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CASE REPORT

Acute hemorrhagic edema of childhood: Case report and comparison with meningococcemia

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Abstract

Edema acute hemorrhagic childhood is a vasculitis of small vessels infrequent and usually affects children between 4 months and 2 years old. Clinically is characterized by the triad of fever, purpuric lesions on the face, ears and extremities and edema. The cutaneous findings are often dramatic and sudden appearance, which clashes with the severity and favorable prognosis with spontaneous resolution within 1-3 weeks. Reporting a case in which the clinical and histopathological findings are consistent with acute hemorrhagic edema of childhood, but with diagnostic uncertainty due to nonspecific signs and symptoms and gifts for other more common conditions.

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INTRODUCTION

Acute hemorrhagic edema of infancy (AHEI) is a rare condition; there are at least 100 cases described in the literature, but it is believed to be an underdiagnosed disease as it is often confused with Henoch-Schönlein purpura or its juvenile form. AHEI occurs between 4 months and 2 years of age and is usually preceded by a non-specific infection.

The course of the disease is benign, although it presents with a dramatic cutaneous picture and clinical presentation of sudden onset that, in some cases, may lead to meningococcemia, sepsis, or other common febrile rash conditions in pediatrics. The diagnosis is essentially clinical and is confirmed by biopsy showing small vessel leukocytoclastic vasculitis. The etiology has not yet been defined, and treatment is symptomatic, given the favorable clinical evolution of this disease.

CASE REPORT

A male child aged 1 year and 8 months from the countryside of Campina Verde, Minas Gerais, presented symptoms compatible with upper airway infection and tonsillitis; he was prescribed with amoxicillin for seven days. After four days of treatment, the child developed an intense swelling of the gums, local ecchymoses, and nodules in the hard palate; amoxicillin was stopped, and topical nystatin was prescribed.

He was registered in the SUS facial Program and the reference for city of origin was listed as Uberlândia-MG. Given the rapid evolution of the symptoms, the parents chose to seek care at the Children's Hospital of Uberaba. He was attended to on August 5, 2014, and his parents observed the sudden appearance of papular erythematous lesions (similar to insect bites) on the left ear (Figures 1 and 2), which evolved quickly to reddish and purplish lesions on both pinna and on the upper and lower limbs, associated with edema (Figures 3, 4, 5), prostration, and fever (38.3°C), followed by signs of shock requiring volume expansion. The patient was then transferred to HC-UFTM for better investigation and management of the symptoms.

The child was admitted in contact isolation due to suspected meningococcemia; he was irritable and had severe edema in the extremities, mainly in the wrists, hands (Figure 1), ankles, and feet (Figure 3), with local heat and hyperemia, and some ecchymoses on the elbows (Figure 6), knees, back, and thighs. Both auricles had severe ecchymoses, with necrotic appearance on the left one (Figures 1 and 2), and purplish maculopapular lesions of varied appearance were observed on the extremities and face (Figures 4 and 6), sparing the abdomen, trunk, and genitalia.

Ceftriaxone, clindamycin, and chloramphenicol were initiated, as indicated by the Hospital Infection Control Committee as part of the protocol for hemorrhagic fevers (among which is spotted fever).



Figure 1. Necrotic lesion on the left pinna.

The patient had no fever after hospitalization, good diuresis, and unaltered gastrointestinal tract. After one day, the patient developed new hyperemic lesions spread throughout the body, including the trunk and abdomen (except genitals) and increase of one of the initial lesions present in the right instep next to the fifth metatarsal (Figure 3). On the third day of hospitalization, the patient was in good general condition and was playing, without irritability or prostration. The lesions decreased gradually.

On August 12, 2015 (seventh day of hospitalization), the unofficial report of biopsy collected on the day of admission (05/08/15) was issued, which showed leukocytoclastic vasculitis; this was confirmed in an official report released on August 18, 2015. The child evolved with remission of the lesions, and was discharged on August 15, 2015 with one crusted lesion on the left ear and general condition unchanged. He was prescribed chloramphenicol for seven days and ceftriaxone + clindamycin for 10 days.

He was discharged before the results of the serology for dengue, leptospirosis, yellow fever, hantavirus, hepatitis A, and spotted fever. The results were given at the ward follow-up consultation on August 22; the results were negative for yellow fever, dengue, leptospirosis, and hantavirus and inconclusive for spotted fever and hepatitis A.



Figure 2. Injury regression.



Figure 3. Foot and ankle edema

Report of the biopsy

Materials: Total skin of the right arm.

Macroscopy: Light brown-skinned ellipse measuring 0.8 x 0.5 x 0.2 cm. Shows no macroscopic alterations.

Microscopy: Skin fragments showing unaltered epidermis. The dermis presents intense inflammatory infiltrate composed predominantly of neutrophils with leukocytoclasia around the vessels with tumescent endothelium and fibrinoid necrosis of the wall. A mild extravasation of red blood cells can be observed.

DIAGNOSIS Leukocytoclastic vasculitis

Note: Considering the clinical and pathological features, the symptoms are compatible with a diagnosis of AHEI.



Figure 4. Medallion-like, edematous, purpuric lesion on the lower limbs.



Figure 5. Edema and injuries on the extremity.

DISCUSSION

First described by Snow in 1913 as "purpura, urticaria, and angioedema of hands and feet in an infant," AHEI was later termed post-infectious cockade by Seidlmayer and acute hemorrhagic edema of childhood by Finkelstein in 1938[1]. There are approximately 100 cases reported, but AHEI is believed to be underdiagnosed; many authors advocate that it is a type of Henoch-Schönlein purpura in infants[2].

AHEI is a rare and benign form of small vessel leukocytoclastic vasculitis that affects children between 4



Figure 6. Medallion-like, symmetrical, purpuric lesion on the upper limbs.

months and 2 years of age and is clinically characterized by the triad of fever; swelling of the extremities; and well-defined, symmetrical purpuric plaques, located mostly in the face, ears, and extremities, with little involvement of the trunk[1,3].

Vasculitis occurs due to an immunologically mediated inflammatory vascular process, which causes functional and structural damage to the vessel wall. According to the predominant cell type in the inflammatory infiltrate of the process, vasculitis is classified as neutrophilic, lymphocytic, or granulomatous. It is also classified in relation to location, with the involvement of small, medium, and/or large vessels.

Necrotizing vasculitis is characterized by segmental areas of transmural infiltration by neutrophils, disruption of vascular architecture, and associated fibrinoid necrosis. The histopathological term used for this set of alterations is leukocytoclastic vasculitis. Endothelial edema and granulocyte debris (leukocytoclasia) are frequently observed, but are not necessarily present at diagnosis[4].

Other occasional manifestations are reticular purpura, necrotic lesions-especially in the ear, and urticaria. The occurrence of purpuric mucosal lesions (conjunctiva and soft palate) has also been described. Visceral involvement is rare and comprised mild and transient renal disorders as well as gastrointestinal disorders. Some authors consider the absence of visceral involvement and systemic disease as a necessary criterion for the diagnosis of AHEI[3].

Although cutaneous findings are dramatic and emerge rapidly, the prognosis is favorable, with spontaneous resolution within 1-3 weeks. The association of fever and purpuric lesions is a challenge for the clinician[1]. Within the universe of diseases that occur with this association, one must always consider Henoch-Schonlein purpura, meningococcemia, and septicemia, the main differential diagnoses of AHEI[2,4].

A higher prevalence of AHEI is observed in the winter months, which may be related to the greater likelihood of vasculitis after infectious episodes. Seventy-five percent of cases were preceded by infections (*Streptococcus*, *Mycoplasma*, *Escherichia coli*, *Staphylococcus*), vaccines (measles, DTP, HiB), or drugs (penicillins, cephalosporins, sulfamethoxazole-trimethoprim, paracetamol)[1,3].

The etiology and pathophysiology remain unclear. However, some authors consider AHEI to be mediated by immune complexes[4].

The diagnosis is essentially clinical and is confirmed by biopsy. In the peripheral blood, eosinophilia, leukocytosis, and thrombocytosis may be observed. The erythrocyte sedimentation rate is normal or slightly elevated. Serum complement levels are normal. Other tests, such as coagulation, urinalysis, renal and liver function, ASO, immunoglobulin (Ig) A and IgM, antinuclear factor, and VDRL, are normal. Systemic involvement injury recurrence are rare[1,4].

Histopathological findings include leukocytoclastic vasculitis with involvement of small vessels of the dermis rarely extending to the subcutaneous tissue, fibrinoid necrosis, extravasation of red blood cells, and interstitial edema. Direct immunofluorescence (DIF) reveals deposits of complement 3 (C3), fibrinogen, and IgM. IgA, IgG, and IgE may be observed, with much lower frequency. Therefore, the clinical characteristics, age, and evolution of the disease allow for the differential diagnosis; the absence of IgA deposits is not mandatory for diagnosis[1].

The relationship between AHEI and Henoch-Schönlein remains controversial. Both are types of leukocytoclastic vasculitis of the small vessels and usually develop after an infectious episode[4]. Henoch-Schönlein purpura usually affects children aged 2-8 years, manifests as purpuric lesions that do not present annular and target appearance, and affect mainly the legs, thighs, and gluteal regions, sparing the face and trunk; it rarely presents an underlying edema.

Furthermore, there are frequent extracutaneous manifestations (two-thirds of patients have gastrointestinal and joint manifestations, 20%-100% have renal involvement); it has a mean duration of 30 days, and recurrences are frequent (up to 50% of cases). Histologically, fibrinoid necrosis is rare; immunofluorescence reveals IgA, C3, and fibrin deposits-suggesting activation of the alternative complement pathway. In contrast, the immunohistological pattern of AHEI is the presence of IgA in one third of cases, deposits of C1q, fibrinogen, C3, IgG, IgM, and IgE in the wall and around the small vessels[1,3].

The absence of visceral involvement and good prognosis are characteristics of AHEI. Reports of atypical cases with characteristic findings of both diseases have been considered as overlapped AHEI and Henoch-Schönlein purpura, as there

is disagreement among the authors about whether AHEI is a distinct clinical entity or a variant of Henoch-Schönlein purpura in infants. It has been suggested that differences between the two diseases could be secondary to age-related changes in the maturation of the immune system mediated by IgA[2].

No treatment is indicated since the disease is benign and self-limited, following its course of 1-3 weeks. There is no evidence that use of systemic corticosteroids and antihistamines shortens the course of the disease, although they are used as a therapeutic approach. The present case report alerts for this vasculitis to diagnosed early, avoiding unnecessary treatments and concerns. There has been only one mortality associated with AHEI, which was due to the complication of ileo-ileal intussusception[4].

Other differential diagnoses are purpura fulminans, meningococcemia, erythema multiforme, drug eruptions, neonatal lupus erythematosus, Sweet's syndrome (painful erythematous-violaceous skin lesions, fever, leukocytosis with neutrophilia, and dermis with neutrophilic inflammatory infiltrate that is dense at histology), Gianotti-Crosti disease (acrolocated symmetrical erythematopapulous eruption in the face, buttocks, and extremities in children aged 2-6 years), and Kawasaki's disease[2].

According to an article published in the *Pediatrics Journal* in 1999, the symptoms of meningitis in infants are often non-specific: irritability, apathy, and refusal to eat, associated with fever, should raise suspicion for this diagnosis. The signs of meningeal irritation are not common in this age group and may appear only at a later stage of the disease.

Conversely, increased intracranial pressure, which is the rule for bacterial meningitis and manifests as headache in older children, manifests in infants as a bulging anterior fontanelle and sutural diastasis.

Altered consciousness, ranging from clouding of consciousness to coma, may be present in meningitis at any age, as well as focal neurological signs; when present at diagnosis, they may indicate a worse prognosis. Seizures are reported in up to 20%-30% of children with bacterial meningitis on admission and the first days of hospitalization, but are not usually related to prognosis, since they are restricted to the initial period of the disease.

The systemic manifestations associated with bacterial meningitis include arthralgia, myalgia, petechiae or purpura, and shock, which may occur with any infectious agent; however, they are significantly more frequent with meningococcus.

Meningococcal disease may manifest in three forms: meningitis, meningococcemia, and meningitis with meningococcemia. Typical isolated cases of meningitis are clinically indistinguishable from meningitis of other bacterial etiologies.

Meningococcemia is characterized by skin lesions, petechial and/or purpuric, which may be preceded by a maculopapular rash. The lesions are mainly located on the extremities and the pressure areas on the skin. Petechiae, which are initially superficial, can coalesce and reach deeper planes, becoming hemorrhagic suffusions and ecchymoses.

In fulminant meningococcemia, the disease has an extremely rapid evolution and is associated with signs of shock (decreased consciousness, tachycardia, tachypnea, decreased pulse amplitude, slow capillary refill, hypotension, and oliguria) and disseminated intravascular coagulation. In this form, the CSF tends to be normal initially[5].

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