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Acute Hemorrhagic Edema of Infancy: Case Reports and a Review of the Literature

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Acute hemorrhagic edema of infancy (AHEI) is an unusual form of leukocytoclastic vasculitis that affects children younger than 2 years and frequently is preceded by drug intake, vaccination, or a variety of infections. It is characterized by an abrupt onset of fever, purpuric lesions, and peripheral edema on the face and extremities that may be confused with other dermatoses. The course is benign with spontaneous resolution. We present 2 infants with AHEI and review the clinical manifestations, histology, and differential diagnosis.

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Acute hemorrhagic edema of infancy (AHEI) is a benign form of leukocytoclastic vasculitis characterized by purpuric lesions and edema confined to the skin. The vasculitis generally resolves without intervention and complete recovery is expected.[1-4] The first case was reported by Snow[5] in 1913 and later characterized by Finkelstein[6] in 1938. Before 1990, additional reports were confined to the European literature.[1] Since 1990, more than 40 cases of AHEI have been reported in the English language literature,[7] but we are aware of only 6 published cases of AHEI in American children.[1,4,7-10] We present 2 patients with AHEI, describe the clinical and histopathologic manifestations of this disorder, and review the differential diagnosis.

Case Reports

Patient 1—A 12-month-old infant presented with purpuric lesions of the left ear of 1 day's duration. Three weeks prior he was treated with amoxicillin for 10 days for bilateral otitis media and then cefdinir for 10 days for persistent right otitis media. Three days before the lesions occurred, the patient was inoculated with his 12-month vaccines. After presentation, the lesions quickly progressed to edema and purpuric lesions of the extremities. He had a fever for 1 day and diarrhea, vomiting, and congestion for 2 days.

On physical examination, he was alert and febrile but appeared nontoxic. He had peripheral edema and multiple purpuric targetoid plaques of the face and extremities (Figures 1 and 2). One purpuric plaque was present on the maxillary gingiva. Mild rhinitis was present, but the remainder of the physical examination was unremarkable.

Results from laboratory studies revealed a hemoglobin level of 11.1 g/dL (reference range, 11.0–15.0 g/dL); a white blood cell (WBC) count of 8100/µL (reference range, 5000–11,000/µL) with 36.7% neutrophils, 51.1% lymphocytes, 9.9% monocytes, and 2.3% eosinophils; and a platelet count of 369,000/µL (reference range, 200,000–470,000/µL). Findings from coagulation studies were normal. Initial urinalysis was positive for blood but was a catheterized collection. Repeat urinalyses were negative for blood, protein, and WBCs. Creatinine levels remained within reference range throughout admission. Urine, nasopharyngeal, blood, and cerebrospinal

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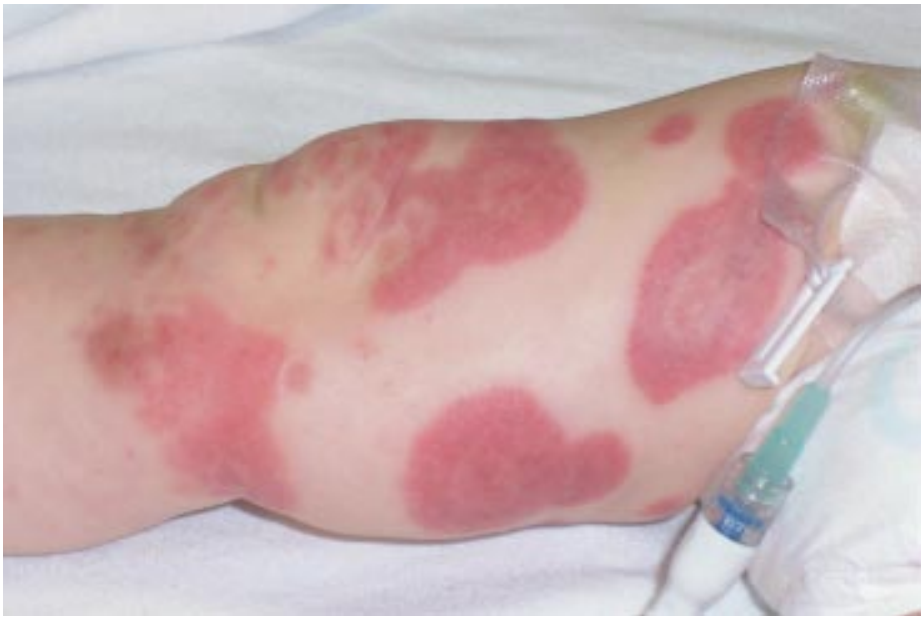

Figure 1. Erythematous targetoid plaques on the right leg.

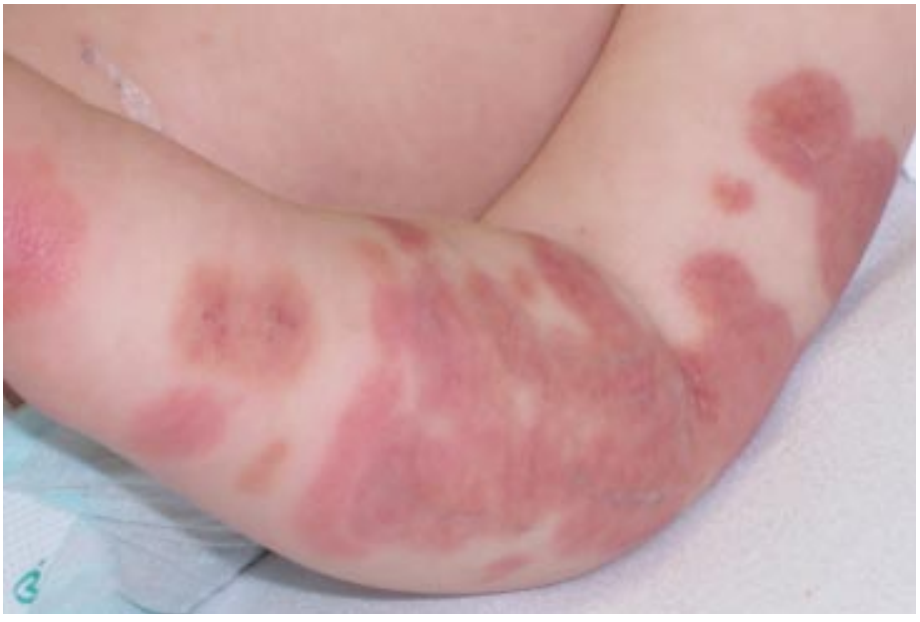

Figure 2. Purpuric targetoid plaques on the left arm and forearm.

fluid cultures were negative for bacteria. Serologic test results for *Rickettsia rickettsii* and *Rickettsia typhi* IgG antibodies as well as *Mycoplasma pneumoniae* IgG and IgM antibodies were negative.

Patient 2—An 11-month-old infant was hospitalized with peripheral edema and purpuric lesions on the face of 1 day's duration. Shortly thereafter, these hemorrhagic lesions progressed to the arms and legs. The patient had a history of chronic congestion consisting of rhinorrhea, cough, and conjunctivitis. He was using an albuterol metered-dose inhaler and nonprescription cough syrup but had taken no other medications. His medical history was remarkable for double outlet right ventricle with pulmonary stenosis. At 1 month of age, he received a Blalock-Taussig shunt with balloon tamponade.

Physical examination revealed an alert and afebrile infant. There were multiple purpuric targetoid plaques extending in a generalized distribution over the cheeks, arms, and legs. The trunk and diaper area were spared. Mild edema of the face and extremities was present. Serous drainage from both eyes was noted, but there was no conjunctival injection. No involvement of the mucous membranes was identified. A grade 3/6 systolic ejection murmur was present. The remainder of his physical examination was unremarkable.

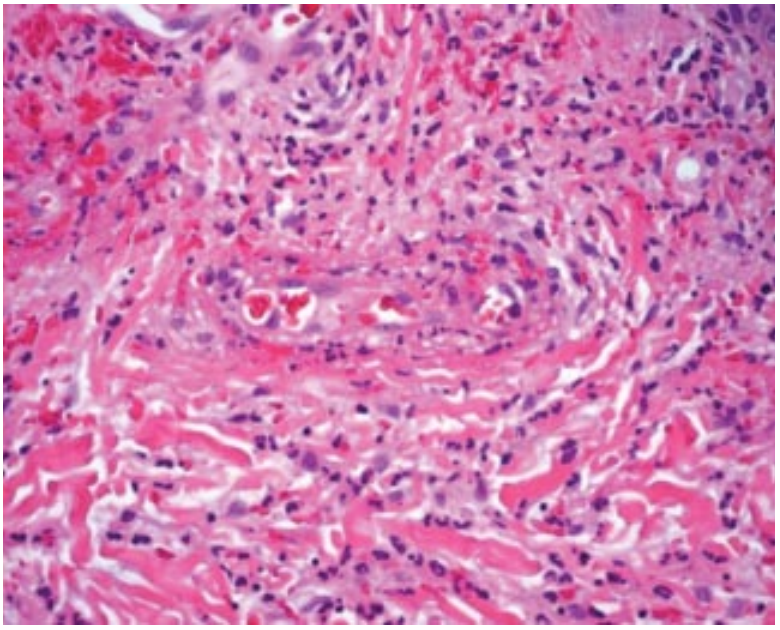

Figure 3. Nuclear dust, extravasated erythrocytes, and fibrinoid change of the blood vessel walls (H&E, original magnification ×400).

Laboratory studies revealed a hemoglobin level of 18.7 g/dL; a WBC count of 11,500/µL with 32% neutrophils, 60% lymphocytes, and 7.6% monocytes; and a platelet count of 405,000/µL. Urinalysis was negative for protein, WBCs, or red blood cells. A lumbar puncture was performed and results of cerebrospinal fluid Gram stain, analysis, and culture were negative for bacteria. Results of a chemistry profile and coagulation study were normal. Stool examination, throat culture, and blood culture results were negative. Findings of an atypical pneumonia workup were negative. An echocardiogram showed no evidence of vegetation. A punch biopsy was performed on a well-developed purpuric lesion and sent for hematoxylin and eosin staining. The stain revealed a normal epidermis with a superficial and deep perivascular neutrophilic infiltrate with the blood vessel walls demonstrating fibrinoid change. Nuclear dust and extravasated erythrocytes were present (Figure 3).

The lesions rapidly progressed and began to spontaneously fade. The patient remained afebrile and exhibited no systemic signs or symptoms. The patient was discharged 2 days after admission. The lesions reportedly resolved within 2 weeks. No recurrence was observed at 6-month follow-up.

Comment

Acute hemorrhagic edema of infancy usually is described in children aged 5 to 24 months, with 1 case reported at birth.[1-4] Although drug intake; vaccination; or a variety of infections including viral upper respiratory tract infections, conjunctivitis, pharyngitis, otitis media, bronchitis, pneumonia, urinary tract infections, and pneumococcal bacteremia have been documented in children with AHEI, the etiology remains unknown.[7] Acute hemorrhagic edema of infancy is a benign, self-limited condition with excellent prognosis for complete recovery. One case, however, diagnosed as AHEI with gastrointestinal tract involvement, resulted in a fatal outcome.[11]

The clinical manifestations of AHEI include fever, large purpuric lesions, and tender edema of the face and extremities. Despite the fever and cutaneous lesions, the patients are otherwise healthy. Mucous membrane and visceral involvement are rare.[2,4] Complete resolution usually occurs within 1 to 3 weeks without intervention and recurrence is rare.[1,4]

The histopathologic appearance of AHEI is consistent with leukocytoclastic vasculitis. Fibrinoid necrosis of vessel walls and a neutrophilic infiltrate with nuclear dust and extravasated erythrocytes are present.[8] IgA deposition may be observed in up to one-third of specimens, but the lack of IgA deposition may be pertinent to distinguish AHEI from Henoch-Schönlein purpura (HSP), as patients with HSP usually have IgA deposition.[9]

The presentation of several conditions is similar to AHEI. It is important to clinically differentiate AHEI from those disorders that require an effective treatment. The clinical differential diagnosis includes Sweet's syndrome, erythema multiforme, Kawasaki disease, purpura fulminans, and HSP (Table 1).[4,10] Sweet's syndrome consists of characteristic skin lesions, fever, malaise, and leukocytosis. The skin manifestations include erythematous

Table 1.

Differential Diagnosis of AHEI

	AHEI	Sweet's Syndrome	Erythema Multiforme	Kawasaki Disease	Purpura Fulminans
Clinical appearance	Large purpura and ecchymoses, often targetoid of face, ankles, wrists	Erythematous tender plaques	Targetoid plaques	Generalized macular erythema	Large ecchymoses and hemorrhagic necrosis
Predisposing factors	Medications, vaccinations, infections	Presumed infectious or paraneoplastic	URTI, HSV, or *Mycoplasma pneumoniae* infection	Presumed infectious etiology	Disseminated intravascular coagulation
Pathology	Leukocytoclastic vasculitis	Diffuse neutrophilic infiltrates with leukocytoclasis, papillary dermal edema	Lymphocytic interface dermatitis with individually necrotic keratinocytes	Perivascular lymphocytic infiltrate	Fibrin thrombi, mild perivascular infiltrates, no vasculitis

Abbreviations: AHEI, acute hemorrhagic edema of infancy; URTI, upper respiratory tract infection; HSV, herpes simplex virus.

tender plaques on the face, neck, upper trunk, and extremities. Involvement of the joints and viscera are associated features. Histologically, both Sweet's syndrome and AHEI demonstrate diffuse neutrophilic infiltrates.[12] Leukocytoclastic vasculitis may occur in Sweet's syndrome, but the presence of massive papillary dermal edema and the clinical presentation are characteristic.

Erythema multiforme is characterized by targetoid lesions, lack of peripheral edema, and involvement of the mucous membranes. It is commonly associated with a preceding upper respiratory tract infection, herpes simplex virus infection, or M *pneumoniae* infection. Other factors implicated in the etiology of erythema multiforme include drugs, pregnancy, and internal malignancy.[12] Histologically, erythema multiforme is characterized by a lymphocytic interface dermatitis resulting in individually necrotic keratinocytes. A mononuclear cell infiltrate may involve dermal blood vessels. In AHEI, polymorphonuclear leukocytes infiltrate the dermal blood vessels.[4,13]

Patients with Kawasaki disease are most commonly toxic-appearing children ranging in age from 7 weeks to 12 years. Manifestations include high fever, conjunctival injection, oropharyngeal lesions (ie, mucosal injection, strawberry tongue, fissured lips), lymphadenopathy, and a generalized macular erythema. The arteritis is an acute multisystem vasculitis of unknown etiology involving arterioles, capillaries, and venules.[4] Histologic examination of the skin shows a mild perivascular lymphocytic infiltrate.[13]

Purpura fulminans occurs secondary to fulminant septic shock, usually following a systemic bacterial infection. Unlike AHEI, the lesions are not characteristically en cockade pattern. Patients with purpura fulminans also appear more toxic than patients with AHEI. Histologically, purpura fulminans is characterized by fibrin thrombi within capillaries and venules associated with diffuse and extensive hemorrhage. A mild perivascular inflammatory cell infiltrate may be present, but true vasculitis is not identified.[4]

The primary differential diagnosis is HSP (Table 2). Unlike AHEI, which affects children aged 5 to 24 months, HSP usually presents in children aged 3 to 10 years and is characterized by palpable urticarial lesions located on the lower extremities and buttocks. In contrast, patients with AHEI present with large purpura and ecchymoses on the face, ankles, and wrists, with more extensive edema. Visceral involvement such as arthralgia, gastrointestinal symptoms, and renal pathology also are features of

Table 2.

Comparison of AHEI and HSP

	AHEI	HSP
Age of onset	5–24 mo	3–10 y
Clinical appearance	Large purpura and ecchymoses of face, ankles, wrists	Palpable urticarial lesions of lower extremities and buttocks
Visceral involvement	Typically absent	Arthralgia, GI and renal involvement
Pathology	Leukocytoclastic vasculitis	Leukocytoclastic vasculitis
Immunopathology	Rare vascular IgA deposition with C1q deposition	Vascular IgA deposition, no C1q deposition

Abbreviations: AHEI, acute hemorrhagic edema of infancy; HSP, Henoch-Schönlein purpura; GI, gastrointestinal.

HSP and rarely are seen in patients with AHEI.[4,5,14] Moreover, HSP typically presents with an increase in serum IgA not seen in AHEI. Both AHEI and HSP have histologic features of leukocytoclastic vasculitis, but these disorders differ in immunopathology. In HSP, vascular IgA deposition is found in almost all cases on direct immunofluorescence examination but only in a minority of cases of AHEI.[2,4,9,14,15] Both AHEI and HSP may have IgM, fibrinogen, and C3 deposition, but vascular C1q deposition only occurs in patients with AHEI.[14]

Acute hemorrhagic edema of infancy is a benign variant of leukocytoclastic vasculitis affecting children younger than 2 years. An abbreviated course with complete recovery requiring no intervention can be expected. It is important to recognize AHEI as a benign disorder and distinguish it from other disorders or diseases that require an expedited course of action.

REFERENCES

1. Dubin BA, Bronson DM, Eng AM. Acute hemorrhagic edema of childhood: an unusual variant of leukocytoclastic vasculitis. *J Am Acad Dermatol*. 1990;23(2, pt 2):347-350.
2. Legrain V, Lejean S, Taiben A, et al. Infantile acute hemorrhagic edema of skin: study of ten cases. *J Am Acad Dermatol*. 1991;24:17-22.
3. Ince E, Mumcu Y, Suskan E, et al. Infantile acute hemorrhagic edema: a variant of leukocytoclastic vasculitis. *Pediatr Dermatol*. 1995;12:224-227.
4. Cunningham BB, Caro WA, Eramo LR. Neonatal acute hemorrhagic edema of childhood: case report and review of the English-language literature. *Pediatr Dermatol*. 1996;13:39-44.
5. Snow IM. Purpura, urticaria and angioneurotic edema of the hands and feet in a nursing baby. *JAMA*. 1913;61:18-19.
6. Finkelstein H. *Lehrbuch der Sauglingskrankheiten*. 4th ed. Amsterdam, Netherlands: Auff Edit Amsterdam; 1938.
7. Morrison RR, Saulsbury FT. Acute hemorrhagic edema of infancy associated with pneumococcal bacteremia. *Pediatr Infect Dis J*. 1999;18:832-833.
8. Long D, Helm KF. Acute hemorrhagic edema of infancy: Finkelstein's disease. *Cutis*. 1998;61:283-284.
9. Crowe MA, Jonas PP. Acute hemorrhagic edema of infancy. *Cutis*. 1998;62:65-66.
10. Pride HB, Maroon M, Tyler WB. Ecchymoses and edema in a 4-month-old boy. *Pediatr Dermatol*. 1995;12:373-375.
11. Larrègue M, Lorette G, Prigent F, et al. Acute haemorrhagic edema of the skin of the new-born with lethal intestinal complication [in French]. *Ann Dermatol Venereol*. 1980;107:901-905.
12. Saraclar Y, Tinaztepe K, Adalioglu G, et al. Acute hemorrhagic edema of infancy (AHEI): a variant of Henoch-Schönlein purpura or a distinct entity? *J Allergy Clin Immunol*. 1990;86:473-483.
13. Weedon, D. *Skin Pathology*. 2nd ed. London, England: Churchill Livingstone; 2002.
14. Habif TP. Exanthems and drug eruptions. In: Habif TP. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 4th ed. Philadelphia, PA: Mosby; 2004:457-496.
15. da Silva Manzoni AP, Viecili JB, de Andrade CB, et al. Acute hemorrhagic edema of infancy: a case report. *Int J Dermatol*. 2004;43:48-51.