On Target: A Case of Acute Hemorrhagic Edema of Infancy

Case: A 16-month-old female presented to a referring emergency department with a 2-day history of a progressive rash and swelling that started on her right lower extremity and spread to her upper extremities, trunk, and face (Fig 1). The patient had recently been hospitalized at the referring hospital for bronchiolitis caused by respiratory syncytial virus and was being treated with amoxicillin for otitis media. Her mother had stopped the antibiotic 1 day before presentation after development of a rash and had given the patient diphenhydramine, with no improvement. The patient had a fever with the preceding illness but on admission to the emergency department was afebrile. She had received hepatitis B and diphtheria-tetanus-acellular pertussis vaccines at her 15-month well-child examination 3 weeks before the onset of the rash. The patient had 1 day of decreased oral intake and decreased urine output and a 2-day history of loose stools. Family history is significant for multiple maternal family members with reaction to penicillin causing hives and edema. At the referring hospital, intraosseous (IO) access was obtained after multiple attempts to place intravascular access were unsuccessful, secondary to diffuse body edema. In our emergency department, the medical team attempted to obtain intravascular access with ultrasound guidance; however, they were also unsuccessful because of the patient’s persistent edema. The patient received normal saline via the IO line in addition to oral acetaminophen and diphenhydramine.

Physical examination revealed a fussy but consolable, well-nourished toddler with diffuse body edema, scratching at her arms and thighs. She was afebrile, tachycardic to 134 beats per minute, and hypertensive to 126/97 mm Hg. Erythematous annular lesions surrounded the patient’s eyes, extending around the perioral region and onto the chin. Her pinnae were erythematous and edematous. She had multiple erythematous papules, some coalescing into erythematous, edematous plaques scattered diffusely over her abdomen, chest, back, buttocks, and all 4 extremities, with sparing of genital and anal areas. These erythematous plaques contained a central duskeness surrounded by an erythematous rim resembling targetoid lesions (Fig 2). Multiple purpuric patches were scattered over the right posterior thigh, chest, back, and bilateral upper extremities. Laboratory examination revealed normal urinalysis, liver and renal function test results, serum levels of complement proteins C3 and C4, and complete blood count with mild leukocytosis. Fecal occult blood test results were negative. Dermatology was consulted in the emergency department, and they diagnosed acute hemorrhagic edema of infancy (AHEI) based on the physical examination.

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KEY WORDS
acute hemorrhagic edema of infancy, steroids, urticaria, vasculitis

ABBREVIATIONS
AHEI: acute hemorrhagic edema of infancy
EM: erythema multiforme
HSP: Henoch-Schönlein purpura
IO: intraosseous

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Question: What is AHEI and how can it be differentiated from other targetoid rashes such as erythema multiforme (EM), urticaria, or fixed drug reaction?

Discussion: AHEI is an uncommon, self-limiting acute cutaneous vasculitis that was first described by Snow in 1913. Nearly 100 years later, Blasini et al described AHEI as a rare, benign acute cutaneous vasculitis that occurs between 4 and 24 months of age. The authors concur with Snow that the disease is self-limiting and further characterize it as edematous purpuric plaques on the extremities, the acute appearance of edema, and fever. AHEI is more commonly reported in the winter season, and illness duration is 5 to 35 days. Bacterial or viral infections, medications, and immunizations have all been recognized as possible contributors to the onset of AHEI.

Due to its vasculitic nature and appearance, AHEI has been suggested as a variant of Henoch–Schoenlein purpura (HSP), a more well-known clinical entity. Saracilar et al compared the clinical, serologic, and immunohistologic findings of 12 patients with AHEI versus the expected findings in HSP. Although the histopathologic findings were similar, the immunohistologic pattern found in this series of patients was a different pattern from HSP. They concluded that AHEI should be considered as a separate, clinicopathologic entity or a possible variant of HSP. Clinically, HSP occurs in older children, the lesions are characteristically on the lower extremities, and patients have the potential for multiorgan complications. Considering its clinical features, AHEI was characterized by da Silva Manzoni et al as a unique disorder, distinct from HSP.

In addition to making a distinction between AHEI and HSP, other diagnoses such as urticaria, EM, and fixed drug reaction should be considered when a child presents with erythematous annular lesions. Urticaria has the typical pruritic and erythematous undulating plaques similar to AHEI; however, the central area of duskeness is typically lacking. In addition, urticarial lesions are transient and often resolve with oral diphenhydramine. EM typically manifests as a target lesion with 3 distinct areas whereas AHEI usually contains 2 areas. The characteristic EM targetoid lesion has a central area of erythema or purpura that may be dusky (similar to AHEI), a middle lighter colored area (lacking in AHEI), and an outer zone of erythema completing a concentric target. EM lesions are normally fixed, symmetric, and pruritic. In addition, EM may have predominant mucosal involvement, which is not seen with AHEI. A fixed drug reaction, although it may appear very similar to AHEI, is typically limited to a few lesions. A fixed drug reaction with more than a few lesions will typically only occur after multiple exposures, and it is not associated with systemic symptoms. AHEI has associated edema of hands, feet, or face/ears that is not characteristic of urticaria, EM, or fixed drug reaction.

CASE CONTINUATION:
The rash and edema progressed to involve more body surface area within hours of admission, and the patient refused all fluids by mouth. The ecchymotic lesions on her trunk and upper extremities increased in size. Because her left lower extremity was more edematous compared with the right, a radiograph was obtained and confirmed IO catheter infiltration. The IO line was removed, and a nasogastric tube was placed to provide maintenance fluids. The patient continued on hydroxyzine (1 mg/kg per dose) and diphenhydramine (1 mg/kg per dose) orally every 6 hours without clinical improvement. On hospital day 2, she was started on prednisolone 2 mg/kg per day. Within 12 hours of receiving corticosteroids, her edema and ecchymosis decreased. She remained on oral prednisolone 2 mg/kg per day. Within 12 hours of receiving corticosteroids, her edema and ecchymosis decreased. She remained on oral steroids for the remainder of her hospitalization, and her rash, edema, and pruritus continued to decrease daily until the day of discharge. In total, she completed 5 days of prednisolone (2 mg/kg per day) and 5 days of ranitidine (1 mg/kg per dose, twice daily).
Question: What treatment regimens have been successful at reducing symptoms in AHEI?

Discussion: Historically, the treatment of AHEI has been limited to supportive care such as antihistamines for pruritus and analgesics for discomfort. Saraclar et al. described 12 infants with AHEI who were all administered antihistamines and who had complete resolution in 5 to 11 days. Acun et al. concurred that spontaneous, complete resolution without complications usually occurs within 5 to 14 days, but the disease may endure as long as 35 days. da Silva Manzoni et al. describe the case of a 9-month-old male with AHEI treated with corticosteroids. The administration of corticosteroids was an attempt to avoid rapid progression of the disease, as the patient had acute, rapidly expanding and profuse cutaneous lesions. In contrast to the literature, there was clear improvement 24 hours after the onset of the disease once the prednisolone therapy was started. As soon as administration of the medication was discontinued, there was a quick relapse followed by improvement when it was re-administered.

CONCLUSIONS:
Our patient had AHEI that involved a large percentage of her surface area, caused discomfort, and prevented her from maintaining appropriate hydration without medical intervention. Although steroids are not routinely recommended in the treatment of AHEI, our patient appeared to benefit from this medical therapy. It may be reasonable to consider corticosteroids when caring for a patient with severe AHEI.

Learning Points:
1. AHEI has a broad differential diagnosis and can vary in severity upon clinical presentation.
2. AHEI has historically been treated symptomatically with spontaneous resolution.
3. There may be an indication in severe AHEI requiring hospitalization for treatment with steroids.

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DOI: 10.1542/hpeds.2013-0054

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