# Coxsackie B3 Virus-induced Acute Hemorrhagic Edema of Infancy

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**ABSTRACT** Acute hemorrhagic edema of infancy (AHEI) is a cutaneous leukocytoclastic small vessel vasculitis of unknown incidence. It affects mostly infants aged 4 to 24 months. The distinctive features of AHEI include a generally healthy-appearing child with low-grade or absent fever and rarely painful targetoid purpuric edematous lesions. The disease usually resolves spontaneously within 3 weeks without late sequelae. The main differential diagnosis of AHEI is Henoch-Schönlein purpura (HSP). Initially, purpura fulminans should also be ruled out. We report the case of a 5-year-old girl with low fever and rapidly progressive skin lesions who had been admitted to the pediatric clinic. The child presented with palpable annular targetoid and purpuric plaques of different size predominantly affecting the face and extremities. In addition, there was a painful, hemorrhagic edema on the dorsum of her hands and feet. Based on the course of the disease and the typical clinical presentation, i.e., extensive characteristic skin lesions in a young child in a good general health condition, a diagnosis of AHEI was established. A virus serology test showed increased titers of enterovirus and coxsackievirus. Isolation of virus from feces confirmed an infection with coxsackie B3 virus. To our knowledge, this is the first report linking coxsackie B3 virus infection to AHEI.

**KEY WORDS:** purpura, vasculitis, targetoid hemorrhagic edema, infancy, coxsackie B3 virus

## INTRODUCTION

Acute hemorrhagic edema of infancy is a rare and benign cutaneous small vessel leukocytoclastic vasculitis affecting infants between 4 and 24 months of age with a male to female ratio of 2:1. Annular targetoid and purpuric plaques as well as edematous, contusion-like lesions on the extremities and face are the characteristic skin manifestations of AHEI (1). In contrast to the alarming skin lesions and occasional fever, the affected children are generally in an unimpaired state of health, and the disease generally resolves spontaneously within 3 weeks and without late sequelae. Infections, drug exposure, and vaccinations have been reported as major triggers (1). We present the unusual case of AHEI in a child which apparently was triggered by a coxsackie B3 virus infection.

## CASE PRESENTATION

A 5-year-old girl was admitted to the pediatric clinic because of rapidly progressive disseminated skin lesions. On clinical examination she presented with multiple annular, targetoid, and urticarial plaques on the lower extremities and left arm that had appeared within the last 24 hours (Figure 1A). The skin lesions measured between a few millimeters to several centimeters and were particularly painful over the talocalcanean joint. Except a slightly raised temperature

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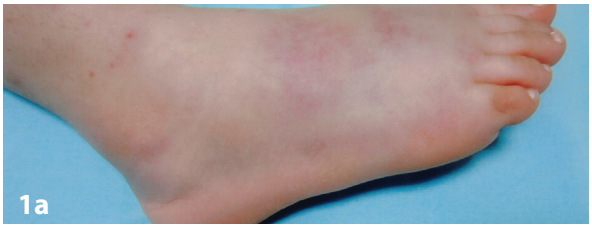

**Figure 1A.** Diffuse painful, hemorrhagic edema on the dorsum of the right feet.

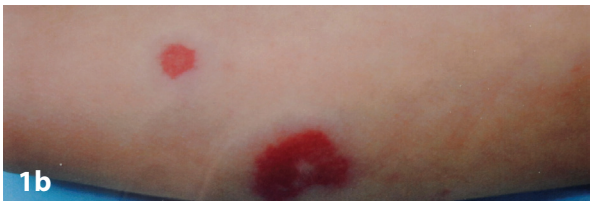

**Figure 1B.** Palpable annular targetoid-like purpuric plaque on the left elbow.

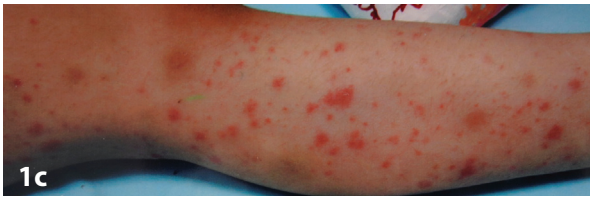

**Figure 1C.** Multiple targetoid and urticarial plaques on the right leg.

of 37.2 °C, the child was in a good general health condition. Complete blood count and a comprehensive blood chemistry panel were unrevealing. ANA, ENA, and complement factors C3, C4, and CH50 were within the normal range. Bacterial cultures from the throat, nose, and urine and tests for a parasitic intestinal infection were negative. Abdominal ultrasound and chest X-ray were likewise unremarkable.

Despite a negative history of trauma and negative X-ray, a lower leg cast was applied upon the clinical suspicion of a bone fracture. The skin lesions were diagnosed as erythema nodosum, and systemic therapy with ampicillin-sulbactam and ibuprofen was started. Additionally, the child received topical treatment with methylprednisolone aceponate ointment. As new lesions continued to develop, a second dermatological consultation was requested seven days after admission. At that time multiple slightly painful, edematous, partly hemorrhagic lesions on the upper and, in particular, the lower extremities were present (Figure 1B and Figure 1C). In addition, edematous, contusion-like lesions were observed on the right ankles, left periorbital region, and chin (Figure 2). The child's good general health condition was unchanged, and the fever had resolved. Based on the typical clinical presentation, a diagnosis of acute hemorrhagic edema of infancy was established. All previous treatments were discontinued except ibuprofen on demand for pain relief.-

A serological test had meanwhile revealed increased antibody titers to enterovirus (1:160) and coxsackievirus (1:160). Enterovirus RNS was identified by PCR in feces, and pharyngeal secretions and virus isolation from feces was positive for coxsackie B3 virus. Thus, an acute infection with coxsackie B3 virus was established and assumed as probable cause of AHEI.

Within the next two and a half weeks, the skin lesions slowly disappeared with the characteristic change in skin color as observed in the resolution of bruises (Figure 3).

## DISCUSSION

The first description of AHEI was published by Snow in 1913 under the title of "Purpura, urticarial and angioneurotic edema of hands and feet in a nursing baby" (2) and was later termed "Acute edema of infancy" by Finkelstein in 1930 (1). In the literature, AHEI has been reported under different names such as Finkelstein disease, Seidlmayer syndrome, Finkelstein-Seidlmayer disease, rosette form purpura, infantile post-infectious iris-like purpura, and medallion-like purpura (3). The disease predominantly affects children between 4 and 24 months of age and is mainly triggered by viral infections, drugs, or vaccination. The exact incidence is unknown. AHEI is the clinical manifestation of a leukocytoclastic vasculitis characterized by the sudden onset of an often symmetrical rash of round, dark red, edematous plaques 1 to 5 cm in diameter and with a purpuric or hemorrhagic appearance (2). Although unusual, formation of hemorrhagic blisters may occur (4). The lesions are not pruritic but may be associated with painful edema

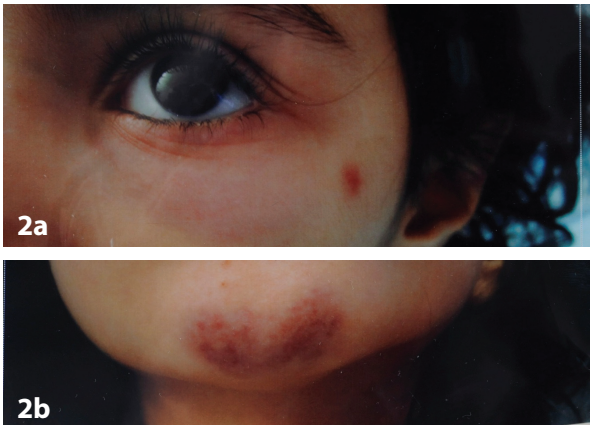

**Figure 2.** Characteristic edematous, contusion-like lesions in the periorbital region (a) and on the chin (b).

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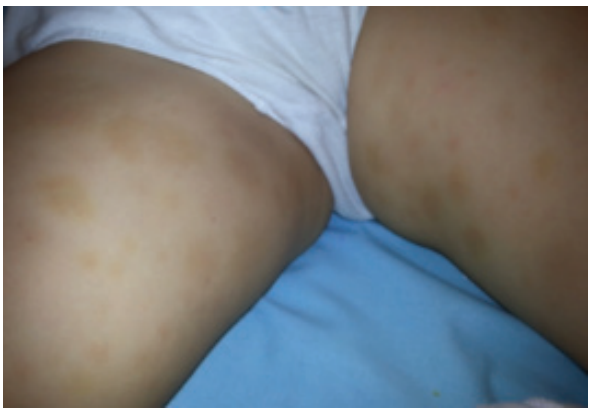

**Figure 3.** Typical resolution of the lesions on the thigh with a change in color to green and yellow resembling hematoma at two and a half weeks after admission.

affecting mainly the extremities, the face and, in particular, the ears. The trunk and mucous membranes are mostly spared. Extracutaneous manifestations are rare. In a review of 287 patients, extracutaneous involvement (gastrointestinal, renal, and joint involvement) was found in 25 patients. All these patients recovered completely without any treatment (5).

The diagnosis of AHEI is based on the course of the disease and the characteristic clinical presentation which may be accompanied with low grade fever. In general, the children are in a good health condition. The discrepancy between the often striking skin lesions and the unimpaired general health of the children is indicative for AHEI. Spontaneous resolution of the rash usually occurs within 3 to 5 weeks (5). There are no specific laboratory findings in AHEI. Unspecific mild alterations of laboratory parameters (leukocytosis, thrombocytosis, and elevation of C-reactive protein) are sometimes observed. Due to the fact that in the majority of cases a diagnosis can be established clinically, a skin biopsy is rarely required (6). Histopathology shows a small vessel leukocytoclastic vasculitis involving the venules and postcapillary venules with or without fibrinoid necrosis and with a predominantly neutrophilic infiltrate in the dermis (7). Direct immunofluorescence is mostly negative. The presence of granular C3 deposits, fibrinogen, and immunoglobulins IgM, IgG, IgE, and IgA inclusively in the wall of the small dermal vessels has been reported (8). C1q deposition in the vessel wall and perivascular IgA can be demonstrated in one third of the cases (2).

The precise etiology of AHEI is unknown. Affected children often have a history of an upper respiratory tract infection like otitis media (in up to two thirds of the cases), pneumonia, or urinary tract infection. There have been several reports of AHEI occurring after *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, rotavirus, and coxsackievirus infection (3). Association of AHEI with the administration of various vaccines has also been reported (3). Since vaccinations and medications have been reported as triggers for AHEI, a type III hypersensitivity immune complex disease in which immune complex deposits in vessels and organ causing tissue damage has been suggested as the possible etiology (9). Within this infectious framework, a case of coxsackievirus B5 triggering AHEI has also been reported recently (1).

Enteroviruses, members of the family *Picornaviridae,* are small, non-enveloped viruses with a single-stranded, positive-sense RNA genome of about 7.4 kb. The genus *Enterovirus* includes polio-, coxsackie-, echo-, and some other enteroviruses. There are two groups of coxsackievirus, type A and B. Type A coxsackievirus is characterized by cutaneous tropism and causes hand-foot-mouth disease, unspecific petechial rashes (10), and herpangina (also called Zahorsky disease). Infection with type B coxsackievirus

**Table 1.** Summary of clinical characteristics of acute hemorrhagic edema of infancy and purpura Henoch-Schönlein

| | **Acute hemorrhagic edema of infancy** | **Purpura Henoch-Schönlein** |
|---|---|---|
| Age of onset | 3 months to 2 years | 3 to 6 years |
| Clinical appearance | Coin or medallion -like, cockade purpuric skin lesions. Painful edema. | Urticarial papules that evolve into palpable purpura |
| Distribution | Face, ears, lower extremities, scrotum. | Lower extremities, buttocks |
| Rash duration | 1 to 3 weeks | 4 to 6 weeks |
| Associated symptoms | Irritability, malaise | Malaise, abdominal pain, arthralgia |
| Trigger factors | Infection, vaccinations, medications | Infection, vaccinations, medications |
| Histology | Leukocytoclastic vasculitis | Leukocytoclastic vasculitis |
| Direct immunofluorescence | Perivascular IgM (rarely IgA) and C1q deposits | Perivascular IgA and fibrinogen deposits |
| Complications | Not reported | Gastrointestinal, renal, urogenital. |
| Treatment | Supportive care (analgesics) and antibiotics in case of bacterial infection | Organ-directed treatment (steroids, antimicrobials dapsone) |

may lead to Bornholm disease (also named epidemic pleurodynia), myocarditis, pancreatitis, and aseptic meningitis (11). Coxsackievirus can be isolated from the stool, oropharynx, and rectal swabs by cell culture or PCR (12).

With regard to prognosis and treatment, AHEI is generally a benign and self-limited disease which resolves completely without sequelae. The use of analgesics for pain control and antibiotics in case of concomitant bacterial infection is the preferred therapy However, residual lesions such as hyperpigmentation, skin atrophy, and depressed scars have been observed on rare occasions (8).

The most important differential diagnosis of AHEI is purpura Henoch-Schönlein (HSP). There are several differences that allow differentiation between these two diseases (Table 1). HSP commonly affects older children (3 to 6 years) than AHEI (3 to 24 months) and presents with erythematous macules and small urticarial papules that rapidly evolve into palpable purpura. The lesions mainly affect the buttocks and legs. The diagnosis of HSP is based on clinical signs and histopathological findings. Schönlein first described HSP as a triad of purpuric rash, arthritis, and abnormalities of the urinary sediment, and Henoch described abdominal pain. The histology of HSP shows signs of leukocytoclastic vasculitis. Immunohistochemistry reveals granular deposits of perivascular IgA and fibrin without C1q depositions, suggesting activation of the complement system via the alternative pathway (2), whereas in AHEI IgM and C1q are more common and IgA deposits are found only in a small percentage of patients (8,13).

Extracutaneous involvement is much more common in HSP and comprises oligoarthritis, renal (acute nephritis, nephrotic syndrome, acute renal failure), gastrointestinal (abdominal colics, bleeding, intussusception), genital (orchitis), and neurological (seizures, cerebral vasculitis) manifestations that may cause chronic morbidities (8,14) (Table 1). In a study comparing clinical signs in adults and children, children more often had joint involvement and abdominal pain than adults. Joint involvement was observed in up to 74% of the cases, renal disease in 54%, and gastrointestinal symptoms in up to 51% of all cases (15). Management of patients with HSP depends on organ involvement and requires intensive systemic therapy with corticosteroids, antibiotics, or dapsone.

In the early stage of AHEI, purpura fulminans always needs to be ruled out given its potential fatality. One study showed that 15% of children admitted to the hospital with fever and a hemorrhagic rash had meningococcal disease (16). A clinical score of 5 items allows us to estimate the probability of diagnosing meningococcal disease: hemorrhagic skin lesions, diffuse distribution of lesions, maximum diameter of at least one lesion of greater than 2 mm, reduced general condition, and neck stiffness. The presence of at least 2 criteria favors the diagnosis of meningococcal disease with a specificity of 97% and a false positive rate of only 12% (16). The febrile clinical form of AHEI can therefore initially be confused with purpura fulminans.

Kawasaki disease is a syndrome of unknown cause affecting children under 5 years. It is a systemic vasculitis affecting medium caliber arteries of muscular type and coronary arteries and may lead to coronary artery aneurysm or stenosis. Patients with Kawasaki syndrome present with persistent fever, lymph node swelling, and bilateral conjunctivitis. Cutaneous changes manifest as polymorphic rashes and changes of the buccal mucosa, including the typical strawberry tongue (7).

One of the most commonly affected sites of child abuse is the skin. Burns, bruises, petechiae, or edema are indicative of acute trauma; however, AHEI may occasionally be misinterpreted as child abuse. The time course of the rash, the variability of the skin lesions, and the fever, if present, may aid in separating AHEI from child abuse.

## CONCLUSION

AHEI has an alarming clinical presentation but is a benign disease with an excellent prognosis. The diagnosis of AHEI is primarily based on clinical grounds. The typical disseminated targetoid purpuric and edematous plaques in small children in an otherwise unimpaired state of health should prompt clinicians to consider a diagnosis of AHEI.

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