

Acute Hemorrhagic Edema of Infancy: Guide to Prevent Misdiagnosis

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PRACTICE POINTS

- Acute hemorrhagic edema of infancy (AHEI) is an uncommon benign leukocytoclastic vasculitis of unknown precise pathophysiology that is thought to be immune complex mediated.
- Clinical history, physical examination, and histopathologic analysis combine to allow the important differentiation between AHEI and Henoch-Schönlein purpura (HSP).
- Differentiation between AHEI and HSP determines treatment decisions and indicates the need for counseling on potential associated renal and gastrointestinal risks of HSP.

We report the case of a 10-month-old previously healthy boy who presented with acute rash, edema, and low-grade fever in the setting of recent diarrhea. We differentiate between acute hemorrhagic edema of infancy (AHEI) and Henoch-Schönlein purpura (HSP).

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Acute hemorrhagic edema of infancy (AHEI) is an uncommon leukocytoclastic vasculitis affecting children aged 6 to 24 months; Henoch-Schönlein purpura (HSP) is the most common misdiagnosis. The 2 entities should be differentiated, as HSP may have renal and gastrointestinal (GI) comorbidities that need serial follow-up, whereas AHEI follows a benign course without systemic sequelae. Patient history and physical examination are the

most important factors in differentiating the 2 diseases; histopathologic and direct immunofluorescence (DIF) analyses may lend further diagnostic confidence.

We report the case of a 10-month-old previously healthy boy who presented with acute rash, edema, and low-grade fever in the setting of recent diarrhea. We differentiate between AHEI and HSP to help prevent misdiagnosis by health care providers.

Case Report

A 10-month-old previously healthy boy presented to the emergency department (ED) for evaluation of a rash and swelling of 4 days' duration. He had nonbloody diarrhea 1 week prior; soon after, he developed bilateral lower leg edema and rash. On evaluation in a different ED, he had a low-grade fever (rectal temperature, 38.0°C) but normal blood work, including complete blood cell count, basic metabolic panel, and coagulation studies. The patient was discharged to outpatient follow-up with his pediatrician who reported normal urinalysis.

Due to progression of the rash, the patient presented to our ED 3 days after his initial ED assessment. Dermatology was consulted. At the time of presentation, he was afebrile but with GI upset and fussiness. His parents denied additional symptoms or blood in urine or stool. Physical examination revealed a nontoxic-appearing infant with scattered palpable, annular, purpuric papules coalescing into plaques on both legs and feet (Figure 1), with sparse petechiae noted on the lower abdomen. The cheeks had scattered purpuric papules and plaques bilaterally, a few with a small central crust (Figure 2), and the right superior helix had a faint purpuric macule. The hands had a few pink edematous coalescing papules.

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FIGURE 1. Edematous, palpable, purpuric coalescing papules on the right leg.



FIGURE 2. Purpuric papules and plaques on the face.

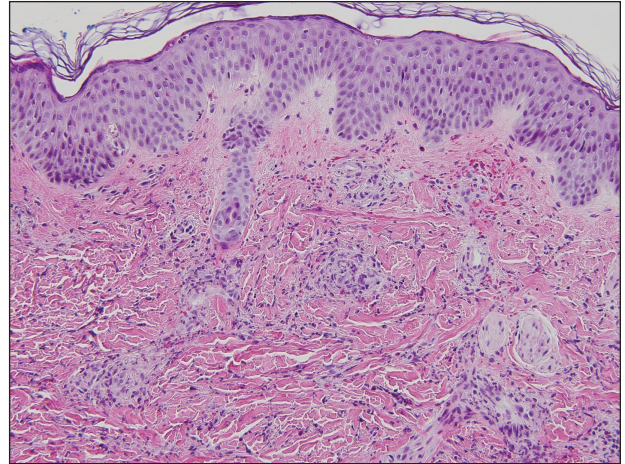


FIGURE 3. Evolving leukocytoclastic vasculitis on histopathology (H&E, original magnification $\times 20$).

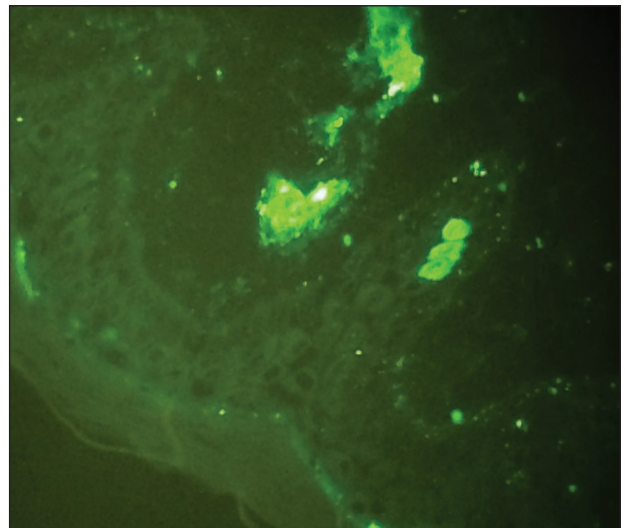


FIGURE 4. Direct immunofluorescence with IgA granular deposition in multiple dermal blood vessels.

Histopathologic analyses with hematoxylin and eosin staining (Figure 3) and DIF (Figure 4) were performed from within a representative purpuric plaque on the right hip. Direct immunofluorescence was performed to evaluate for an IgA vasculitis versus an alternative type of vasculitis. The hematoxylin and eosin–stained specimen demonstrated a dermal perivascular infiltrate involving superficial and deep vessels with neutrophils, karyorrhexis, and erythrocyte extravasation. The endothelium was intact, with a mild suggestion of fibrinoid change of the blood vessel walls. Direct immunofluorescence revealed granular deposition of IgA, C3, and fibrinogen in multiple dermal blood vessels. Combined, the specimens were interpreted as evolving IgA-associated leukocytoclastic vasculitis.

The case was reviewed with our 2 department pediatric dermatologists; a diagnosis of AHEI was made based on the clinical and supportive histopathological presentations. The patient's parents chose active treatment with a 2-week taper of oral prednisone because of the patient's discomfort with edema. No GI or adverse renal sequelae, including findings on urinalysis, were reported at 1-month hospital follow-up with dermatology and pediatrics.

Comment

Incidence and Clinical Characteristics—Acute hemorrhagic edema of infancy is an uncommon leukocytoclastic vasculitis first described in the United States by Snow¹ in 1913. Other names for the disorder include acute

hemorrhagic edema of young children, cockade purpura and edema, Finkelstein disease, and Seidlmayer disease.² Boys are affected more often than girls, with most children presenting at 6 to 24 months of age. Most affected children experience a prodrome of simple respiratory tract illness (most common), diarrhea (as in our case), or urinary tract infection.² The exact pathophysiology behind AHEI is unknown, but it is thought to be an immune complex-mediated disease evidenced by the fact that infection, use of medication, or immunization precedes most cases.^{3,4}

Diagnosis—Acute hemorrhagic edema of infancy is diagnosed clinically, with or without the support of skin biopsy. It should be differentiated from HSP because of renal and GI sequelae that HSP portends compared to the benign course of AHEI.² Notably, some health care providers consider AHEI a benign variant of HSP.^{2,3}

Characteristically, AHEI patients are nontoxic-appearing infants with a low-grade fever who develop relatively large (1–5 cm) targetoid purpuric lesions and indurated nonpitting edema of the extremities.^{2,5} Purpura in AHEI frequently occurs on the face, ears, and upper and lower extremities, whereas purpura in HSP most commonly presents on the buttocks and extensor legs with sparing

of the face. Henoch-Schönlein purpura most often affects children aged 3 to 6 years compared to AHEI's younger demographic (age <2 years).^{4,5} Clinically, HSP presents with palpable purpura and 1 or more of the following features: diffuse abdominal pain, arthritis/arthralgia, renal involvement, and skin or renal biopsy showing predominant IgA deposition.^{2,6}

Both AHEI and HSP show leukocytoclastic vasculitis on histopathology.^{2-4,6,7} Positive perivascular IgA staining on DIF is strongly associated with HSP, but nearly one-quarter of AHEI cases also show this deposition pattern^{2,4,7}; therefore, DIF alone cannot exclude a diagnosis of AHEI.

Differential Diagnosis—Alternative diagnoses to consider with AHEI include drug-induced vasculitis, erythema multiforme, HSP, Kawasaki disease, meningococemia, nonaccidental skin bruising, Rocky Mountain spotted fever, septic vasculitis, and urticarial vasculitis (Table).^{2-4,6-8}

Treatment—Acute hemorrhagic edema of infancy is self-limited, with only rare reports of extracutaneous involvement. Supportive treatment is indicated because spontaneous recovery without sequelae is expected within 21 days.^{2,3,6} If edema is symptomatic, as was the case with our patient, corticosteroids may shorten the disease course.³

Differential Diagnosis of Acute Hemorrhagic Edema of Infancy^{2-4,6-8}

Disease Entity	Differentiating Features
Acute hemorrhagic edema of infancy	Nontoxic-appearing child aged <2 y; low-grade fever; recent viral infection; symmetric edema and purpura on face, ears, and extremities; absence of abdominal pain and renal involvement; leukocytoclastic vasculitis on H&E staining; positive DIF with perivascular IgA deposition (nearly 25% of cases)
Drug-induced vasculitis	History of new medication; palpable purpura; superficial vessel vasculitis on H&E staining
Erythema multiforme	Targetoid macules and papules; epidermal necrosis on H&E staining
Henoch-Schönlein purpura	Child aged 3–6 y; palpable purpura on buttocks and extensor legs; diffuse abdominal pain; arthritis/arthralgia; renal involvement; leukocytoclastic vasculitis on H&E staining; positive DIF with perivascular IgA deposition
Kawasaki disease	Polymorphous rash with or without edema; oral mucosal erythema; fever; cervical lymphadenopathy; conjunctivitis
Meningococemia	Toxic-appearing child; fever; hypotension; purpura fulminans
Nonaccidental skin bruising	History of trauma, fractures, ecchymosis, and purpura in unusual locations; erythrocyte extravasation on biopsy
Rocky Mountain spotted fever	Toxic-appearing child with fever, headache, and myalgia; possible history of tick bite; hemorrhagic and/or necrotic skin lesions
Septic vasculitis	Toxic-appearing child with fever; hypotension; hemorrhagic and/or necrotic skin lesions; superficial and deep vessel vasculitis; epidermal necrosis on H&E staining
Urticarial vasculitis	Recurrent urticarial lesions with associated burning or pain lasting >24 h; leukocytoclastic vasculitis on H&E staining

Abbreviations: H&E, hematoxylin and eosin; DIF, direct immunofluorescence.

Conclusion

Our case highlights the need to combine clinical history, physical examination, and histopathologic analysis to differentiate between AHEI and HSP, which is important for 2 reasons: (1) it helps with the decision to undertake active or observational treatment, and (2) it helps the clinician counsel the patient and guardians regarding potential associated renal and GI risks.

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