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Acute Hemorrhagic Edema of Infancy

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1. Introduction

Acute hemorrhagic edema of infancy (AHEI) is a benign cutaneous small vessel leucocytoclastic vasculitis. The disease characterized by low-grade fever, acral inflammatory edema and large rosetta-, annular-, or targetoid-shaped ecchymotic purpura primarily over the face and extremities. The outbreak is frequently preceded by an immunization, drug intake or various infections. In spite of violent and alarming clinical presentation in a non-toxic infant, spontaneous recovery without any sequelae occurs within a few weeks. Although some have suggested that AHEI is a purely cutaneous variant of Henoch-Schönlein purpura, most authors prefer to regard it as a separate clinical entity among the cutaneous small vessel vasculitic diseases of infancy.

2. Background

Although, AHEI was first described by Snow as a purely cutaneous variant of Henoch-Schönlein purpura in American literature in 1913 (Snow, 1913), it was well-recognised by Seidlmayer (Seidlmayer, 1936) and Finkelstein (Finkelstein, 1938) in European literature in 1930ies. Since then in Europe, many cases have been reported under different clinical terms, including Finkelstein disease and Seidlmayer's 'cockade' purpura or syndrome. The name AHEI first appeared in Spanish written and used by Del Carril (Del Carril et al., 1936). Other names used for the disease include purpura en cocarde avec oedema, urticarial vasculitis of infancy, acute benign cutaneous leukocytoclastic vasculitis (Saraclar et al., 1990) of infancy and infantile post-infectious iris-like purpura and oedema. Already, more than 100 cases of AHEI have been published in medical literature worldwide. However, the current number of reported cases are being still unknown. This is probably because, the most papers on the subject being written different languages in the world and AHEI is called Henoch-Schönlein purpura in the United States. Although most of the prints were in case reports (Babic et al., 2008; Can et al., 2006; Di Lernia et al., 2004; Garty et al., 2002; Michael, 2006; Millard et al., 1999; Macea et al., 2003; Obeid et al., 2008; Serna et al., 1994, Silveira & Braganca, 2006), case series were also published (Alp et al., 2009; Caksen et al., 2002; Fiore et al., 2008; Gelmetti et al., 1985; Gonggryp & Todd, 1998; Ince et al., 1995; Karremann et al., 2009; Krause et al., 1996; Legrain et al., 1991; Poyrazoglu et al., 2003; Saraclar et al., 1990; Sites et al., 2008). Today, AHEI is considered as a separate entity, but not a variant of Henoch-Schönlein purpura, with clinical findings and prognosis.

3. Epidemiology

The exact incidence of AHEI is not well known because of rarity of the disease. So, multicenter epidemiologic studies are needed. Some authors believe that AHEI is often mistaken for other diseases and, therefore, its incidence may be more frequent. It is also probable that, using the synonyms for AHEI in the same population for different cases and to consider the disease as Henoch-Schönlein purpura may change the incidence.

3.1 Age

Usually, AHEI affects infants between 4 months and 2 years of age. However, cases at birth (Cunningham et al., 1996, 1999) and over 2 years of age (Alp et al., 2009; Dubin et al., 1990; Poyrazoglu et al., 2003; Slutsky et al., 2010), with classical features of AHEI, have been reported. Also, rare cases have been reported in older children up to 60 months of age (Alp et al., 2009; Fiore et al., 2008; Legrain et al., 1991). So, it can be suggested that AHEI can be diagnosed from newborn to 60 months of age. Actually, newly added reports of AHEI in English literature between 2008 and 2010 (Alp et al., 2009; Babic et al., 2008; Cicero, 2008; Ferraira et al., 2010; Fiore et al., 2008; Halıcıoglu et al., 2010; Jain & Patel, 2008; Javidi et al., 2008; Kumar et al., 2008; Karremann et al., 2009; Obeid et al., 2008; Slutsky et al., 2010; Sites et al., 2008) with the review by AlSufyani (AlSufyani, 2009) make the mean age approximately 16.56 months instead of 13.75 months reported by AlSufyani (AlSufyani, 2009). Indeed, there have been some reports of cases occurring beyond the age of 3 years; however, these cases have the features that overlap with those of Henoch-Schönlein purpura (Legrain et al., 1991; Shah et al., 2002).

3.2 Sex

Male predominance is clear in the literature. Case series are also support this data (Alp et al., 2009; Fiore et al., 2008; Ince et al., 1995; Legrain et al., 1991; Poyrazoglu et al., 2003; Saraclar et al., 1990). Also, AlSufyani suggests the male to female ratio approximately 4.64/1 (AlSufyani, 2009). However, adding the reported cases between 2008 and 2010 (Alp et al., 2009; Babic et al., 2008; Cicero, 2008; Ferraira et al., 2010; Fiore et al., 2008; Halıcıoglu et al., 2010; Jain & Patel, 2008; Javidi et al., 2008; Kumar et al., 2008; Karremann et al., 2009; Obeid et al., 2008; Slutsky et al., 2010; Sites et al., 2008) makes the male to female ratio approximately 4.34/1. Also, Fiore and colleagues reported the ratios of boys as %67 and girls as %33 in their systematic review (Fiore et al., 2008). But, they have reviewed 155 reports written in 6 languages, not only English literature.

3.3 Effect of seasons

AHEI, usually presents during the winter months. This may be associated with its potential etiology. However, some have presented in the spring, autumn (Fiore et al., 2008; Legrain et al., 1991; Poyrazoglu et al., 2003) and summer (Saraclar et al., 1990).

4. Etiology and pathogenesis

AHEI is probably an immune complex-mediated vasculitis and the pathophysiology is still not fully understood. The frequency of preceding infections and seasonal variation

indicate an infective cause, but drugs and/or immunizations are also suspected. Legrain (Legrain et al., 1991) and AlSufyani (AlSufyani, 2009) reported these related causes up to %75 and %84.6 respectively. Obviously, it is difficult to attribute AHEI to an infection, drug or immunization as these are often present together; however, a few case reports have shown clearance of the first attack, as well as relapses, of AHEI after appropriate treatment of the associated infections (Dubin et al., 1990; Gonggryp & Todd, 1998; Ince et al., 1995; Morrison et al., 1999; Tomac et al., 1996). In addition, Cunningham and colleagues (Cunningham et al., 1996, 1999) have reported a newborn with the clinical findings of AHEI. Her mother had severe gastroenteritis 6 weeks prior to delivery and many lesions on the baby were faded and faint, suggesting that the process had evolved in utero. In conclusion, the authors hypothesized that there was a maternal-fetal transfer of the infectious agent or the immune complex triggering the skin lesions. This probably supports the role of infections and immune complexes in the pathogenesis of AHEI. Other infections described as prodromes that have been accused in the pathogenesis are upper respiratory tract infections (Alp et al., 2009; Babic et al., 2008; Blasini et al., 2007; Caksen et al., 2002; Dubin et al., 1990; Fiore et al., 2008; Gelmetti et al., 1985; Halicioğlu et al., 2010; Ince et al., 1995; Karremann et al., 2009; Kumar et al., 2008; Lai-Cheong JE et al., 2007; McDougall et al., 2004; Michael, 2006; Millard et al., 1999; Paradisi et al., 2001; Poyrazoğlu et al., 2003; Saraclar et al., 1990), pharyngitis (Gattorno et al., 1997; Gonggryp & Todd, 1998), tonsillitis (Legrain et al., 1991; Karremann et al., 2009), otitis (Caksen et al., 2002; Crowe et al., 1998; Karremann et al., 2009; Krause et al., 1996; Lantner et al., 1996; Macea et al., 2003), conjunctivitis (Legrain et al., 1991), neck abscess, bronchopneumonia (Alp et al., 2009; Saraclar et al., 1990), bronchitis (Karremann et al., 2009), pneumococcal bacteremia (Morrison et al., 1999), pulmonary tuberculosis (Gonggryp & Todd, 1998), cellulitis (Can et al., 2006), urinary tract infections (Saraclar et al., 1990) and gastroenteritis (Caksen et al., 2002; Chatproedprai & Wanankul, 2007; Fiore et al., 2008; Garty et al., 2002; Poyrazoğlu et al., 2003; Silveira & Braganca, 2006).

Also, specific microorganisms have been isolated in the cases with AHEI, such as coxsackie B₄ virus (Krause et al., 1996), cytomegalovirus (Kuroda et al., 2002; Saraclar et al., 1990), rotavirus (Di Lernia et al., 2004), herpes simplex virus-1 (Garty et al., 2006), hepatitis A virus (Bozaykut et al., 2002) and parvovirus B19 (Erguven & Karaca Atakan, 2009). *Escherichia coli* grew in some of the children with urinary tract infections (Fiore et al., 2008) and *Campylobacter* (Gonggryp & Todd, 1998) were isolated in some of the patients with diarrhea. Additionally, failure to convincingly relate AHEI to prodromal infectious caused by group A streptococcus or *Mycoplasma pneumoniae* is not surprising, considering that these agents mostly cause infections in children 5 years of age or older (Jaggi & Shulman, 2006; Principi & Esposito, 2002).

A wide range of medications have been reported such as anti-inflammatory and/or antipyretics including ibuprofen (Blasini et al., 2007), aspirin and paracetamol (da Silva Manzoni et al., 2004; Fiore et al., 2008; Karremann et al., 2009; Legrain et al., 1991; Poyrazoğlu et al., 2003; Saraclar et al., 1990), antimicrobials including penicillins (Legrain et al., 1991; Saraclar et al., 1990), amoxicillin (Blasini et al., 2007; Gattorno et al., 1997), sulfamonomethoxazole (Halicioğlu et al., 2010), erythromycin (Krause et al., 1996), tobramycin (Blasini et al., 2007), trimethoprim-sulfamethoxazole (Poyrazoğlu et al., 2003), cefaleksim (Crowe et al., 1998; da Silva Manzoni et al., 2004;), ceftriaxone (Can et al., 2006), ceftibuten (Fiore et al.,

2008) and other medications such as cough syrup (Dubin et al., 1990; Gonggryp & Todd, 1998) and probiotics (Fiore et al., 2008).

Vaccines have also been implicated in the pathogenesis of AHEI, including diphtheria-pertussis-tetanus (Krause et al., 1996; Saraclar et al., 1990), poliomyelitis vaccine (Saraclar et al., 1990), hemophilus influenza conjugated (Krause et al., 1996), measles (Gonggryp & Todd, 1998; Saray et al., 2002), rubeola (Poyrazoglu et al., 2003), BCG (Lai-Cheong JE et al., 2007) and influenza A/H1N1 vaccine (Ferraira et al., 2010).

In the skin, postcapillary venules are the most commonly involved vessels. Leucocytoclastic vasculitis is the histological feature of AHEI that has been linked pathogenetically to immune complex deposition, complement activation and chemotaxis of neutrophils, with secondary damage to vessel walls due to the release of enzymes by activated neutrophils (Legrain et al., 1991, Saraclar et al., 1990). However, complement deficiency (Yavuz, 2000) or hypocomplementemia due to activation of the classical pathway of complement system (Watanabe & Sato, 2007) have not been showed in AHEI as they have been suggested. The location of vasculitic lesions to the extremities and especially the legs in children is thought to be related to increased hydrostatic pressure leading to immune complexes and fibrin deposition (Legrain & Taieb, 2000). Also, it has been suggested that proportionally larger had and face in infants corresponds to increased blood supply and susceptibility to facial purpura (Amitai et al, 1993).

5. Histopathology

Classically histological examination shows features of an intense dermal leucocytoclastic vasculitis involving small blood vessels in the dermis with (Acun et al., 2006; AlSufyani, 2009; Blasini et al., 2007; Braun-Falco & Dietrich Abeck, 2002; Caksen et al., 2002; Caliskan et al., 1995; Can et al., 2006; Chatproedprai & Wananukul, 2007; Colantonio et al., 1997; Crowe & Jonas, 1998; Cunningham et al., 1996, 1999; Bozaykut et al., 2002; da Silva Manzoni et al., 2004; Di Lernia et al., 2004; Dubin et al., 1990; Fiore et al., 2008; Fujimura et al., 2001; Garty et al., 2006; Gelmetti et al., 1985; Goraya & Kaur, 2002; Gonggryp & Todd, 1998; Gattorno et al., 1997; Javidi et al., 2008; Krause et al., 1996; Kuroda et al., 2002; Lakshmi & Srinivas, 2003; Lantner et al., 1996; Lee et al., 2006; Long & Helm, 1998; Macea et al., 2003; Michael, 2006; Millard et al., 1999; Morrison & Saulsbury, 1999; Paradisi et al., 2001; Poyrazoglu et al., 2003; Pride et al., 1995; Roh et al., 2004; Tomac et al., 1996; Saray et al., 2002; Scaramuzza et al., 1997; Serna et al., 1994; Shah et al., 2002; Silveira et al., 2006; Sites et al., 2008; Smitt et al., 2002, Watanabe & Sato, 2007; Wong & Harrington, 2004) (Fig. 1a, b) or without (Ince et al., 1995; Legrain et al., 1991; Saraclar et al., 1990) fibrinoid necrosis and erythrocyte extravasation. However, lymphohistiocytic perivascular infiltration with extravasation of erythrocytes and without fibrinoid necrosis was also reported by Legrain and colleagues (Legrain et al., 1991). The infiltrating inflammatory cells are predominantly neutrophils with less number of eosinophils (Krause et al., 1996; Macea et al., 2003; Millard et al., 1999; Saraclar et al., 1990).

6. Immunofluorescence study and immunologic characteristics

Immunofluorescence studies are usually negative (AlSufyani, 2009; Can et al., 2006; Cunningham et al., 1996; da Silva Manzoni et al., 2004; Gonggryp & Todd, 1998; Javidi et al.,

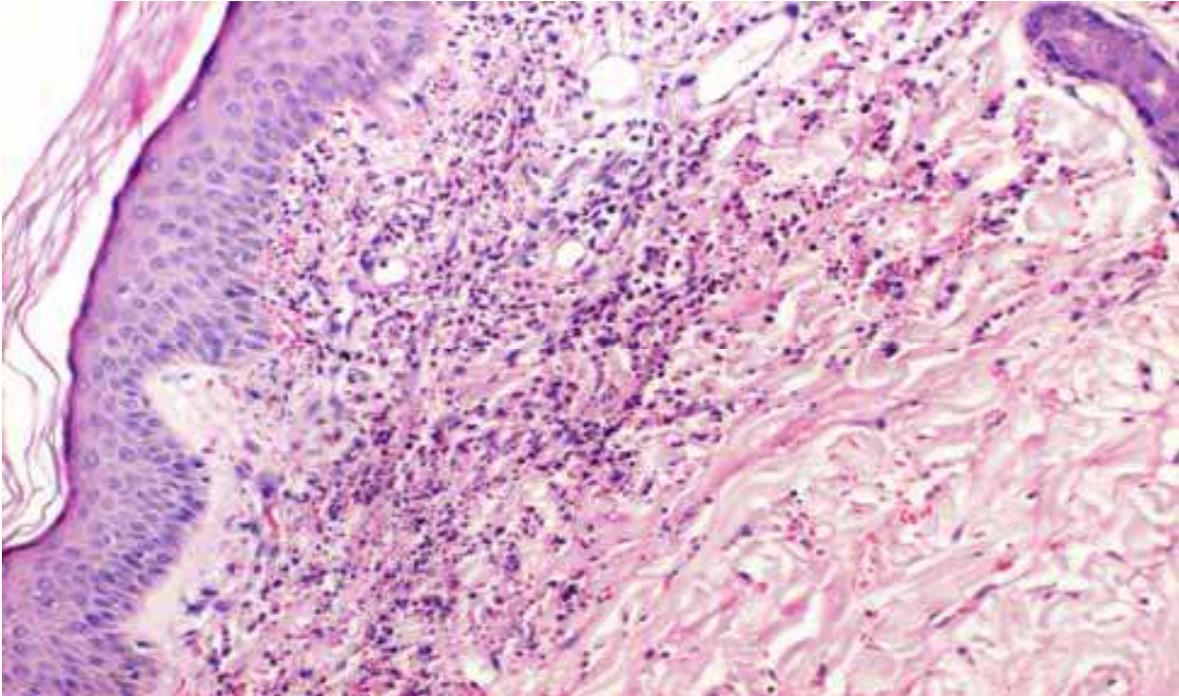


Fig. 1a. Hematoxylin and eosin-stained pathologic specimen from a purpuric skin lesion, showing perivascular leucocyte infiltration (x10).

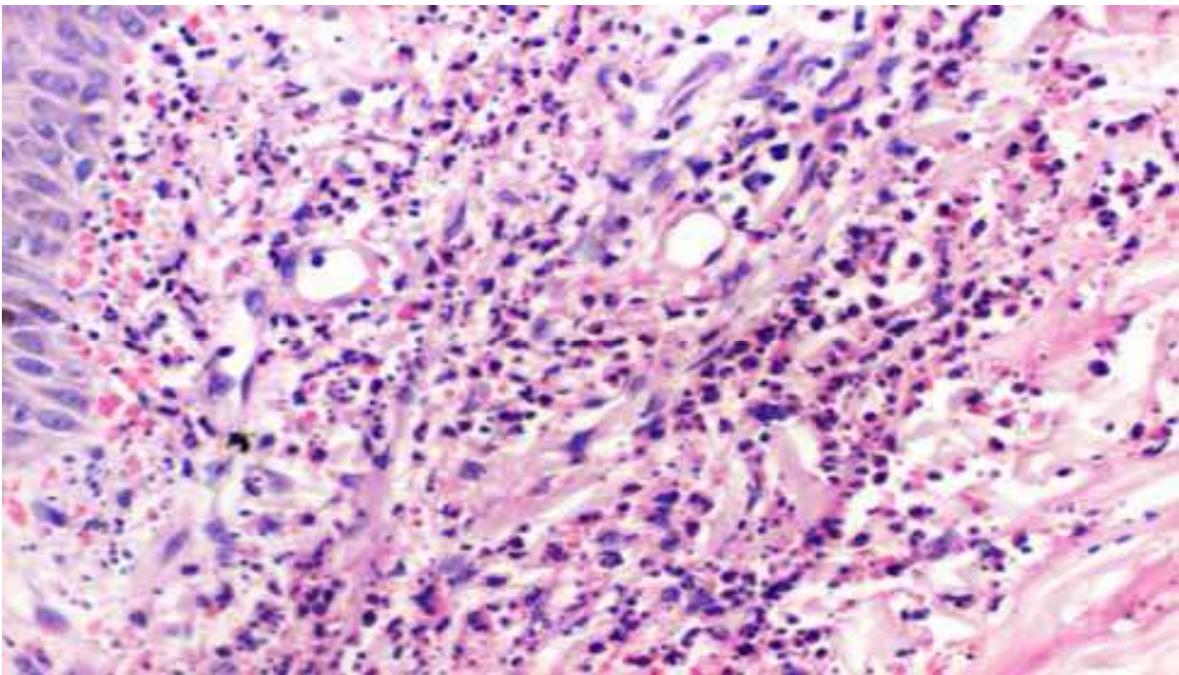


Fig. 1b. Extravasation of red blood cells, neutrophilic perivascular infiltration with leukocytoclasia, and fibrinoid necrosis (x40).

2008; Krause et al., 1996; Legrain et al., 1991; Paradisi et al., 2001; Serna et al., 1994). However; C₃, C_{1q}, fibrinogen, IgM, IgG, IgE and IgA were detected in the specimens with varying degrees of positivity (Amitai et al., 1993; Blasini et al., 2007; Caksen et al., 2002; Chatproedprai & Wananukul, 2007; Garty et al., 2006; Gattorno et al., 1997; Kuroda et al.,

2002; Legrain et al., 1991; Long & Helm, 1998; Michael, 2006; Paradisi et al., 2001; Roh et al., 2004; Tomac et al., 1996; Saraclar et al., 1990). In the study of Saraclar and colleagues, in the skin biopsy of 9 cases perivascular C₃, fibrinogen, IgM, IgG, IgE and IgA were detected 100%, 100%, 78%, 22%, 33% and 33% respectively (Saraclar et al., 1990). After the publication of their article they also examined an infant and in the lesional skin biopsy specimens of these 10 cases IgA, IgG, IgM, IgE and C_{1q} depositions were found in 30%, 20%, 80%, 30% and 100% respectively (Saraclar et al., 1992). So, based on these findings they suggested that the presence of C_{1q} and absence or infrequency of IgA deposition may help physicians to confirm AHEI rather than Henoch-Schönlein purpura. Additionally, Fiore et al. reported the deposition of IgA as 24% in their review (Fiore et al., 2008). Watanabe & Sato reported decreased levels of C₄, C_{1q} and CH50 in the serum of a 19-month-old boy with AHEI (Watanabe & Sato, 2007). So, they suggested that activation of the classical pathway of the complement might represent one of the pathogenic mechanisms underlying the development of AHEI. In summary, all of these immunohistologic and immunoserologic findings indicate that AHEI is an immunorelated disease.

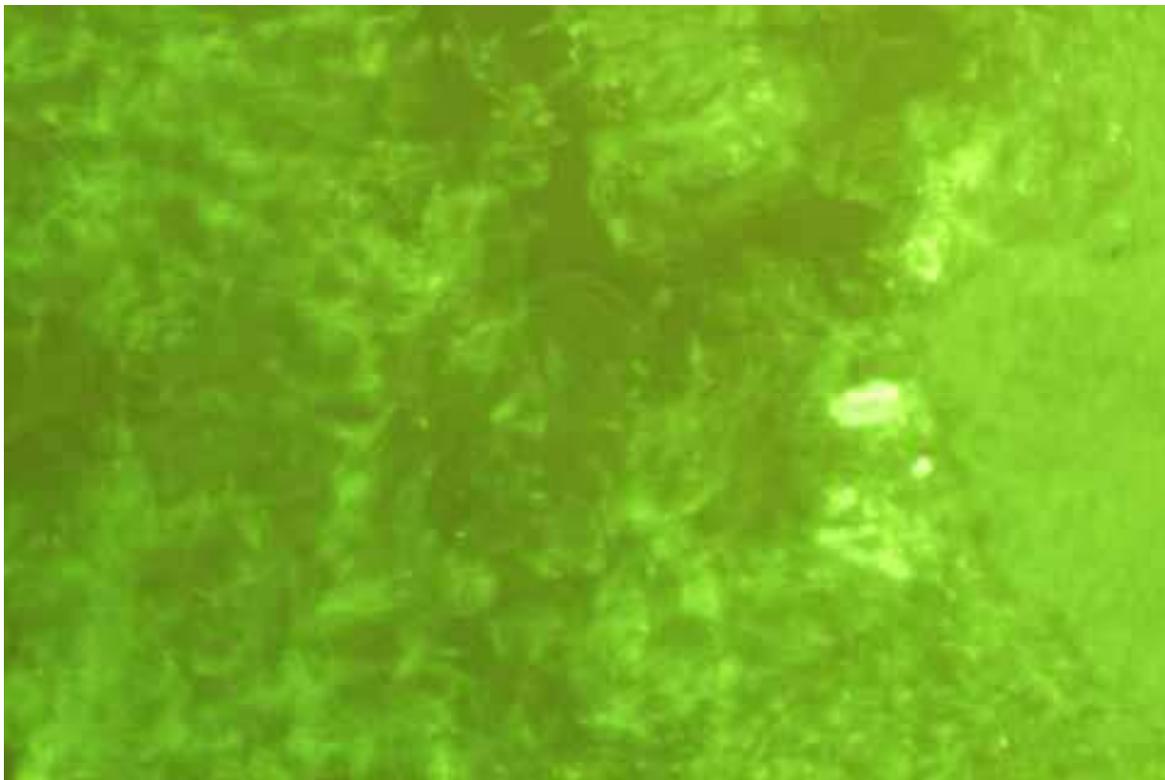


Fig. 2. Immunofluorescence study of epidermis with deposition of perivascular IgA.

7. Clinical features

The characteristic clinical features of AHEI are fever, purpura and edema. Additionally, the most striking feature is the contrast between the acuteness of the cutaneous signs and the good general condition of the child (Alp et al., 2009; Amitai et al., 1993; Dubin et al., 1990; Fiore et al., 2008; Ince et al., 1995; Lantner & Simon, 1996; Tomac et al., 1996; Saraclar et al., 1990). In the review of Fiore and colleagues, general appearance was reported as severely reduced in 1.0%, mildly reduced in 7.0% and very satisfactory in remaining 92% (Fiore et al.,

2008). Additionally, atypical presentations such as painful edema (Dubin et al., 1990; Gonggryp & Todd, 1998; Krause et al., 1996; Lantner & Simon, 1996; Millard et al., 1999; Morrison & Saulsbury, 1999; Shah et al., 2002), itching (AlSufyani, 2009; Caksen et al., 2002), irritability (Crowe & Jonas, 1998; Kuroda et al., 2002; Lantner & Simon, 1996) and decreased appetite (Lantner & Simon, 1996) may occur. Fever is typically low grade, but may range from mild to severe and also afebrile cases have been published in the literature (AlSufyani, 2009; Amitai et al., 1993; Dubin et al., 1990; Fiore et al., 2008; Gonggryp & Todd, 1998; Karreman et al., 2009; Krause et al., 1996; Saraclar et al., 1990; Scaramuzza et al., 1997; Serna et al., 1994). In the review of Fiore and colleagues fever of low grade was reported in 45% of the children (Fiore et al., 2008).

Purpura is the most dramatically presenting exanthema of AHEI and often appears in a cockade pattern in combined lesions (Legrain et al., 1991; Saraclar et al., 1990; Seildmayer, 1936). The eruption usually starts with erythematous macules (Krause et al., 1996; Scaramuzza et al., 1997), papules (Lantner & Simon, 1996; McDougall et al., 2004; Tomac et al., 1996), or urticarial plaques (da Silva Manzoni et al., 2004; Legrain et al., 1991; Saraclar et al., 1990) that rapidly progress into annular (Lee et al., 2006; McDougall et al., 2004), rounded or oval (Alp et al., 2009), medallion-like (Karreman et al., 2009), cockade (Caksen et al., 2002), or targetoid-shaped purpuric lesions (Alp et al., 2009; Amitai et al., 1993; Caksen et al., 2002, Caliskan et al., 1995; Can et al., 2006; Crowe & Jonas, 1998; Cunningham et al., 1996; da Silva Manzoni et al., 2004; Di Lernia et al., 2004; Dubin et al., 1990; Fiore et al., 2008; Gelmetti et al., 1985; Gonggryp & Todd, 1998; Ince et al., 1995; Krause et al., 1996; Lantner & Simon, 1996; Lee et al., 2006; Legrain et al., 1991; Long & Helm, 1998; McDougall et al., 2004; Poyrazoglu et al., 2003; Saraclar et al., 1990; Scaramuzza et al., 1997; Serna et al., 1994; Silveira et al., 2006; Tomac et al., 1996; Watanabe & Sato, 2007) (Fig. 1a, b). However, other morphologies have been described, such as reticulated (Legrain et al., 1991), petechiae (Karreman et al., 2009), rosette-like (Paradisi et al., 2001), scalloped-border (Millard et al., 1999; Yu et al., 2007), tense hemorrhagic blistered or fluid containing lesions (either vesicles or bullae) (Al-Sheyyab et al., 1995; da Silva Manzoni et al., 2004; Gonggryp & Todd, 1998; Gattorno et al., 1997; Gattorno et al., 1999; Lai-Cheong et al., 2007; Lee et al., 2006; Legrain et al., 1991; Millard et al., 1999; Suehiro et al., 2007; Watanabe & Sato, 2007), arcuate and polycyclic (Di Lernia et al., 2004; Macea et al., 2003). Skin lesions may progress to 1 to 6 cm in diameter (Michael, 2006; Smitt et al., 2002). The rashes are usually sharply edged and the centre of the lesions may rarely have the colour of the normal skin (Legrain et al., 1991; Saraclar et al., 1990). Lesions usually occur in the face (mainly cheeks) (Alp et al., 2009; AlSufyani, 2009; Caksen et al., 2002; Fiore et al., 2008; Karreman et al., 2009; Krause et al., 1996; Legrain et al., 1991; Poyrazoglu et al., 2003; Saraclar et al., 1990), auricles (Fig. 2) and upper (Millard et al., 1999) (Fig. 3) or lower extremities (Alp et al., 2009; AlSufyani, 2009; Caksen et al., 2002; Fiore et al., 2008; Karreman et al., 2009; Krause et al., 1996; Legrain et al., 1991; Michael, 2006; Poyrazoglu et al., 2003; Saraclar et al., 1990) (Fig. 4) with relative sparing of the trunk (Fiore et al., 2008). Additionally, Fiore and colleagues reviewed that purpura had a relative frequency on the left side of the body (Fiore et al., 2008). Skin or mucous membranes are uncommonly involved in AHEI such as conjunctiva (McDougall et al., 2004; Poyrazoglu et al., 2003), buccal mucosa (Halicioğlu et al., 2010; Roh et al., 2004), palate (Blasini et al., 2007; Chatproedprai & Wananukul, 2007; Gelmetti et al., 1985; Poyrazoglu et al., 2003), gums (Di Lernia et al., 2004), uvula, tongue, pharynx (Amitai et al., 1993; Di Lernia et al., 2004; Dubin et al., 1990; Krause et al., 1996; McDougall et al., 2005), calf



Fig. 3a. Purpuric involvement of the feet in a 30-month-old male patient with AHEI.



Fig. 3b. Ecchymotic and purpuric lesions with edema of the lower extremities in a 7-month-old girl.

(as hematoma) (Karreman et al., 2009), penis (Fiore et al., 2008; Poyrazoglu et al., 2003), scrotum (Dubin et al., 1990; Karreman et al., 2009; Poyrazoglu et al., 2003), buttocks (Amitai et al., 1993; da Silva Monzani et al., 2004; Legrain et al., 1991; Michael, 2006; Paradisi et al., 2001; Roh et al., 2004; Saraclar et al., 1990; Serna et al., 1994; Shah et al., 2002), joints (Al-Sheyyab et al., 1995; Gattorno et al., 1997) and perineum (Lantner & Simon, 1996). Extracutaneous manifestations rarely occur; however, renal involvement with microscopic hematuria, proteinuria and hypocomplementemia (Watanabe & Sato, 2007); transient and microscopic hematuria (Al-Sheyyab et al., 1995; Amitai et al., 1993; Gonggryp & Todd, 1998; Legrain et al., 1991; Millard et al., 1999); intusseption (Yu et al., 2007); bowel involvement as positive stool for occult blood (Al-Sheyyab et al., 1995; Di Lernia et al., 2004; Garty et al., 2002; Gonggryp & Todd, 1998; Yu et al., 2007) and abdominal pain with elevated transaminases (Obeid et al., 2008) associated with AHEI were reported. Proteinuria is usually transient (Legrain et al., 1991; Saraclar et al., 1990), but can be persistent (Millard et al., 1999). Hypertension is also rare and transient (Caksen et al., 2002) with no renal involvement. Cases of diarrhea, abdominal pain and vomiting have been reported (Di Lernia et al., 2004; Legrain et al., 1991), however these cases have shown an underlying cause, such as coxsackie virus (Legrain et al., 1991) and rotavirus (Di Lernia et al., 2004) growth in the stool.



Fig. 4. Purpuric skin lesion on ear in a 11-month-old boy with AHEI.

Edema is classically asymmetrical nonpitting (mainly tender), usually affects the auricles, face and limbs (frequently dorsum of the hands and feet) (Alp et al., 2009; AlSufyani, 2009; Amitai et al., 1993; Caksen et al., 2002, Caliskan et al., 1995; Can et al., 2006; Crowe & Jonas, 1998; Cunningham et al., 1996; da Silva Manzoni et al., 2004; Di Lernia et al., 2004; Dubin et al., 1990; Fiore et al., 2008; Garty et al., 2006; Gonggryp & Todd, 1998; Ince et al., 1995; Krause et al., 1996; Lantner & Simon, 1996; Lee et al., 2006; Legrain et al., 1991; Long & Helm, 1998; McDougall et al., 2004; Michael, 2006; Millard et al., 1999; Paradisi et al., 2001;



Fig. 5. Ecchymotic and purpuric lesions of upper extremities in a 10-month-old girl.



Fig. 6. Ecchymotic and purpuric lesions of the lower extremities in a 7-month-old girl.

Poyrazoglu et al., 2003; Saraclar et al., 1990; Scaramuzza et al., 1997; Serna et al., 1994; Silveira et al., 2006; Tomac et al., 1996; Watanabe & Sato, 2007). However, other parts of the body may be involved resembling nephrotic syndrome such as the eyelids (Caksen et al., 2002; Gonggryp & Todd, 1998; Karreman et al., 2009; Legrain et al., 1991; Paradisi et al., 2001; Saraclar et al., 1990), lips (McDougall et al., 2004), penis (Fiore et al., 2008; Poyrazoglu et al., 2003) and scrotum (Millard et al., 1999; Saraclar et al., 1990; Yu et al., 2007). Also, the edema can cause weight gain (Saraclar et al., 1990).

8. Laboratory findings

The laboratory investigations are nonspecific. Leukocytosis with lymphocytosis or eosinophilia (Alp et al., 2009; Amitai et al., 1993; Colantonio et al., 1997; Cunningham et al., 1996; Fiore et al., 2008; Lantner & Simon, 1996; Legrain et al., 1991; Roh et al., 2004; Tomac et al., 1996; Saraclar et al., 1990; Scaramuzza et al., 1997; Watanabe & Sato, 2007), thrombocytosis (Di Lernia et al., 2004; Fiore et al., 2008; Garty et al., 2006; Halicioğlu et al., 2010; Ince et al., 1995; Lantner & Simon, 1996; Legrain et al., 1991; Tomac et al., 1996) and increased erythrocytes sedimentation rate or C-reactive protein (Alp et al., 2009; AlSufyani, 2009; Blasini et al., 2007; Caksen et al., 2002; Can et al., 2006; Colantonio et al., 1997; Di Lernia et al., 2004; Fiore et al., 2008; Garty et al., 2002; Halicioğlu et al., 2010; Javididi et al., 2008; Kuroda et al., 2002; Lee et al., 2006; Macea et al., 2003; Millard et al., 1999; Paradisi et al., 2001; Poyrazoglu et al., 2003; Watanabe & Sato, 2007) are common findings. The coagulation tests are usually normal, but elevated fibrinogen (Di Lernia et al., 2004) was noted. Additionally, hypoalbuminemia has been reported associated with intussusception (Yu et al., 2007). Urinalysis is frequently normal, however cases of proteinuria (Legrain et al., 1991; Saraclar et al., 1990; Watanabe & Sato, 2007) and microscopic hematuria (Al-Sheyyab et al., 1995; Amitai et al., 1993; Gonggryp & Todd, 1998; Legrain et al., 1991; Millard et al., 1999; Watanabe & Sato, 2007) have been reported. The stool is typically negative for blood, but positive stool for occult blood (Al-Sheyyab et al., 1995; Di Lernia et al., 2004; Garty et al., 2002; Gonggryp & Todd, 1998; Yu et al., 2007) have been documented. Antinuclear antibodies (ANAs), ASO titre, antideoxyribonucleic acid (anti DNA) antibodies and rheumatoid factor are always negative. However, elevated anti-DNAse B titer (Gonggryp & Todd, 1998) and IgG antineutrophil cytoplasmic antibody (Ozaltın et al., 2004) have been reported in two patients. Complement levels are normal in the patients, although cases with increased serum C₃ (Saraclar et al., 1990), decreased serum C₄ (Cunningham et al., 1996; Watanabe & Sato, 2007) and CH50 (Watanabe & Sato, 2007) levels have been mentioned. Classically, serum immunoglobulin levels are normal, however patients with increased levels of IgG (Legrain et al., 1991), IgM (Caksen et al., 2002; Di Lernia et al., 2004), IgE (Saraclar et al., 1990) and IgA (Di Lernia et al., 2004; Legrain et al., 1991) have been reported. Circulating immune complexes are normal, although some have reported positive findings (Saraclar et al., 1990; Scaramuzza et al., 1997). Additionally, Ozaltın and colleagues reported positivity of IgG ANCA in a patient with AHEI (Ozaltın et al., 2004). However, the importance of this finding has not been known. Generally, most of these uncommon laboratory findings are case reports and need future evaluations.

9. Diagnostic criteria and differential diagnosis

The diagnostic criteria can be proposed as follows (AlSufyani, 2009; Krause et al., 1996).

- Between 4 months and 2 years of age.
- Purpuric or ecchymotic target-like skin lesions with edema especially on the face, auricles and extremities with or without mucosal involvement.
- Lack of systemic disease or visceral involvement.
- Spontaneous recovery within 4-24 days.

Common laboratory investigations are follows.

- Leukocytosis with lymphocytosis or eosinophilia.
- Elevated erythrocytes sedimentation rate or C-reactive protein.
- Leucocytoclastic vasculitis with or without fibrinoid necrosis involving small blood vessels in the dermis on histological examination.
- Negative immunofluorescence studies are usual or rarely positivity of C₃, C_{1q}, fibrinogen, IgM, IgG, IgE and IgA in varying degrees can be detected.

AHEI and Henoch-Schönlein purpura (HSP) both fall within the spectrum of the leucocytoclastic vasculitis. Some authors believe that these two conditions are different disease entities (Cunningham et al., 1999; da Silva Manzoni et al., 2004; Gonggryp & Todd, 1998; Ince et al., 1995; Krause et al., 1996; Millard et al., 1999; Saraclar et al., 1990; Tomac et al., 1996) whereas others regard them as distinct but with some cases showing overlap (Legrain et al., 1991; Shah et al., 2002). Some of the points that differentiate these two entities are (Table 1); age of onset (3-7 years for HSP and 4 months-2 years for AHEI) (Legrain et al.,

	AHEI	HSP
Age	4-24 months	3-7 years
Sex	Slight male predominance in both diseases	
Prodromes	Respiratory infections, drug intake and immunization in both diseases	
Seasons	Usually winter months in both diseases	
Morphology of skin lesions	Purpuric, ecchymotic lesions	Papular, petechial and urticarial lesions
Location of skin lesions	Face, auricles and extremities with relative frequency on the left side of the body	Lower part of the body
Edema	Constant and nonpitting, mainly tender	Inconsistent
Visseral involvement	Uncommon	Frequent
Duration of disease	1-3 weeks	One month or more
Relapses	Rare	Frequent
Histopathology	Leucocytoclastic vasculitis with frequent fibrinoid necrosis	Leucocytoclastic vasculitis
Immunofluorescence study	Perivascular C1q deposits	Perivascular IgA deposits

Table 1. Comparison of epidemiological, clinical and pathological findings of AHEI and HSP

1991; Saraclar et al., 1990; Tomac et al., 1996), morphology of skin lesions with location on the part of the body (papular, petechial, urticarial lesions located predominantly on the lower legs and gluteal regions in HSP and ecchymotic, cockade purpuric lesions mainly located on face and extremities in AHEI) (Legrain et al., 1991; Saraclar et al., 1990; Tomac et al., 1996), edema (not a clinical finding of HSP, but a classical finding of AHEI, commonly nonpitting with tender) (Legrain et al., 1991; Saraclar et al., 1990; Tomac et al., 1996), visceral involvement (frequently seen in HSP, but uncommon in AHEI) (Gelmetti et al., 1985; Legrain et al., 1991; Saraclar et al., 1990), duration of disease (one month or more in HSP, usually resolves between 1-3 weeks in AHEI) (Fiore et al., 2008; Legrain et al., 1991; Saraclar et al., 1990) and relapses (frequent in HSP, rare in AHEI, however there have been cases of AHEI showing multiple relapses) (Amitai et al., 1993; Dubin et al., 1990; Karreman et al., 2009; Legrain et al., 1991; Saraclar et al., 1990).

Also, duration of complete recovery in each attack is different between HSP (approximately 4 weeks) and AHEI (approximately 12 days) (Karreman et al., 2009; Legrain et al., 1991; Tomac et al., 1996). However, there have been cases of AHEI with long duration of attacks up to 24 days (Legrain et al., 1991). On laboratory, some authors suggested that these two diseases should be separated on the basis of the negative immunofluorescence studies of skin biopsies in the cases with AHEI (Millard et al., 1999; Saraclar et al., 1990). Although, as it was discussed in 'Immunofluorescence study and immunologic characteristics' some reported cases had positive direct immunofluorescence with any of C₃, C_{1q}, fibrinogen, IgM, IgG, IgE and IgA (Amitai et al., 1993; Blasini et al., 2007; Caksen et al., 2002; Chatproedprai & Wanankul, 2007; Garty et al., 2006; Gattorno et al., 1997; Kuroda et al., 2002; Legrain et al., 1991; Long & Helm, 1998; Michael, 2006; Paradisi et al., 2001; Roh et al., 2004; Tomac et al., 1996; Saraclar et al., 1990). However, Saraclar and colleagues suggested that presence of C_{1q} and absence or infrequency of IgA deposition may be helpful for physicians to confirm AHEI rather than HSP (Saraclar et al., 1992). Additionally, Goraya (Goraya et al., 2002) and Shah (Shah et al., 2002) reported that the observed immunohistologic differences between the two diseases are secondary to the immaturity of the IgA immune system at the ages of 12 and 24 months. In these age groups the IgA levels are at 19% and 25% of adult values, respectively. So, this might explain the observed clinical and immunologic differences between these two disorders.

The other differential diagnosis of AHEI includes meningococemia, erythema multiforme, Kawasaki disease, purpura fulminans, eruptions of viral infections, drug-induced vasculitis, septic vasculitis, Sweet's syndrome (acute febrile neutrophilic dermatosis), dermatologic manifestations of hematologic diseases and child abuse (Caksen et al., 2002; Cunningham et al., 1996; Dubin et al., 1990; Ince et al., 1995; Legrain et al., 1991; Saraclar et al., 1990; Smitt et al., 2002). All these disorders can be differentiated from AHEI by results of history, physical examination and appropriate laboratory studies, including examination of skin biopsy specimen.

10. Treatment

There is no specific treatment for AHEI because of its natural course. Multiple treatments have been reported to be beneficial, such as topical hydrocortisone 1% cream twice daily (Long & Helm, 1998), systemic prednisone with a dose of 1.5-2 mg/kg/day (Dubin et al., 1990; Ince et al., 1995; Poyrazoglu et al., 2003), prednisolone with a dose of 0.5-1

mg/kg/day (AlSufyani, 2009; Blasini et al., 2007; da Silva Manzoni et al., 2004; Halıcıoğlu et al., 2010; Roh et al., 2004), methylprednisolone with a dose of 1 mg/kg twice daily (Garty et al., 2006) and betamethasone with a dose of 1 mg/kg/day (Paradisi et al., 2001). Also, oral antihistamines such as hydroxyzine, diphenhydramine (Alp et al., 2009; Caksen et al., 2002; Ince et al., 1995; Poyrazoğlu et al., 2003; Tomac et al., 1996), dapsone (Gonggryp & Todd, 1998) and oral nonsteroidal anti-inflammatory drugs (Karremann et al., 2009; Poyrazoğlu et al., 2003) have been suggested for management. Some authors believe that these treatments have a role in changing the course of the disease (Alp et al., 2009; Saraclar et al., 1990), but some do not (Krause et al., 1996; Legrain et al., 1991). Treatments with antimicrobials for a confirmed concurrent infection have been shown to be of some value during the course of AHEI (Caksen et al., 2002; Colantonio et al., 1997; Garty et al., 2002; Gonggryp & Todd, 1998; Ince et al., 1995; Karremann et al., 2009; Morrison & Saulsbury, 1999; Tomac et al., 1996).

11. Prognosis

AHEI is generally benign and self-limited. Spontaneous and complete resolution occurs within 4-24 days (Acun et al., 2006; Alp et al., 2009; AlSufyani, 2009; Blasini et al., 2007; Braun-Falco & Dietrich Abeck, 2002; Caksen et al., 2002; Caliskan et al., 1995; Can et al., 2006; Chatproedprai & Wananukul, 2007; Colantonio et al., 1997; Crowe & Jonas, 1998; Cunningham et al., 1996, 1999; Bozaykut et al., 2002; da Silva Manzoni et al., 2004; Di Lernia et al., 2004; Dubin et al., 1990; Fiore et al., 2008; Fujimura et al., 2001; Garty et al., 2006; Gelmetti et al., 1985; Goraya & Kaur, 2002; Gonggryp & Todd, 1998; Gattorno et al., 1997; Javidi et al., 2008; Karreman et al., 2009; Krause et al., 1996; Kuroda et al., 2002; Lakshmi & Srinivas, 2003; Lantner et al., 1996; Lee et al., 2006; Long & Helm, 1998; Macea et al., 2003; Michael, 2006; Millard et al., 1999; Morrison & Saulsbury, 1999; Paradisi et al., 2001; Poyrazoğlu et al., 2003; Pride et al., 1995; Roh et al., 2004; Saraclar et al., 1990; Saray et al., 2002; Scaramuzza et al., 1997; Serna et al., 1994; Shah et al., 2002; Silveira et al., 2006; Sites et al., 2008; Smitt et al., 2002; Tomac et al., 1996; Watanabe & Sato, 2007; Wong & Harrington, 2004). Attacks have not been usually reported in the literature. This may be because long-term follow-up is not available in most cases. However, attacks associated with AHEI have been reported in some cases and the duration of these attacks were not completely different from the duration of the main disease (Alp et al., 2009; Amitai et al., 1993; Dubin et al., 1990; Karreman et al., 2009). With either treatment or a conservative approach, AHEI usually resolves completely with no sequelae, but there have been reports of residual hyperpigmentation (Saraclar et al., 1990), slight atrophy (Macea et al., 2003) and depressed scars instead of cheeks (AlSufyani, 2009). Also, Smitt and colleagues stated that only necrotic areas may leave a scar (Smitt et al., 2002). On the other hand, AlSufyani suggested that scarring is genuine to the disease process itself and it is not clear whether earlier administration of either treatment would have prevented scarring (AlSufyani, 2009). Also, complications such as intussusception (Yu et al., 2007) and torsion of testis (Gelmetti et al., 1985) have been reported.

12. Conclusion

Acute hemorrhagic edema of infancy is an uncommon cutaneous leukocytoclastic vasculitis. Various infections, drug use and vaccination are discussed as triggering factors more than

90 years after the first description of the disease. Also, the benign and self-limited course and excellent prognosis with mild to absent systemic involvement is well established. Today, it has been considered as a distinct entity either than a variant of Henoch-Schönlein purpura. Physicians might develop the skills necessary to consider the diagnosis of acute hemorrhagic edema of infancy when presented with a non-toxic infant having large targetoid purpuric lesions and edema in nonpitting character.

13. Acknowledgment

I give my thanks and gratitude to Prof. Ismail Reisli from Department of Pediatric Immunology for his suggestions about writing the text. I also thank to Assoc. Prof. Hatice Toy from Department of Pathology for the pictures of histopathology and immunofluorescence studies.

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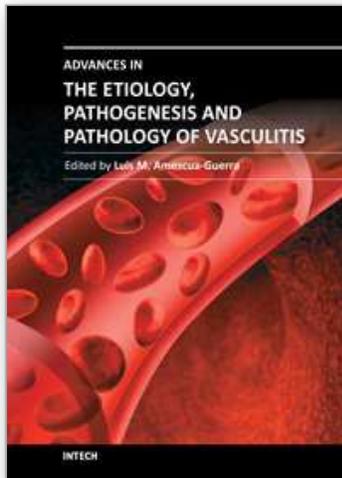
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Advances in the Etiology, Pathogenesis and Pathology of Vasculitis

Edited by Dr. Luis M Amezcua-Guerra

ISBN 978-953-307-651-5

Hard cover, 438 pages

Publisher InTech

Published online 17, October, 2011

Published in print edition October, 2011

This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of-the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Hayrullah Alp (2011). Acute Hemorrhagic Edema of Infancy, *Advances in the Etiology, Pathogenesis and Pathology of Vasculitis*, Dr. Luis M Amezcua-Guerra (Ed.), ISBN: 978-953-307-651-5, InTech, Available from: <http://www.intechopen.com/books/advances-in-the-etiology-pathogenesis-and-pathology-of-vasculitis/acute-hemorrhagic-edema-of-infancy>

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