Case Report

Stroke in Henoch-Schönlein Purpura Associated with Methicillin-Resistant Staphylococcus aureus Septicemia: Report of a Case and Review of the Literature

Kanya Temkiatvises MD*,
Yongchai Nilanont MD*, Niphon Poungvarin MD, FRCP*

** Division of Neurology, Department of Medicine,Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok*

Neurological involvement in Henoch-Schönlein purpura (HSP) such as stroke is uncommon manifestiation, particularly in association with Staphylococcus aureus (S. aureus). The authors reported a 17-year-old man who developed sudden onset of right hemiparesis while he was admitted in the hospital about his prolonged fever, palpable purpura and upper gastrointestinal bleeding. He also had evidence of MRSA septicemia before the onset of right hemiparesis. Skin biopsy was done and showed that there was leukocytoclastic vasculitis with IgA deposition. He had received completed course of antibiotics and then he was subsequently improved after steroid therapy in the next 2 weeks. Review of case reports from previous English literatures, discovered the association between MRSA infection and HSP which can cause several CNS manifestations including stroke symptoms from cerebral vasculitis.

Keywords: *Stroke, Henoch-Schönlein purpura, Cerebral vasculitis, MRSA septicemia*

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Henoch-Schönlein purpura (HSP) is an immune complex mediated generalized small vessel vasculitis, characterized by palpable purpura, arthralgia, abdominal pain, and/or renal abnormalities. It usually affects younger children from 5 to 15 years old. The pathogenetic mechanisms underlying HSP are poorly understood but there have been reports about the association of HSP with *Staphylococcus aureus* (*S. aureus*) infection which was first reported in 1987[1-5]. Neurological involvement in HSP is less common than other organ systems, particularly in association with *S. aureus* infection. CNS involvement in HSP, first described by Osler in 1914, is characterized by mild symptoms such as headache, irritability, peripheral neuropathy, behavioral changes, and reduction in the level of consciousness[6]. Most common neurological presentations are headache and behavioral changes[7,8]. Severe neurological complications including seizures, hemiparesis, or coma are rare but have been previously reported in the English literature[7-10].

The authors reported a 17-year-old man who presented with prolonged fever, palpable purpura, upper gastrointestinal bleeding and then developed sudden onset of right hemiparesis. Before the onset of right hemiparesis, he had evidence of MRSA septicemia. Skin biopsy was done and showed that there was leukocytoclastic vasculitis with IgA deposition. He had received completed course of antibiotics and then he was subsequently improved after steroid therapy in the next 2 weeks.

Case Report

A 17-year-old right-handed man was referred to Siriraj Hospital with generalized weakness for 4 days. Three weeks before admission, he had a motorcycle accident resulted in abrasion wounds on his right knee. He went to a drug store for pain relieving drugs. A few days later, after taking those medications, he

Correspondence to: Poungvarin N, Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Prannok Rd, Bangkoknoi, Bangkok 10700, Thailand. E-mail: niphonp.thailand@gmail.com, sinpg@mahidol.ac.th

developed painless erythematous rash on both soles with no itching. He stopped all drugs but skin rash had still not subsided.

One week later, he developed low-grade fever with peri-umbilical pain. He went to a private hospital. On examination, his body temperature was 38°C, blood pressure was 190/110 mmHg. Purpura at both arms and legs were recorded. He was admitted and investigated for prolonged fever and hypertension for three days. Empirical antibiotics (ceftriaxone and gentamicin), amlodipine, and dexamethasone 5 mg (single dose) were given.

He was discharged after abdominal pain and fever had subsided. The next day, he had a new onset of left abdominal pain, fever, and passing black stool. Then he went to another hospital and was diagnosed with upper gastrointestinal hemorrhage (UGIH). Symptomatic and supportive treatments were given then his symptoms improved but he still had fever and a rash. Methicillin-resistant *Staphylococcus aureus* (MRSA) was obtained from two hemocultures. He was treated with intravenous penicillin (12 mU per day) and ciprofloxacin (500 mg per day). Two days after treatment, he still had a high fever and developed generalized muscle weakness, and then was referred to Siriraj Hospital. He was healthy and denied any medications or substances abuse in the past. He lost 5 kilograms of his body weight within 3 weeks.

Examination revealed a body temperature of 36.5°C, blood pressure of 150/100 mmHg, pulse rate of 110/min and respiratory rate of 16/min. There were palpable purpura of both feet and hands. No Osler node or Janeway lesion was detected. Cardiovascular system was normal. Nervous system revealed proximal muscle weakness (grade 3/5 MRC grading) of both upper and lower extremities with normal deep tendon reflex.

Initial laboratory tests showed CBC hemoglobin of 12.5 g/dl, white blood cell count of 13980/ul (N74%, L15%, Mo7%, E2%) and a platelet count of 327,000/ul. Blood urea nitrogen concentration was 8 mg/dl and serum creatinine concentration was 0.5 mg/dl. Hypokalemia (K 2.8 mmol/L) was detected. Other blood chemistry profiles were within normal range. Anti-HIV and VDRL were non-reactive. Urinalysis was normal.

He had potassium replacement and vancomycin combination with gentamicin (sensitive to MRSA from previous culture) was prescribed. Potassium level finally rose to 4.4 mmol/L resulting in full recovery of all his motor power.

Three days later, he suddenly developed transient but definite dysarthria and right facial weakness (lasted 3 minutes). He had no headache or visual loss and neurological examinations were normal. He had no fever and blood pressure was then 110/70 mmHg. Computerized tomography (CT) of the brain showed a small area (5 x 5 mm) of cerebral hemorrhage at left lentiform nucleus (Fig. 1A). MRSA septicemia with mycotic aneurysm was suspicious but both transthoracic and transesophageal echocardiograms revealed no clot or vegetation. Serum erythrocyte sedimentation rate was 48 mm/hr, C-reactive protein was 26.2 mg/L (normal value < 3.12 mg/L). Doppler ultrasonogram of renal arteries showed no significant stenosis, normal kidney size, and parenchyma. Urine vanillylmandelic acid, plasma renin activity, and serum aldosterone were all within normal ranges. He received intravenous vancomycin and gentamicin for 14 days. His symptoms were gradually improved, i.e. no fever but purpura persisted. Repeated hemocultures reported no growth.

Two weeks after admission he developed sudden right hemiparesis, right upper motor neuron facial palsy, and dysarthria. Physical examination revealed right hemiparesis (grade II/V of right arm and grade IV/V of right leg).

Repeated CT brain demonstrated multiple lacunar infarctions at bilateral lentiform nuclei and head of left caudate, old spot hemorrhage at left lentiform nucleus. CT angiography of the brain showed normal internal carotid and vertebrobasilar vessels without any focal narrowing (Fig. 1B). Cerebral angiogram was normal. Lumbar puncture revealed clear colorless cerebrospinal fluid (CSF) with opening pressure of 120 mmH_2O, and closing pressure of 90 mmH_2O. CSF analysis revealed normal glucose and protein levels, one lymphocyte, and 23 red blood cells per microlitre. CSF cultures were negative for bacteria.

Skin biopsy showed leukocytoclastic vasculitis with IgA deposition, thus the diagnosis of Henoch-Schönlein purpura with cerebral vasculitis was established. Methylprednisolone was given for 3 days then changed to 45 mg of oral prednisolone. All clinical symptoms including neurological signs and skin rash were resolved. Prednisolone has been tapered off in five months.

Discussion

The presented patient fulfilled all the criteria for the diagnosis of HSP from the American College of Rheumatology Classification 1990, that were age of

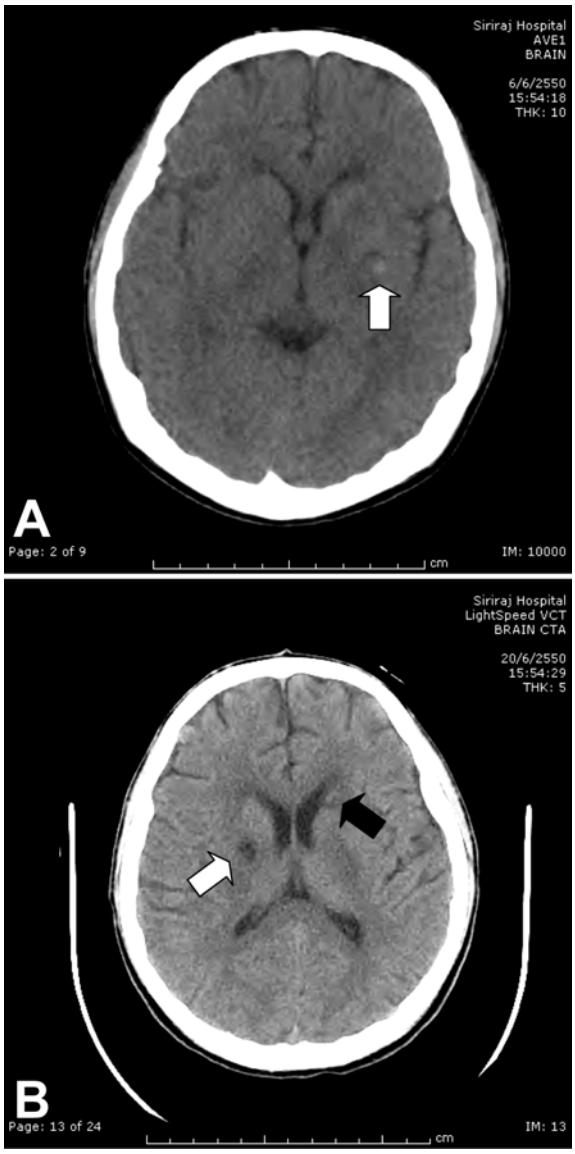

Fig. 1 A: Computerized topography (CT) of the brain showed a small area (5 x 5mm) of cerebral hemorrhage at left lentiform nucleus (arrow). B: The next CT Brain demonstrated multiple lacunar infarction at bilateral lentiform nuclei (arrow, white) and head of left caudate (arrow, black)

onset ≤ 20 years, palpable purpura, acute abdominal pain, and biopsy evidences of granulocytes in the walls of small venules[11]. Sensitivity and specificity of these diagnostic criteria are nearly 90%. Approximately 50 percent of patients have hematuria and proteinuria, but only 10 to 20% have renal insufficiency[12]. Thus, it is not surprising that the presented patient had no renal symptoms.

There are many questions concerning the diagnosis in the presented patient, because he had evidence of MRSA septicemia that could have septic emboli to the brain and causing cerebral hemorrhage or infarction. However, two reported hemocultures taken immediately at the onset of stroke revealed no organism. Especially in the second episode of stroke, he had been treated with a completed course of antibiotics. Therefore, the most likely mechanism of stroke in this patient was cerebral vasculitis from HSP. However, there have been reports from English literatures about the association between MRSA infection and HSP[1-5]. All the patient's characteristics have been tabulated in Table 1. They proposed staphylococcal toxins from *Staphylococcus aureus* act as superantigens, causing T-cell stimulation. Production of cytokines can cause tissue damage or induce polyclonal production of IgA and IgG antibodies, resulting in immune complex formation. Duration between the onset of staphylococcal infection and the appearance of HSP was varying from 5 to 40 days (mean: 23 days). All patients had renal involvement but none had any symptoms of CNS manifestation as in the presented patient.

Usually neurological involvement in HSP is less common than other organ systems. In a previous case report from Belman et al, headaches and mental status changes are the most frequent neurological complications of HSP, followed by seizures, focal neurological deficits, mononeuropathies, and polyradiculopathies[8]. Most cases of cerebral vasculitis in HSP, lesions were confined in parieto-occipital cortex but lesions in the presented patient mostly involved subcortical deep structural area. Eun SH et al reported that most HSP occur in children from 5 to 15 years old, with a male:female ratio of 2:1[9]. Neurological symptoms usually develop less than two weeks after the onset of HSP. Most patients experienced seizures and followed by hemiparesis, mental changes, and subdural hematoma. Subarachnoid hemorrhage, intraparenchymal bleeding and infarction, transient blindness and blurred vision, and encephalopathy had also been reported.

Because HSP is a condition of small vessel vasculitis, cerebral vasculitis from HSP cannot be excluded by normal cerebral angiography, which has a limitation for detecting small vessel diseases as in the presented patient. MRI brain is highly sensitive but not specific to demonstrate cerebral vasculitis[13]. Cerebrospinal fluid abnormalities are non specific, but useful in implicating an inflammatory process within

Table 1. Characteristics of patients with Henoch-Schönlein purpura associated with *Staphylococcus aureus* infection

Age/ Sex	Type of infection (underlying diseases)	Duration (days)*	Clinical symptoms	Renal Bx	Skin Bx	Treatments	Outcomes
60[1,3] Male Japanese	Subphrenic abscess after an operation for acute appendicitis	5	RPGN with NS Arthralgia Purpura	+	+	Vancomycin, Hemodialysis	Maintainance hemodialysis
21[3] Male Japanese	Abscess of the abdominal cavity from trauma	14	RPGN with NS Arthralgia Purpura	+	-	Prednisolone 30 mg daily Plasma exchange	Maintainance hemodialysis
27[3] Male Japanese	Abscess of the abdominal cavity (retroperitoneal tumor)	30	NS Arthralgia Purpura Abdominal pain	+	-	Prednisolone 30 mg daily Cyclophosphamide 50 mg daily	Complete remission
60[3] Male Japanese	Vertebritis (prostate hypertrophy)	30	NS Arthralgia Purpura Abdominal pain	+	-	Prednisolone 40 mg daily	Renal insufficiency
57[3] Male Japanese	Pneumonia (cerebral hemorrhage)	40	RPGN with NS Arthralgia Purpura	+	-	Plasma exchange	Death (hepatic failure)
61[3] Male Japanese	Subcutaneous abscess in diabetes mellitus	29	RPGN with NS Arthalgia Purpura	+	-	Prednisolone 30 mg daily	Death (sepsis)
50[2] Greece	Infected saphenectomy wound one months after coronary artery bypass surgery	6	ARF Purpura Abdominal pain	-	+	Vancomycin Gentamicin Prednisolone 1 mg/kg/day	Complete remission
28[4] Female Japanese	Postpartum infection	30	ARF Purpura Abdominal pain	+	+	Methylprednisolone Prednisolone 80 mg daily Teicoplanin + prednisolone 10 mg daily then 30 mg dialy	Initial worsening symptoms then complete remission
21[5] N/A	Endocarditis (heroin addict)	N/A	Nephritis Purpura Bloody diarrhea	+	+	N/A	Complete remission

Abbreviations: RPGN, rapidly progressive glomerulonephritis; NS, nephritic syndrome; ARF, acute renal failure; Bx, biopsy; N/A, not available; +, done; -, not done

* Duration is the time between the onset of staphylococcal infection and the appearance of Henoch-Schönlein purpura

the CNS and excluding infection and malignant diseases that may present similarly. Pooled case reports revealed two important findings of CSF, that are raised cell count (mainly lymphocytosis) and increasing protein content in 50-80% diagnosis of HSP patients[13].

Classical leukocytoclastic vasculitis in post-capillary venules with IgA deposition in the presented patient's skin biopsy is pathognomonic evidence for the HSP[12]. Practically, the biopsy should contain a skin specimen of less than 24 hours old lesion because

the more chronic lesions, the more vessel damage resulting in more advancing of the lesion and leading to non-specific leakage of all isotypes of immunoglobulin.

According to a few case reports, there have been no randomized control trials in treatment of cerebral vasculitis in HSP, especially associated with MRSA infection. Hashimoto M, et al reported that steroid could cause worsening symptoms of glomerulonephritis associated with HSP, if there was no adequate treatment in MRSA infection. However, corticosteroid was still necessary in patients who had persistent disease activity of nephritis, but special attention should be paid to possible reactivation of the MRSA infection [4]. The presented patient was treated with anti-MRSA medication (vancomycin and gentamicin) and followed by a high dose of corticosteroid.

In conclusion, MRSA septicemia can be associated with HSP, which can cause several CNS manifestations including stroke symptoms from cerebral vasculitis.

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โรคหลอดเลือดสมองในผู้ป่วยโรค Henoch-Schönlein purpura ที่สัมพันธ์กับการติดเชื้อ Staphylococcal aureus ที่ดื้อต่อยา methicillin ในกระแสเลือด: รายงานผู้ป่วย 1 ราย และทบทวนวารสาร

กัญญา เต็มเกียรติวิเศษ, ยงชัย นิละนนท์, นิพนธ์ พวงวรินทร์

Henoch-Schönlein purpura (HSP) เป็นกลุ่มอาการของโรคที่เกิดจากการอักเสบของหลอดเลือดขนาดเล็กในร่างกาย มีอาการและอาการแสดงได้ในหลายระบบ ส่วนมากมักมีอาการในระบบผิวหนัง ทางเดินอาหาร และไต อาการและอาการแสดงในระบบประสาทส่วนกลางพบได้น้อย จากการศึกษาในอดีตยังไม่ทราบสาเหตุของโรคที่แน่ชัด แต่มีรายงานความสัมพันธ์ระหว่าง HSP และ การติดเชื้อ Staphylococcal aureus ที่ดื้อต่อยา methicillin ในกระแสเลือด ซึ่งส่วนใหญ่ผู้ป่วยมักมีอาการ และอาการแสดงทางระบบไตเป็นหลัก โดยไม่มีรายงานผู้ป่วยที่มีอาการและอาการแสดงทางระบบประสาทส่วนกลางเลย โดยเชื่อว่าสารพิษที่ผลิตจากเชื้อชนิดนี้ จะกระตุ้นระบบภูมิคุ้มกันของร่างกาย ทำให้เกิดการอักเสบและทำลายเนื้อเยื่อต่าง ๆ การรักษาผู้ป่วยในกลุ่มนี้มักต้องให้ยาปฏิชีวนะกำจัดเชื้อชนิดนี้ก่อน หลังให้การรักษาถ้าผู้ป่วยยังคงมีอาการและอาการแสดงของการอักเสบอยู่ จึงค่อยพิจารณาให้ยาสเตียรอยด์ต่อคณะผู้รายงานนำเสนอผู้ป่วยชายไทยอายุ 17 ปี ที่เป็นโรคนี้ มาด้วยอาการไข้ มีผื่นชนิดเลือดออกใต้ผิวหนัง เลือดออกในทางเดินอาหาร ผลเพาะเชื้อจากเลือดพบว่ามีการติดเชื้อชนิดนี้ในกระแสเลือด หลังให้การรักษาด้วยยาปฏิชีวนะ ผู้ป่วยมีปัญหาอ่อนแรงที่แขนขาซีกขวาอย่างฉับพลัน ผลตรวจชิ้นเนื้อพยาธิสภาพที่ผิวหนัง พบลักษณะการอักเสบของหลอดเลือดขนาดเล็กแบบ leukocytoclastic vasculitis และย้อมติดสีอิมมูโนโกลบูลินชนิดเอ ซึ่งเป็นลักษณะจำเพาะของโรค HSP