month in the majority of cases.15 On the follow up there was a gross hematuria appeared between third week after the initial symptoms of HSP, normal glomerular filtration rate and creatinine serum. The case was diagnosed with recurrent HSP nephritis and treated outside hospital with ACE inhibitor, diuretic, and angiotensin receptor blocker. Based on epidemiologic

data the recurrent of gross hematuria in our case is more likely to be caused by HSP rather than APSGN since the later has a relatively low risk recurrent.19

The overall prognosis of HSP is favourable, but the long term outcome is dependent on the degree of renal involvement.3,5,19 Systemic review of 12 studies of 1133 children with HSP found predictable risk factors for renal manifestation in HSP, it conclude that nephrotic range proteinuria with or without edema or hypoalbuminemia, an elevated blood urea nitrogen or serum creatinine, and/or hypertension has a worse prognosis.15After three months follow up, our patient showed normal physical examination with normal complete blood count and urinalysis.

**SUMMARY**

A 4 year 10 month old Balinese boy without previous renal diseases had an edema, headache, and urinalysis found nephrotic range proteinuria with erythrocyte dysmorphic. The APSGN diagnosis confirmed from four fold increase of ASO titer, decrease of glomerular filtration rate, coccus gram positive from throat swab, and decrease of C3 complement level. We confirmed the HSP diagnosis on the fifth day of hospitalization based on palpable purpura on extremities and buttock, without thrombocytopenia, and leucocytoclastic vasculitis on skin biopsy. We reported a case with APSGN and HSP appear concurrently after GAS infection. He was treated with anti- hypertensions and methyl prednisolone intravenous injection. Although he developed nephritis HSP three weeks after the initial symptoms of HSP, the prognosis of this patient was excellent, he showed normal physical examination and normal complete blood count and urinalysis after 3 months follow up.

**REFERENCES**

1. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005;5:685.

2. Rodriguez-Iturbe B, Musser

JM. The current state of

p o s t s t r e p t o c o c c a l glomerulonephritis. J Am Soc Nephrol. 2008;19:1855.

3. Dedeoglu F, Kim S, Sundel R.

Clinical manifestations and diagnosis of Henoch-Schönlein Purpura. TePas E: Up To Date Basow DS; 2011.

4. Al-Sheyyab M, Batieha A, el- Shanti H, Daoud A. Henoch Schonlein Purpura and streptococcal infection: a prospective case-control study. Ann Trop Paediatr.

1999;19(3):253-5.

5. Niaudet P, Appel GB, Hunder GG. Renal manifestation of Henoch-Schonlein purpura. Forman JP: Up To Date Basow DS; 2011.

6. Watanabe T. Atypical Clinical

Manifestations of Acute

P o s t s t r e p t o c o c c a l Glomerulonephritis. An Update on glomerulopathies: clinical and treatment aspects; 2011.

7. Rivera F, Anaya S, Perez- Alvarez, Sanchez de la Nieta M, Vozmediano MC, Blanco J. Henoch-Schönlein nephritis associated with streptococcal infection and persistent hypocomplementemia: a case report. Journal of Medical Case Reports. 2010;4:50.

8. Lau KK, Suzuki H, Novak J.

Pathogenesis of Henoch Schonlein Purpura nephritis. Pediatr Nephrol. 2010;25:19–

26.

9. Niaudet P. Poststreptococcal glomerulonephritis in children. Kim SM: Up To Date Basow DS; 2011.

10. Ivory DM, Folzenlogen DD.

Post-streptococcal Syndromes, A Rheumatologist Perspective. The Internet Journal of Rheumatology.

2010;6:2.

11. Eison TM, Jones DP, Chesney RW, Wyatt RJ. Post- streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatr Nephrol. 2011;26:165–80.

12. West CD, McAdams AJ.

Serum and glomerular IgG in

p o s t s t r e p t o c o c c a l glomerulonephritis are correlated. Pediatr Nephrol.

1998;12:392–6.

13. Brewer ED, Berry PL.

Glomerulonephritis and Nephrotic Syndrome. In: McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB,

editors. Oski’s Pediatrics Principles and Practice. 3rd edition. Philadelphia: Lippincott William Wilkins;

1999. p. 495-9.

14. Ballinger S. Henoch– Schonlein purpura. Current Opinion on Rheumatology.

2003;15:591–4.

15. Jauhola O, Ronkainen J, Koskimies O, Ala-Houhala, Arikoski P, Holtta T, et al. Clinical course of extrarenal symptoms in Henoch- Schonlein purpura: a 6-month prospective study. Arch Dis Child. 2010;95(11):871-6.

16. Ozen S, Pistorio A, Lusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/ PRES criteria for Henoch schonlein purpura, childhood polyarteritis nodosa, childhood wagener granulomatosis and

childhood takayasu arteritis: Ankara 2008. Part II: final classification criteria.Ann Rheum Dis. 2010;69:798-806.

17. Schmitt R. Studies of the pathogenesis of IgA nephropathy and Henoch- Schönlein purpura, with special reference to Streptococcus pyogenes infections and complement. Faculty of Medicine Doctoral Dissertation Series:Lund University; 2012.

18. Saca E, Hazza I, El-Imam O, Kawar M. Spectrum of biopsy- proven renal disease in the pediatric age group at King Hussein medical center. J Res Med Sci. 2007;14(1):34-7.

19. Pachman LM. The spectrum of vasculitis in pediatric rheu- matic disease. Rheumatología.

2001;17(3):102-5.