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Severe hemorrhagic bullous lesions in Henoch Schonlein purpura: three pediatric cases and review of the literature

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Abstract Henoch Schonlein purpura (HSP) is a small-sized blood vessels vasculitis, resulting from immunoglobulin A-mediated inflammation. It is the most common acute systemic vasculitis in childhood and mainly affects skin, gastrointestinal tract, joints and kidney. Skin lesions, usually presenting as erythematous maculopapules, petechiae, and purpura, often involve lower extremities and buttocks, but may also extend to the upper extremities, face and trunk. Conversely to adults, hemorrhagic bullous evolution has been seldom described in childhood. The pressure is likely a factor into the pathogenesis of bullae. We report on three new pediatric cases of HSP with hemorrhagic bullous skin lesions, and a review of the literature. Bullous evolution represents an unusual, but well-recognized cutaneous manifestation that may be a source of diagnostic dilemma, but does not seem to have any prognostic value in the outcome of HSP.

Keywords Bullous Henoch Schonlein purpura ·
Childhood vasculitis

Introduction

Henoch Schonlein purpura (HSP) is a small-sized blood vessels vasculitis, resulting from immunoglobulin A (IgA)-mediated inflammation. It is the most common acute systemic vasculitis in childhood and mainly affects skin, gastrointestinal tract, joints and kidney. Skin lesions, usually presenting as erythematous maculopapules, petechiae, and purpura, often involve lower extremities and buttocks, but may also extend to the upper extremities, face, and trunk [1, 2]. Conversely to adults, hemorrhagic bullous evolution has been seldom described in childhood [3]. The pressure is likely a factor in the pathogenesis of bullae.

We report on three cases of HSP presenting with hemorrhagic and bullous skin lesions and a review of the related literature. This unusual cutaneous manifestation may cause diagnostic challenge, even if it does not appear to have a prognostic value.

Case report

Patient 1

A previously healthy 9-year-old white girl was admitted to our Hospital in January 2007. Her past medical history was unremarkable, and no drug intake was reported. She complained of periumbilical abdominal pain and arthralgia at lower extremities in December 2006. Over a week, various ecchymoses and petechiae occurred at her legs, arms and trunk. She was referred to a regional Hospital where blood tests revealed increased C-reactive protein (CRP 2.53 mg/dL; normal value 0.5 mg/dL), full blood count normal, mild increase in anti-streptolysin O (ASLO) (352 IU/L, nv

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<200). Daily urine test was normal. After a short course of amoxicillin and non-steroidal anti-inflammatory drug (ibuprofen), the girl was discharged with the diagnosis of HSP. Shortly, she developed hands and feet edema with limb pain. Within a few days, large, tense hemorrhagic bullae developed over lower and upper extremities, while petechiae spreaded over face and neck. Simultaneously, severe periorbital edema was noted. Owing to the severity of the disease, the girl was brought to our attention. At admission, the body temperature was 37.5°C, pulse 100 per min, respiratory rate 28 per min, and blood pressure 120/74 mm/Hg. The patient was prostrate and drowsy. On examination, diffuse edema of periorbital region, hands and feet and multiple purpuric lesions over buttocks and lower extremities were marked. Moreover, numerous bullae and vesicles emerged over the purpuric rash ranging in size from 2 to 30 mm in diameter. Figures 1 and 2 show some lesions broken and with liquid effusion. The abdomen was tender, painful with mild liver enlargement. Laboratory tests revealed: erythrocyte sedimentation rate (ESR) 25 mm/h (normal value <31 mm/h), CRP 5.2 mg/dL, white blood cells (WBC) 23×10^9 per L with a normal differential count, and platelet count 623×10^9 per L; creatinine, C₃, C₄, and serum immunoglobulin A were all normal. Routine stool analysis revealed occult blood in one test. Total and LDL cholesterol and triglycerides were increased (281 and 146 mg/dL, respectively); abnormal lipid profile was reported in other family members. Total protein and protidogram were normal at admission, while over the following week total protein decreased to 5.5 g/dL and albumin to 2.2 g/dL. The most common virus (Epstein–Barr virus, Cytomegalovirus, and Hepatitis C virus) and bacterial infections were excluded; ASLO and anti-DNase B titers resulted in the normal range. Antinuclear antibodies (ANA), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) were negative. Urinalysis showed proteinuria (1 g/24 h) and hematuria (1,074 RBC per field). Cardiologic evaluation, lung X-ray, and abdominal ultrasound were unremarkable except for a marked thickening of gut wall and effusion in the Douglas pouch. A provisional diagnosis of nephrotic syndrome was made based on the persistent proteinuria reaching 1 g/24 h, associated with microhematuria. Owing to an aggressive infection of the cutaneous lesions, an intravenous antibiotic treatment (imipenem and teicoplanin) was introduced. Two days later, pulsed methylprednisolone (20 mg/kg per daily) for three consecutive days was given, and then oral prednisone (2 mg/kg per daily) to control renal disease. After a mild skin improvement, the disease flared again with multiple new purpuric and hemorrhagic lesions and increase on protein level and red cells count in the urine. Ten days later, due to a significant amelioration of general conditions, skin



Fig. 1 Bullous and crostous lesions on the leg and foot



Fig. 2 Crostous lesions over the dorsum of hand

and urine, the child was discharged with oral prednisone (1 mg/kg per day). Bullae faded within the next 2 weeks and necrotic lesions healed leaving a mild pigmentation and scars. When last seen, December 2007, neither recurrence of cutaneous alterations nor urine abnormalities were reported.

Patient 2

An 11-year-old white boy was admitted to a regional Hospital in February 2006 with 1-day history of high fever and arthralgia at both ankles. The day after, a purpuric rash at soles and ankles became evident. His past medical history was unremarkable and no recent drug intake was reported. On examination, his temperature was 39.5°C, blood pressure 120/60 mm/hg, respiratory rate 32 per min. Multiple palpable purpuric lesions were noted at lower limbs, especially at feet and ankles with few lesions at arms and elbows; both ankles and soles were painful and swollen. Laboratory tests revealed increased CRP (26.3 mg/dL), while blood full count, fibrinogen, C₃ and C₄, ASLO, prothrombin time, the activated partial thromboplastin time, and serum Ig A were within the normal range; urinalysis revealed 3+ hemoglobin and 2+ ketone bodies. Six days later, purpuric lesions developed blisters evolving in multiple hemorrhagic bullae around ankles and over legs. Owing

to bullous evolution of hemorrhagic lesions, the patient was sent to our attention. At admission, the only remarkable manifestation was the severe cutaneous alterations involving lower extremities, buttocks, ankles and arms. Complete work-up excluded the most common viral and bacterial infections; the parameters of inflammation were all normal as well as urinalysis. The outcome of disease was favorable with no renal involvement and complete healing of skin lesions over one month, despite any drug was administered. At 28 months of follow-up, the patient was in general good condition. Neither further bullae nor urine alterations were reported.

Patient 3

A 7-year-old white girl was admitted to a regional Hospital in November 2008, with a severe purpuric palpable rash involving buttocks and legs with low-grade fever. Her past medical history was not noticeable, except for obesity started in infancy, and affecting all family members. Over the following days, she complained of severe abdominal pain and arthralgia. Extensive workup revealed normal ESR, CRP, WBC, C3, C4, creatinine and fibrinogen. As pharyngeal swab resulted positive for *Streptococcus pyogenes*, amoxicillin was given for 10 days.

However, her general condition worsened dramatically and purpuric lesions extended on the arms, abdomen and face. Routine stool analysis revealed occult blood while urinalysis excluded hematuria and proteinuria. ANA, pANCA and cANCA resulted negative. Methylprednisolone pulses (20 mg/kg per daily) for three consecutive days, and then oral prednisone (2 mg/kg per daily) were ineffective in controlling skin lesions that evolved in huge bullae. Azathioprine (2.5 mg/kg per daily) was added, and over 2 months steroids progressively tapered and stopped. An impressive healing of vesicles was noted along with a rapid and sustained amelioration of general condition. At 5 months of follow-up, no skin lesions neither urine alterations have been observed regardless of azathioprine withdrawn.

Discussion

Our patients met the diagnostic criteria for HSP [1, 2]. According the recent proposal of classification, criteria for the diagnosis of HSP are palpable purpura (mandatory criterion) and at least one of the following four criteria: (1) diffuse abdominal pain, (2) biopsy showing predominant IgA deposition, (3) arthritis (acute, at any joint) or arthralgia, and (4) renal involvement (hematuria and/or proteinuria) [4]. Skin biopsy, therefore, is not mandatory in establishing the diagnosis in patients with the typical clinical manifestations.

Besides the typical purpura other cutaneous manifestations may be present in HSP as target-like lesions, subcutaneous nodules and urticarial bullous or vesicular rash. Bullous HSP has been quite frequently noticed in adults in a percentage ranging from 16 to 60% [3]. Conversely, only <2% of children with HSP have been found to develop bullous lesions [2]. So far, the occurrence of hemorrhagic bullae may be challenging for pediatricians facing children with HSP, mostly at onset when the other typical HSP symptoms or signs are lacking. In addition, many other common pediatric diseases, including toxic epidermal necrolysis, erythema multiform, pemphigus, bullous impetigo, dermatitis herpetiformis and staphylococcal-scalded skin syndrome may present with bullous lesions in childhood. Our patients, despite vesicles and bullae as major cutaneous manifestations, met the criteria of HSP [4] and skin biopsy was not required. Although patient #1 had a severe disease course complicated by renal involvement, patients #2 and #3 did not develop any visceral symptoms regardless of the severity of skin involvement. In patient #1, the early prednisone administration was successful in controlling abdominal and joint pain, while purpura evolved in blisters with hemorrhagic and bullous progression. Following a relapse of skin manifestations, methylprednisolone pulses were then introduced with a reasonable control of the disease. In addition to the severity of skin damage, renal involvement with proteinuria and microhematuria developed, although urine alterations subsided within 1 month. Conversely, patient #2 had a mild and transient microhematuria and patient #3 did not develop urine alterations, but persistent and harmful bullous purpura that required azathioprine. All our patients showed a similar progression of purpura that evolved into bullae and vesicles over the second week of the disease and healed over a period ranging from 2 to 4 weeks.

Hemorrhagic bullae in childhood HSP are seldom described. So far, there have been only 17 case reports prior to our patients. The commonest sites of bullae were feet, ankles, legs and buttocks suggesting that pressure is the most likely factor in its pathogenesis. In Table 1, the clinical and demographic data of the pediatric cases published since 1985 through 2008, including our cases are summarized [5–16]. In a previous report of our group on 150 children with HSP, no one had bullous evolution of typical palpable purpura [17], while in the last 3 years, three children with such unusual cutaneous damage have been referred.

In conclusion, bullous evolution represents an unusual, but well-recognized cutaneous manifestation that may be a source of diagnostic dilemma, but does not seem to have any prognostic value in the outcome of HSP. In particular, bullae itself do not correlate with renal involvement given that most of young patients have a good prognosis.

Table 1 Demographic and clinical data of children with hemorrhagic bullous HSP

References	Ethnicity	Sex	Age (years)	Lesion site	Lesion size (mm)	Systemic involvement	Therapy
Garland et al. [5]	White	M	5	Elbows, thighs, buttocks, perioral area	20	GI, J, R	NS
Abdel-AI et al. [7]	Arab	NS	NS	NS	NS	NS	NS
Bari et al. [6]	NS	F	7	Shins	NS	J	NS
Wananukul et al. [8]	Thai	M	5	Pinnas, hands, buttocks, legs, gums, palate	50	GI, J, fever	PSL
Saulsbury [8, 9]	NS	F	7	Feet, ankles	NS	GI	PSL
Saulsbury [8, 9]	NS	F	3	Legs, feet	20	GI, R	PSL
Kobayashi et al. [10]	Japanese	M	10	Shins,	NS	GI, J	None
Liu et al. [11]	Chinese	F	7	Legs, buttocks	10	J	HC
Liu et al. [11]	Chinese	M	14	Buttocks, legs	NS	G, J	HC
Ishii et al. [12]	Japanese	M	4	Face, pinnas, hands, buttocks	20	GI, J	Pulse, PSL
Leung et al. [3]	Chinese	M	8	Feet, ankles	35	GI, J	None
Abdul-Ghaffar et al. [14]	White	M	10	Legs, feet, hands	NS	GI, J, R	PSL
Chan et al. [13]	Chinese	M	14	Legs, buttocks	NS	GI, J	Colchicine
Aydinoz et al. [15]	NS	F	4	Legs	NS	J	NS
Rabelo Jr et al. [16]	White	F	9	Face, arms, buttocks, hands, feet	20	GI	PSL
Rabelo Jr et al. [16]	White	F	9	Legs, feet	10	J, R	PSL
Rabelo Jr et al. [16]	White	F	6	Feet	15	J	None
Trapani et al. [17]	White	M	11	Buttocks, legs, feet, ankles	20	J, fever	None
Trapani et al. [17]	White	F	9	Legs, buttocks, arms, elbows, face	30	J, R	Pulse, PSL
Trapani et al. [17]	White	F	7	Buttocks, legs, feet, ankles	20	J, fever, GI	Pulse, PSL, azathioprine

M male, F female, NS not specified, GI gastrointestinal, J joint, R renal, Pulse methylprednisolone pulse therapy, PSL oral prednisone, HC hydrocortisone

Our report further supports hemorrhagic bullae as one of the cutaneous manifestations in HSP patients and skin biopsy may be avoided when other criteria for HSP are met. Nonetheless, most patients with unusual skin lesions and variable timing of the purpura development, underwent skin biopsy to confirm the diagnosis [10–13].

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