Henoch-Schonlein Purpura in Thai Children: A Report from Single Center

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Henoch Schonlein Purpura (HSP) is the most common vasculitis in childhood. It is a self-limited disease. Recurrent HSP is not uncommon. Colchicine, an anti-inflammatory drug, has been used in prolonged HSP in only a few patients with good response. The present study described pediatric HSP patients in a single center, Thailand. To determine the epidemiology, clinical manifestations, treatments, and outcomes of HSP patients, the authors retrospectively studied 26 patients (age <15 years) diagnosed with HSP at Thammasat University Hospital, from January 01, 2004 through December 31, 2010. The mean age was 7.2 ± 3.8 years; median (range) follow-up was 2 (0.5-39) months. Fifteen (57.7%) patients were female. Clinical manifestations were skin (100%), joint (69.2%), gastrointestinal symptoms (50%) and renal involvement (19.2%). Symptoms lasted within 8 weeks in 21(80%) patients. Recurrences identified in 5 (19%) patients with a mean of 4.8 ± 2.4 times. The clinical outcome was excellent without major complication. Colchicine induced remission of severe and recurrent petechiae in one patient who developed methemoglobinemia after dapsone therapy. Colchicine may be an effective drug for prolonged HSP without renal involvement. The controlled studies to establish benefit effect and optimal regimen of colchicine in HSP is required.

Keywords: *Henoch-Schonlein purpura, Recalcitrant Henoch- Schonlein purpura, Recurrent Henoch-Schonlein purpura, Colchicine, Asian Children*

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Henoch Schonlein Purpura (HSP) is the most common vasculitis in childhood. It is characterised by a systemic leukocytoclastic vasculitis with immunoglobulin (Ig)A-dominant immune deposition[1]. Clinical features include a purpuric rash on the lower extremities, diffuse abdominal pain, arthritis/arthralgia, and hematuria or proteinuria indicating renal involvement[2]. The pathogenesis of HSP remains unknown, although many antigens have been found to trigger HSP[3-5]. Most pediatric patients have a self-limited disease. The extrarenal symptoms typically resolve rapidly without complication. In most case, renal involvement is mild and self-limited. Among Henoch Schonlein nephritis (HSN) patients, 1-7% of patients progress to end-stage of disease[6-8]. The majority of patients have resolution of symptoms within 2 weeks to 3 months[9,10]. Recurrence of disease is not uncommon. 15-40% of patients have recurrences after the resolution of initial symptoms[7,9,10]. The present study reported a case series of pediatric HSP patients from a hospital in suburban area of Pathumthani province, Thailand. The authors reported epidemiology data, clinical manifestations, treatments, and outcomes of HSP in Thai children. The authors also demonstrated a successful treatment of multiple episodes of recurrent petechiae with colchicine.

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Material and Method

Patients

Medical records of pediatric patients (0-15 years) diagnosed as HSP at the Thammasat University Hospital from January 01, 2004 through December 31, 2010 were retrospectively reviewed. The present study was approved by the ethic committee of the Faculty of Medicine, Thammasat University. All patients were diagnosed according to the European League Against Rheumatism/Pediatric Rheumatology Internatinal Trials Organization/Pediatric Rhematology European Society (EULAR/PRINTO/PRES)[11,12] as follows: purpura or petechiae (mandatory) with lower limb predominance

and at least one of the four following criteria: 1) Abdominal pain; 2) Any biopsy showing predominant IgA; 3) Arthritis or arthralgia; 4) Renal involvement.

The demographic data including sex, age at onset, age at diagnosis, and duration of follow-up were recorded. The initial presentations including the criteria endorsed by EULAR/Pres and other symptoms were recorded. The laboratory data at diagnosis of HSP were collected as follows: leucocytosis (> 15,000/mm^3), elevated erythrocyte sediment rate (ESR) (> 20 mm at 1 h), low complement component 3 (C3 < 0.9 mg/dL), low complement component 4 (C4 < 0.1 mg/dL), proteinuria (24-hr urine protein > 4 mg/m^2/h or urine protein/creatinine ratio > 0.2), nephrotic range proteinuria (24-hr urine protein > 40 mg/m^2/h or urine protein/creatinine ratio > 2) and active urine sediment (hematuria, > 5 RBCs/high power field; leukocyturia, > 5 WBCs/high power field; and/or cellular cast).

The clinical diagnosis of Henoch-Schonlein nephritis (HSN) required the presence of active urinary sediment, proteinuria and/or raised serum creatinine levels. Patients with HSN were classified into five grades according to the initial clinical presentation by the modified Meadow's classification[13] as follows: Grade 1, microscopic hematuria; Grade 2, persistent mild proteinuria (< 20 mg/m^2/h) and/or hematuria; Grade 3, nephritic syndrome (hematuria, decrease in glomerular filtration rate (GFR), oliguria, hypertension, edema); Grade 4, nephrotic syndrome (proteinuria > 40 mg/m^2/h, hypoalbuminemia, hyperlipidemia, edema); Grade 5, mixed nephritic-nephrotic syndrome. An estimated GFR (eGFR) was derived by the height index formula of Schwartz[14]. Indications for renal biopsy were nephritic and nephrotic syndrome, heavy proteinuria (proteinuria > 40 mg/m^2/h or urine protein/creatinine ratio > 2), persistent proteinuria after 4 weeks, impaired renal function (eGFR < 80 mL/min/1.73m^2). Renal biopsy specimens were examined by light and immunofluoresence microscopy. The histological observation were categorized according to the classification of the International Study of Kidney Disease in Children (ISKDC)[15] as follows: Grade 1, minimal glomerular abnormalities; Grade 2, pure mesangial proliferation, focal or diffuse; Grade 3, crescents/segmental lesions < 50%, focal or diffuse; Grade 4, crescents/segmental lesions 50-75%, focal or diffuse; Grade 5, crescents/segmental lesions > 75%, focal or diffuse; Grade 6, pseudo mesangiocapillary changes.

The clinical course and outcomes were classified and defined as follows:

Complete remission was defined as no recurrence of any clinical symptoms of HSP.

Recurrence was defined as a reappearance of any clinical symptoms of HSP following resolution of disease for at least 2 weeks.

Clinical outcome of HSN was graded according to Meadow's criteria[13] as follows:

Grade A. Normal: normal physical examination, urine, and renal function.

Grade B. Minor urinary abnormalities: normal on physical examination with microscopic hematuria or proteinuria less than 40 mg/m^2/h.

Grade C. Active renal disease: proteinuria of 40 mg/m^2/hr or greater or hypertension, and glomerular filtration rate (GFR) of 60 mL/min/1.73m^2 or greater.

Grade D. Renal insufficiency: GFR less than 60 mL/min/1.73m^2.

Complete renal remission was considered as grade A.

No renal remission was considered as grade B, C, and D.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation (SD) or median (range). The mortality rate was defined as the number of deaths divided by the total number of patients.

Results

Twenty six patients, 15 female (57.7%) with mean ($\pm$ SD) age at diagnosis of 7.2 $\pm$ 3.8 years (range, 7.8-15.0 years), were enrolled. Median (range) period of follow-up was 2 (0.5-39) months. Patient characteristics are shown in Table 1.

Clinical manifestation and Laboratory data

HSP occurred all year round. A history of preceding viral infection was identified in 11 (42.5%) patients. The presenting symptoms are summarized in Table 1. In most cases, patients were diagnosed within the first week after the onset of symptoms. Twenty one (80.8%) patients presented with purpura or petichiae preceding other manifestations. Only 4 (15.4%) patients had joint symptoms preceding skin manifestation. Skin, joint and gastrointestinal symptoms were the major clinical manifestations presenting in 26 (100%), 18 (69.2%) and 13 (50%) patients, respectively (Table 2). Diffuse abdominal pain was the most frequent gastrointestinal symptoms followed by vomiting. Pain and swollen of joints on lower extremities including ankle (53.8%) and knee (50%) were identified more common than joints on upper extremities. Renal system

Table 1. Patient characteristics

Characteristics	Patients (Total = 26) n (%)
Gender	
Male	11 (42.3)
Female	15 (57.7)
Age at onset (yr, mean ± SD)	7.2 ± 3.8
Follow-up duration (month, median, range)	2 (0.5-39)
Preceding viral infection	12 (46.1)
The first sign at presentation	
Palpable purpura	26 (100)
Joint symptoms preceded skin manifestation	4 (15.4)
Gastrointestinal symptoms preceded skin manifestatition	1 (3.8)
Renal involvement preceded skin manifestation	0 (0)
Duration from onset of symptoms prior to diagnosis* (days, mean)	4.2
Seasonal variation	
Summer	10 (38.5)
Rain	9 (34.6)
Winter	7 (26.9)

*****Excluded 2 patients referred from other hospitals

Table 2. Sign and symptoms of Henoch-Schonlein purpura

Organ systems	Patients (Total = 26) n (%)
Skin involvement (Total)	26 (100)
Palpable purpura	26 (100)
Gastrointestinal involvement (Total)	13 (50)
Abdominal pain	13 (50)
Vomiting	7 (26.9)
Melena	0 (0)
Musculoskeletal involvement (Total)	18 (69.2)
Joint Pain	18 (69.2)
Swollen of joints	14 (53.8)
Limitation of joint movement	5 (19.2)
Large joint involvement (Total)	18 (69.2)
Ankle	14 (53.8)
Knee	13 (50.0)
Wrist	9 (34.6)
Elbow	5 (19.2)
Small joint involvement (Total)	2 (7.7)
Hand	2 (7.7)
Renal involvement (Total)	0 (0)
Edema	0 (0)
Oligulia	0 (0)
Gross hematuria	0 (0)
Recurrence of symptoms (Total)	5 (19.2)
Purpura	5 (19.2)
Abdominal symptoms	4 (15.4)
Joint symptoms	3 (11.5)

was uncommon organ involvement in the present study. Five (19.2%) patients with renal manifestation had Meadow's classification grade 1 or microscopic hematuria (n = 1) and grade 2 or non-nephrotic range

proteinuria (n = 4) (Table 3). Renal insufficiency was not identified in the present study. High ESR was determined in 14 (53.8%) patients. Four (15.4%) patients had leukocytosis. No patient had anemia. Positive stool occult blood was detected in 4 (15.4%) patients.

Clinical course

Twenty (76.9%) patients had at least 2 months of follow-up. Arthritis, arthralgia and gastrointestinal symptoms in 22 (85%) patients rapidly resolved within 2 weeks. Skin involvement in 21(80%) patients resolved within 2 months (Fig. 1). Of 5 patients with proteinuria and hematuria, only one patient had persistent hematuria at 5 months after onset of disease. This patient's hematuria gradually resolved within one year.

Treatment and outcome

Twelve patients with abdominal pain received oral corticosteroid at a dose of 1 mg/kg/day for 6.5 $\pm$ 4.3 days with dramatic response. Nine (34.6%) patients with arthritis or arthralgia received non-steroidal anti-inflamatory drugs (NSAID) for 5.7 $\pm$ 2 days with good response. Among 5 patients with renal involvement, 3 (60%) and 4 (80%) patients had normal urinalysis at 2 and 5 months after onset, respectively. Complete renal remission rate was 80% at last follow-up. One patient had mild proteinuria compatible with Meadow's criteria grade B at 4 months after onset of HSP. Complete remission was observed in 24 (92.3%) patients at the last follow-up. Complications of medications included steroid induced hypertension (n = 1), gastritis (n = 3), striae (n = 2), acne (n = 1) and NSAID induced gastritis (n = 1). Mortality rate was zero.

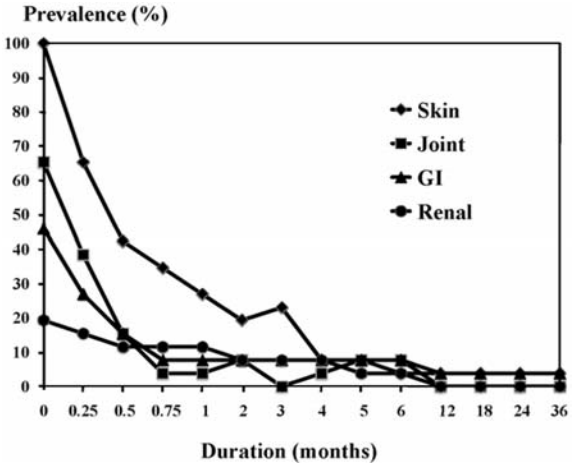

Fig. 1 Prevalence of organ involvements in Henoch Schonlein purpura after disease onset. Abbreviation: GI; gastrointestinal symptoms

Recurrences

Five (19.2%) patients had recurrence of their symptoms following resolution of disease for at least 2 weeks. Purpura and abdominal pain were the common recurrent symptoms (Table 2). The number of recurrences range from 2-8 times with a mean of 4.8 $\pm$ 2.4 times. The first recurrences occurred over a time span ranging from 3 to 12 weeks. Duration from onset to recurrences ranged from 3-42 months. Only 2 (7.7%) patients had recurrences of purpura and petechiae beyond 3 years period.

Colchicine treatment of recurrent petechiae: a case report

A 14 year-old girl was referred from another hospital because of recurrent petechiae and methemoglobinemia due to dapsone. She previously had 7 episodes of extensive petechiae on both lower legs during a 1 year period (Fig. 2A). She had received 5-20 days of dapsone 2 mg/kg/day for each episode of petechiae. The petechiae disappeared after 3 days of drug, but kept recurrent every 3-4 weeks. Dapsone was prescribed for longer periods in each recurrence. Urine protein/creatinine ratio of 2 mg/mg was documented on the first episode of purpura. At the Thammasat University Hospital, the investigations showed a normal complete blood count, an elevated erythrocyte sedimentation rate (ESR), negative result for anti-double strand DNA, antinuclear antibody, antineutrophil cytoplasmic antibody, anti-DNAse B titer, antistreptolysin O titer and normal complement levels. Urinalysis shows 50 red blood cells/high power field with urine protein/creatinine ratio of 1.2 mg/mg. A skin biopsy showed a leucocytoclastic vasculitis with IgA deposition. A renal biopsy demonstrated mesangial deposition of IgA, cellular crescentric lesion of 10% of glomeruli, mesangial hypercellularity and segmental endocapillary proliferation compatible with Henoch-Schonlein nephritis ISKDC class 3. Oral prednisone 60 mg and azathioprine (AZA) 150 mg were started for 1 month with delayed fading of petechiae. Then, Colchicine 0.6 mg was started. All skin lesions resolved within a few days. Meanwhile, prednisone and AZA were continued for a treatment of HSN. Her urine protein/creatinine decreased to 0.17 mg/mg after a 6 month course of all medications. There was no recurrence of purpura until 10 months later. After upper respiratory tract infection, she developed mild petechiae on lower legs for 1 month (Fig. 2B). Urinalysis was normal. A one

month course of colchicine 0.6 mg daily was started with a dramatic fading of petechaie within 1 week. She has now been under follow-up for 15 months since last episode of purpura with no recurrence.

Discussion

The present study reported a cohort of children with HSP from a hospital in suburban area, Thailand. The demographic data, clinical presentations, laboratory data, treatments and outcomes of HSP in Thai children were presented. To the best of the authors knowledge, the authors report the fifth children with a successful treatment of prolonged petechiae with colchicine.

This group of patients had epidemiology data similar to previous studies[7,9,10,16-20]. HSP commonly occurs in children between 5-15 years. Atypical course of HSP is identified in adult and infant[10,21,22]. Adult patients have more severe renal involvement, while infants have milder clinical manifestations[9]. Trapani et al observed exclusively cutaneous and articular involvement in child less than 2 years[10]. Similary, we report HSP in an 18 month-old child with mild arthralgia, and transient purpura which resolved within 3 days. Indeed, HSP in infancy need to be differentiated from acute hemorrhagic edema of infancy (AHEI). Although, some authorities name AHEI as a variant of HSP, but the clinical of AHEI is distinct. AHEI typically presents with mild fever, a violent onset of hemorrhagic skin lesion and edema of extremities, cheeks, auricles followed by spontaneously complete recovery[23]. Similar to previous studies[7,10,19], the authors report 46.1% of upper respiratory tract infection preceding HSP supporting the notion of the infection trigger in the pathogenesis of HSP. Many pathogens including streptococcal infection have been proposed to trigger HSP[3-5]. Several vaccines including influenza vaccine were suspected to be trigger agents of HSP[24-26]. However, these associations are mostly based on anecdotal reports except evidence of streptococcal infection in case-control study[27]. The underlying mechanism explaining the association between streptococcal infection and HSP remains unknown. Recently, Schmitt et al demonstrated deposition of IgA binding streptococcal M protein in skin and kidney of patients with HSP[28]. This finding may explain some part of mechanism of HSP associated with streptococcal infection.

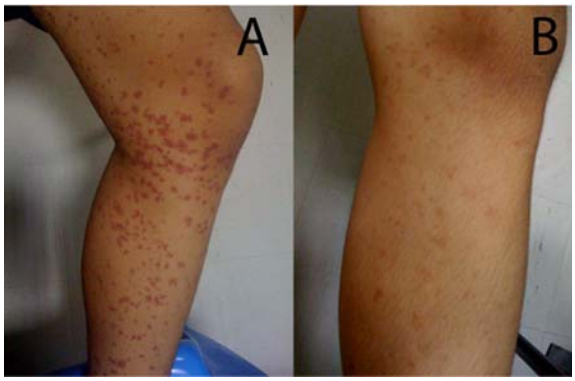

Fig. 2 Recurrent and extensive petechiae over the lower extremities during a 1 year period. A) Recurrent petechiae after dapsone therapy, B) Recurrent petechaie after colchicine therapy

The present study reported clinical manifestations of HSP in Thai children. Similar to previous reports around the world[7,9,10,16,18,20], the author's patients had skin lesion preceding joint, abdominal and renal manifestations. In the present study, common organ involvements were skin, joint followed by abdomen. This finding was comparable to previous studies[7,9,10,16,18,20]. The 19.2% incidence of renal involvement is lower than 30-55% in several reports[7,9,10,16,29,30]. As demonstrated in the present and previous studies, common clinical expression of HSN is mildly transient, isolated microscopic hematuria and/or proteinuria. However, some patients have severe renal involvement and develop end stage renal disease[31]. Thus, severity of renal involvement determines long term prognosis of HSP[31]. Recently, the meta-analysis of randomized controlled trials demonstrated that early corticosteroid did not prevent or altered the course of renal involvement in HSP[32-35]. To date, there is no consensus on the regimen for moderate to severe HSN due to a lack of controls and a small number of patients. Tarshi et al demonstrated in prospective randomized controlled trial study that cyclophosphamide alone failed to obtain a complete recovery of HSN ISKDC category ≥ 3[36]. Several case series demonstrated a remission of severe HSN with a combination of steroid and cyclosporin A[37-39]. However, cyclosporin A dependent and toxicity also reported[37,39]. Several case series demonstrated benefit of AZA coupled with steroid in HSN ISKDC category 3-4[40-43]. The presented study reports a remission of prolonged-proteinuria with a 6 month-course of prednisone and AZA in HSN ISKDC category 3. The authors finding supports the previous studies that AZA is well tolerated with no serious complication. The large randomized controlled trial and multicenter study

should be performed to evaluate the efficacy of AZA, and cyclosporin A in severe HSN.

HSP is a benign and generally self limited disease. The average duration of disease is 4-8 weeks[9,44]. Similarly, 80% of the patients in the present study had symptoms lasting for 8 weeks. The recurrence of HSP is not uncommon. The authors report 19% of recurrent rate which comparable to 15-40% in previous studies[7,9,17,36,44]. It usually occurs within 3-4 months after resolution[9,17]. Skin and abdomen are the most common manifestations of recurrences in the present study. Similar to Trapani et al the authors did not experience renal relapse during recurrences. The symptoms of recurrences usually were milder and shorter than those of first episode[10,45]. However, few patients have experienced chronic prolonged disease or multiple recurrences[46-48]. Several drugs including dapsone and colchicine have been used in prolonged HSP[46-49]. The authors reported 6 recurrences of extensive petechiae and methemoglobinemia after a treatment with dapsone 2 mg/kg/day. Refractory purpura to dapsone was previously reported[49]. In addition, HSN ISKDC category 3 with cellular crescent indicating on-going renal disease was identified after 7 courses of dapsone in the authors' patient. This finding indicated that dapsone didn't have benefit effect on HSN. Previous reports demonstrated an association between relapse and HSN which determine the prognosis of HSP[50,51]. Thus, the treatment to shorten the duration or prevent recurrence of HSP may help to prevent a poor prognosis. Given the risk of methemoglobinemia, recurrent purpura and progression of nephritis, dapsone may not be suitable for prolonged HSP. Steroid alone had no apparent effect on the rash[9]. Pyne et al reported a delayed fading and a refractory purpura to steroid coupled with AZA in adult patient[47]. Similarly, the authors report delayed fading of petechiae to a one month course of steroid coupled with AZA. Colchicine is a natural product for a treatment of go out and familial Mediterranian fever. It inhibits microtubule polymerization leading to inhibition of polymorphonuclear migration to the site of inflammation. To date, there have been only 3 previous reports demonstrating a successful treatment of prolonged typical purpura in HSP with colchicine[46,47,52]. Similar to these reports, colchicine induced a dramatic fading of petechiae within few days in the our patient. Although, recurrent petechiae/purpura was observed in the our patient and previous reports, but it was mild and transient. Interestingly, the patients in the 3 previous reports did not have renal involvement. Since, the benefit effect of colchicine on HSN remains unknown. Therefore, colchicine may be an effective drug for prolonged HSP without renal involvement. The controlled studies are needed to determine benefit effect of colchicine on HSP.

In the present study, no serious complication was observed. The clinical outcome of the authors' patients was excellent. None of our patient had end stage renal disease. In general, renal involvement determines long-term morbidity and mortality of HSP. Based on a systemic review[32], urinalysis during first 6 months is recommended in patients with normal urinalysis at presentation. Whereas, the HSP patients with nephritis or nephrotic syndrome or renal insufficiency should be referred to pediatric nephrologist and need long term follow-up[31].

Conclusion

The authors demonstrated clinical manifestations and good outcomes of HSP in Thai pediatric patients. Colchine may be the first line drug

Table 3. Laboratory data

Laboratory data	Patients (Total = 26) n (%)
Elevated	14/26 (53.8)
ESR Low C3, C4	0 (0)
Proteinuria	4/26 (15.4)
Microscopic hematuria	4/26 (15.4)
Proteinuria and hematuria	3/26 (11.5)
Leucocytosis	4/26 (15.4)
Anemia	0 (0)
Abnormal eGFR (<80 mL/1.73m^2/min)	0 (0)
Stool occult blood	4/26 (15.4)

Abbreviations: ESR; erythrocyte sedimentation rate; eGFR; estimated glomerular filtration rate

Table 4. Medications

Medications	Patients (Total = 26) n (%)
Oral Prednisolone	13 (50)
NSAID	9 (34.6)
Azathioprine	1 (3.8)
Colchicine	1 (3.8)

for prolonged or recurrent purpura in HSP. Controlled trials to determine benefit effect of colchicine on HSN and prolonged HSP are required.

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Potential conflicts of interest

None.

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โรคฮีนอชเชินไลน์เพอร์พิวร่าในเด็กไทย

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โรคฮีนอชเชินไลน์เพอร์พิวร่าเป็นโรคหลอดเลือดขนาดเล็กอักเสบที่พบได้บ่อยในเด็ก โรคนี้มักหายเองและมีพยากรณ์โรคดี การกลับเป็นใหม่ของโรคพบได้ประมาณร้อยละ 30 ของผู้ป่วย รายงานการใช้ยารักษาภาวะที่โรคกำเริบในผู้ป่วยเด็กมีจำกัด ผู้นิพนธ์ทำการศึกษาย้อนหลัง ลักษณะโรคฮีนอชเชินไลน์เพอร์พิวร่าผลการรักษาและภาวะแทรกซ้อนในผู้ป่วยเด็กอายุน้อยกว่า 15 ปี ที่รับการรักษาที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติระหว่างวันที่ 1 มกราคม พ.ศ. 2546–31 ธันวาคม พ.ศ. 2553

ผู้ป่วย 26 ราย อายุเฉลี่ย 7.2 $\pm$ 3.8 ปี มาติดตามการรักษาเฉลี่ยนาน 2 (0.5-39) เดือน ผู้ป่วยมีความผิดปกติเมื่อแรกวินิจฉัย ได้แก่ ระบบผิวหนังร้อยละ 100 ระบบข้อร้อยละ 69.2 ระบบทางเดินอาหารร้อยละ 50 ระบบไตร้อยละ 19.2 ผู้ป่วยร้อยละ 80 มีอาการหายภายใน 2 เดือน ผู้ป่วยร้อยละ 19 มีอาการกำเริบหลังจากอาการหายแล้ว 2 สัปดาห์ การกำเริบเกิดขึ้นโดยเฉลี่ย 4.8 $\pm$ 2.4 ครั้ง ไม่พบภาวะแทรกซ้อนที่สำคัญและผู้ป่วยทุกรายรอดชีวิตเมื่อสิ้นสุดการศึกษา ผู้นิพนธ์รายงานการรักษาผื่นชนิด petechiae ที่เกิดขึ้นซ้ำอย่างรุนแรงตลอดระยะเวลา 1 ปี โดยใช้ยา colchicine อย่างประสบผลสำเร็จในผู้ป่วย 1 ราย หลังเกิดผลข้างเคียงชนิด methemoglobinemia จากยา dapsone