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Infantile Acute Hemorrhagic Edema and Rotavirus Infection

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Abstract: Infantile acute hemorrhagic edema (AHE) is a benign condition characterized by a dramatic onset of inflammatory edema and ecchymotic purpura in a target or cockade pattern. It is considered an uncommon form of cutaneous vasculitis occurring in children younger than 2 years of age. The outbreak is frequently preceded by an immunization or various infections. We describe an 11-month-old girl with rosette-shaped purpuric plaques on the face and limbs, clinically consistent with a diagnosis of AHE of the skin, associated with fever and diarrhea. Laboratory investigations showed a rotavirus infection, which has not previously been reported in association with AHE of the skin. The disease had a benign course without relapses. Appropriate microbiologic investigations are advisable to confirm the possible etiologic role of rotavirus.

Infantile acute hemorrhagic edema (AHE) of the skin is a distinctive cutaneous disorder characterized by large rosette-shaped purpuric lesions on the face and limbs, and by acral edema accompanied by fever occurring almost exclusively in children between the ages of 4 months and 2 years during winter. Spontaneous resolution normally follows within 3 weeks. The nosology of the disease is still being debated. Although some have suggested that AHE is a purely cutaneous variant of Henoch-Schönlein purpura (HSP), most authors prefer to regard it as a separate clinical entity among the cutaneous small vessel vasculitic diseases of childhood. We describe a child with AHE and a concurrent rotavirus infection, which has not been previously reported in association with AHE.

CASE REPORT

An 11-month-old girl was seen for purpuric skin lesions appearing 1 day before her visit. Her birthweight was 3805 g and her length was 52 cm. There was no history of recent infectious diseases or drug therapy.

The cutaneous examination showed many symmetrically distributed, round or oval, ecchymotic, purpuric, targetoid plaques ranging from 2 to 4 cm in diameter, localized on the face (Fig. 1), especially the cheeks and ears, and on the extremities, in particular the lower limbs. Some plaques showed a cockade pattern, while others had coalesced to form large purpuric lesions with polycyclic borders. The ears appeared edematous (Fig. 2); petechiae on the gums and hemorrhagic lacrimation were also noted. The remainder of the physical examination was normal and there were no signs of systemic involvement. During the following 6 days the patient had a mild fever and several episodes of diarrhea. No other systemic symptoms were noted.

Laboratory studies revealed the following: hematocrit 39%, hemoglobin 13.2 mg/dl, leukocytes 9500/mm^3 (55% neutrophils, 38% lymphocytes, 5% monocytes,

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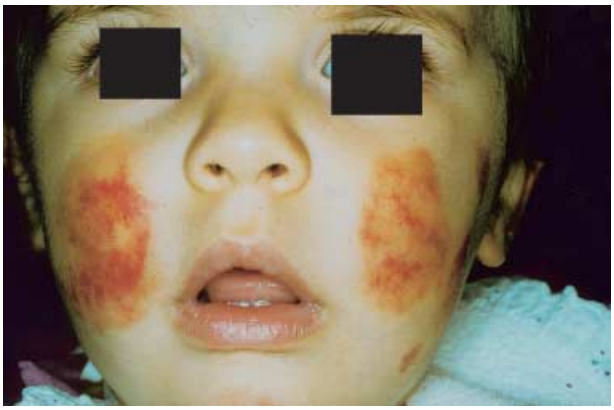

Figure 1. Round or oval, purpuric, targetoid plaques on the face.

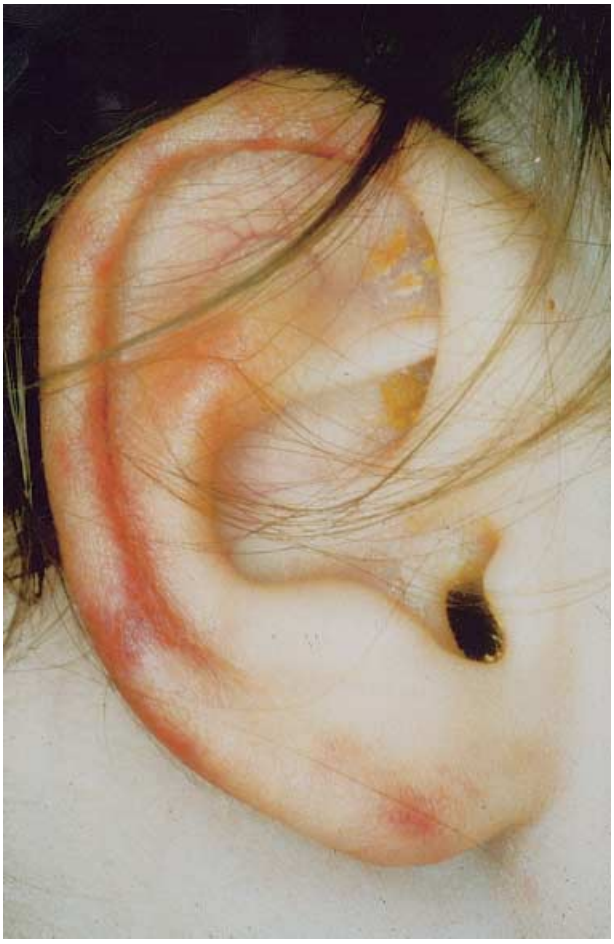

Figure 2. The ears are edematous and purpuric.

2% basophils, 0% eosinophils), platelet count 403,000/mm^3, erythrocyte sedimentation rate (ESR) 26 mm/hr, C3 120.7 mg/dl (normal 60–158 mg/dl), C4 48.9 mg/dl (normal 18–105 mg/dl), C-reactive protein (CRP) 1.07 mg/dl (normal 0.00–0.5 mg/dl), fibrinogen 477 mg/dl (normal 150–450 mg/dl). Quantitative serum immunoglobulins were as follows: IgG 519.5 mg/dl (normal 241–613 mg/dl), IgA 67.5 mg/dl (normal 10–46 mg/dl), and IgM 109 mg/dl (normal 26–60 mg/dl); in the serum electrophoresis α_2-globulin and β-globulin were slightly increased, while γ-globulin was reduced. Urea, electrolytes, and liver function tests were within normal limits. The urinalysis was normal, with the presence of rare leukocytes in the sediment. Tests for ANA and anti-DNA were negative, as well as a tuberculin skin test (5 U).

Nasopharyngeal cultures for *Streptococcus pyogenes*, serologic tests for *Salmonellae*, *Shighellae*, TORCH, *Yersinia enterocolitica*, *Campylobacter jejuni*, *Rickettsia conorii*, *Mycoplasma pneumoniae*, and *Borrelia burgdorferi* were all negative. Stool sample cultures grew rotavirus. The first stool sample was positive for occult blood, the second one was slightly positive, and a third one, after 1 week, was negative. The parents denied permission for a skin biopsy. The skin lesions, as well as the fever and diarrhea, resolved without treatment within 2 weeks. No relapse was observed after a 2-year follow-up. Repeated stool sample cultures after 10 days and 1 month gave negative results. A retrospective diagnosis of AHE was made.

DISCUSSION

The clinical features of our patient, characterized by a dramatic, acute onset of typical large, symmetrical, annular purpuric plaques on the face, ears, and limbs that resolved spontaneously within 2 weeks, were consistent with the diagnosis of AHE. Routine laboratory tests of patients with AHE are not diagnostic, disclosing normal results, or as in our patient, an elevated ESR and an increase in α_2-globulin.

A clinical disorder corresponding to AHE was first described in 1913 by Snow (1). Since then, many cases have been reported in the European literature under different clinical terms, including Finkelstein disease (2) and Seidlmayer's "cockade" purpura or syndrome (3). AHE has rarely been reported in the United States, probably because AHE is called HSP of infancy (4,5). Until now, approximately 80 cases of AHE have been reported in the literature, although the disease may be underreported (4,6,7).

Acute hemorrhagic edema is considered an uncommon form of cutaneous leukocytoclastic vasculitis, which occurs in infants younger than 2 years of age (mean 12.4 months) (7–9). Its etiology remains unknown, although a history of recent upper respiratory or urinary tract infection or immunization is found in 75% of patients (8–10). Thus AHE is believed to represent an immune complex-mediated

disease. The most often reported infective agents include staphylococci, streptococci, and adenovirus, although many other agents, such as *Escherichia coli* and mycobacteria, have been reported in association with AHE. Diarrhea has been observed during episodes of AHE and related to coxsackievirus or *Campylobacter sputorum mucosalis* in stools (10,11). Of interest is that our 11-month-old patient had gastrointestinal symptoms during the skin eruption related to a rotavirus infection, which has been reported in association with various cutaneous manifestations such as Gianotti-Crosti syndrome or exanthems (12,13), but is not known as a cause of AHE.

Rotavirus infections are important etiologic agents of nosocomial infections in childhood, and are the main pathogens of infantile diarrhea in winter months. Thus it is difficult to discern whether the infection was the primary cause that triggered the disease. Culture of stool samples is advisable in laboratory investigations of AHE to confirm the possible etiologic role of rotavirus. Alternative tests for confirmation of the diagnosis of rotavirus infection consist of enzyme immunoassay and latex agglutination studies.

A history of drug intake before the onset of the cutaneous eruption is present in many cases of AHE. The drugs include various antibiotics and antiinflammatory drugs (7,10,14).

The histologic features of AHE are consistent with a small-vessel vasculitis of both capillaries and postcapillary venules of the upper and middermis (7,15). Results of direct immunofluorescence study, for the possible presence of IgM, C3, and fibrinogen, are not significant for a diagnosis; in addition IgA deposits can be found in one-third of the cases, while C1q and IgG have been observed occasionally (7,10).

Other conditions that must be considered in the differential diagnosis are Sweet syndrome, erythema multiforme, Kawasaki disease, purpura fulminans, trauma-induced purpura, and granuloma faciale. Diagnosis is usually possible on the basis of history, physical examination, laboratory investigations, and histologic examination.

It is still debated whether AHE should be regarded as a separate clinical entity within the spectrum of leukocytoclastic vasculitides or just a benign variant of HSP. Amitai et al suggested that AHE should not be considered a distinctive syndrome, but a benign variant of HSP, pointing to a similar pathogenesis for both diseases, but with a different distribution of purpuric lesions with a predilection for the face in infants (AHE) and the buttocks and lower extremities in older children (HSP) (4). In addition, they postulated that the proportionately larger head and face of infants, with a corresponding increase in blood supply, would render them more susceptible to facial purpura (4).

Instances of AHE and HSP overlap have been reported (16), however, most authors consider these two to be distinct clinical and pathologic entities, with some distinctive characteristics (7,9,10). In particular, AHE is observed before 2 years of age and is confined to the skin, with fewer polymorphic skin lesions in comparison to HSP, a more benign course without relapses, and IgA deposits on immunofluorescence studies in only one-third of patients. On the other hand, HSP has an age peak between 3 and 7 years of age, shows papulopetechial or urticarial lesions on the extensor surfaces of the legs and buttocks, and relapses frequently. Renal, gastrointestinal, and joint involvement are common. The deposition of IgA in the basal membrane is the immunopathologic hallmark of HSP.

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