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Case report

TWO PEDIATRIC CASES OF URTICARIA MULTIFORME

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Abstract

Urticaria multiforme is a morphological subtype of acute urticaria, often mistaken for erythema multiforme, serum sickness, or cutaneous vasculitis. Synonyms include acute annular urticaria, acute urticarial hypersensitivity syndrome, echymotic urticaria, and urticaria hemorrhagica. Diagnostic criteria are typical annular and polycyclic urticaria, echymotic changes, pruritus, acral edema, and absence of target lesions, necrosis, or bullous changes. Echymotic changes last 24-48 hours, with rapid response to antihistamines and corticosteroids. It typically affects children aged 4 months to 4 years. We describe two pediatric cases with typical clinical and laboratory features of urticaria multiforme.

A 3-year-old boy was admitted with migratory, erythematous, pruritic wheals that appeared on the fourth day of fever, following antipyretic treatment. No prior medical history or recent vaccinations. By day 2, peripheral edema and diffuse erythema developed. Between days 3-5, polycyclic, ecchymotic wheals appeared along with new itchy lesions. An otherwise healthy 11-month-old girl was hospitalized with erythematous, pruritic wheals and annular, urticaroid, erythema multiforme-like lesions. Symptoms began on day 2 after a 7-day course of antibiotics for an upper respiratory infection. No prior medical history, allergies, or recent vaccinations. After corticosteroid and antihistamine treatment, the lesions resolved completely by over the course of one week in both cases.

Urticaria multiforme (UM) was first described in 1997 and named in 2007 by Shah et al. as a subtype of urticarial. Lesions appear as small urticarial patches that merge into polycyclic plaques with echymotic centers, lasting less than 24 hours. Pruritus and facial/acral edema are common. UM typically resolves in 6-10 days without residual pigmentation. Treatment is symptomatic, with antihistamines as first-line, and corticosteroids for severe cases.

Keywords: Urticaria multiforme, Acral edema, Ecchymotic hue, Prurit, Corticosteroid, Antihistamine.

Introduction

Urticaria multiforme is a morphological subtype of acute urticaria and is often misdiagnosed as erythema multiforme, serum sickness, and cutaneous vasculitis[1,2]. Synonyms that may be encountered in the literature include acute annular urticaria, acute urticarial hypersensitivity syndrome, ecchymotic urticaria, and urticaria hemorrhagica [2]. Diagnostic criteria include typical annular and polycyclic urticaria, ecchymotic changes, pruritus, acral edema, absence of true target lesions, necrosis, and bullous changes. The ecchymotic changes

persist for 24-48 hours with a rapid response to antihistamine and corticosteroid therapy [1-3]. In children, it typically occurs between the ages of four months and four years [3].

Case 1

A 3-year-old boy was admitted with migratory, well-circumscribed, erythematous, pruritic wheals (Figure 1). Symptoms appeared on the fourth day of fever and prescribed antipyretic treatment. There was no previous medical history, history of allergic reactions, or vaccination in the recent period.

On the day of hospitalization, the patient exhibited erythematous, well-circumscribed, pruritic wheals. Laboratory results showed leukocytosis (22 x 10^9/L) and lymphocytosis (0.26). On the second day, peripheral edema and diffuse erythema further characterized the clinical picture (Figure 2). Between the 3rd and 5th days, the clinical picture included the appearance of polycyclic wheals with an ecchymotic hue and the persistence of new, itchy wheals (Figure 3). Management with corticosteroids and antihistamines resulted in complete regression of the lesions by the seventh day in this case.

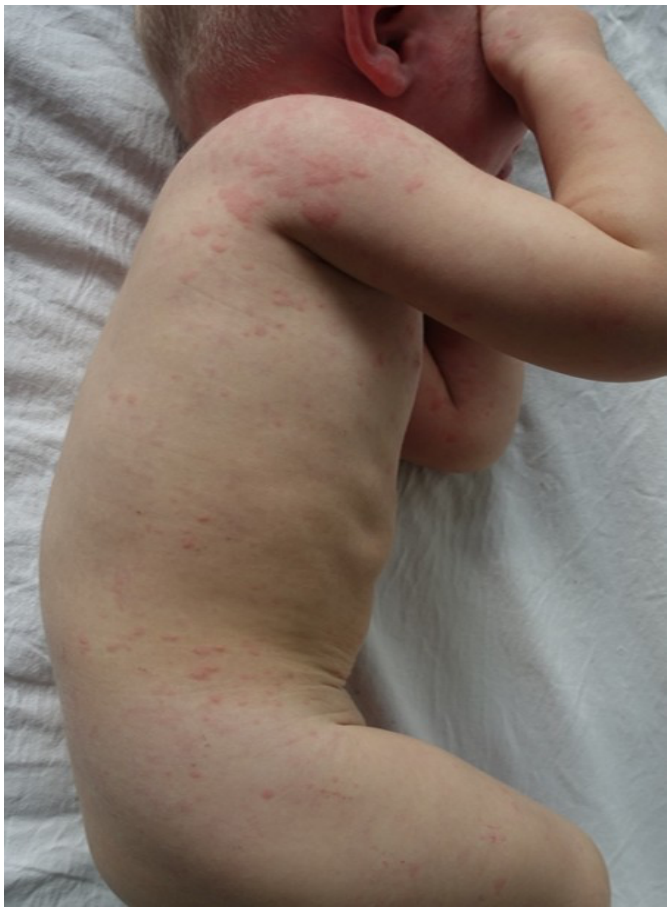

Fig. 1 Migratory, well-circumscribed, erythematous, pruritic wheals

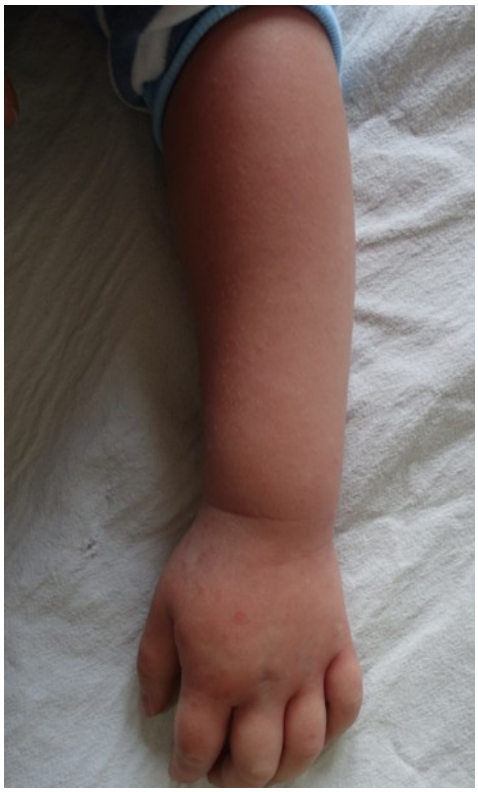

Fig. 2 Peripheral edema, diffuse erythema.

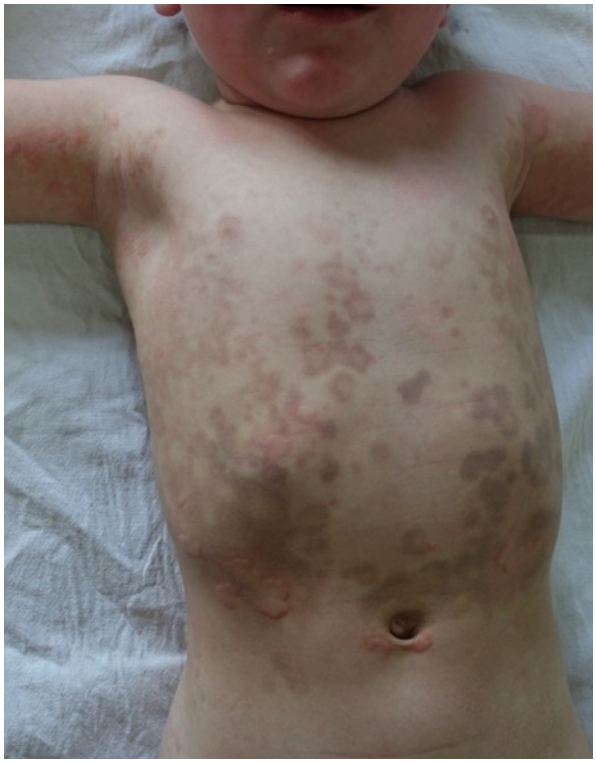

Fig 3. Polycyclic wheals, ecchymotic hue

Case 2

An otherwise healthy 11-month-old girl was hospitalized with erythematous, well-circumscribed, pruritic wheals on the face and body, along with the appearance of annular, erythema multiforme-like lesions (Figure 4). Symptoms appeared on the second day after a 7-day course of antibiotic treatment for an upper respiratory infection. There was no prior medical history, no record of allergic reactions, and no recent vaccinations.

The following day, upon hospitalization, the clinical picture revealed the appearance of more urticarial lesions with areas of confluence. Laboratory tests showed leukocytosis and high CRP levels, with other results within reference ranges. After initiating treatment with corticosteroids, antibiotics, and antihistamines, the patient experienced a complete resolution of the lesions by the seventh day, demonstrating the effectiveness of this therapeutic approach in managing the condition.

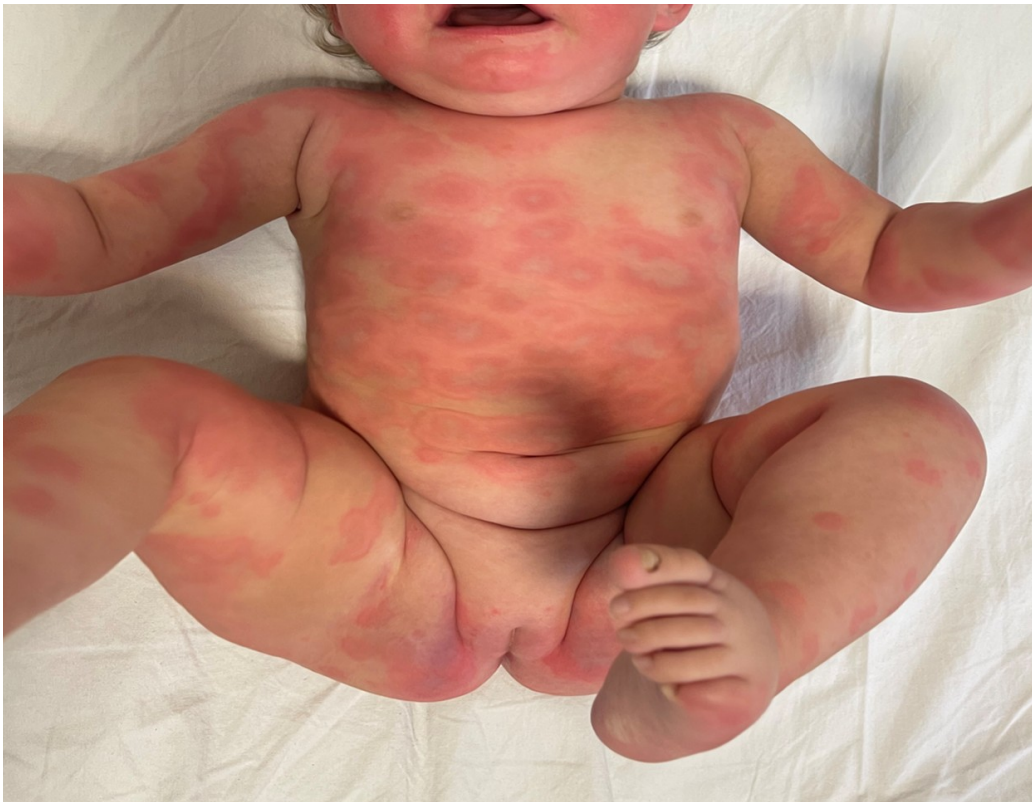

Fig. 4 Migratory, well-circumscribed, erythematous with ecchymotic hue, pruritic wheals

Discussion

Urticaria multiforme (UM) was first described in 1997 by Tamayo-Sánchez *et al.* Ten years later, in 2007, Shah *et al.* reported a new series of 19 cases and proposed the term "urticaria multiforme" due to its similarity to erythema multiforme. Unlike Tamayo-Sánchez *et al*., Shah *et al*. considered the disorder a subtype of urticaria, as they discovered that patients had dermographism and pruritus, while Tamayo-Sánchez *et al*. were unsure whether pruritus was present, as they did not find excoriations in any of their patients [1,2].

UM typically affects infants and very young children and tends to be associated with fever and good general health. Rare cases have been described in adolescents and adults [4]. The typical lesions initially appear as small urticarial lesions that spread outward and merge into large arciform plaques with polycyclic borders and an ecchymotic center. Individual lesions last less than 24 hours, can affect any body part and are associated with face, hands, and feet edema. Facial and/or acral edema is commonly observed in UM, with a reported prevalence of 60% to 89% [5,6]. Pruritus, a nearly universal finding associated with urticaria, has been noted in up to 94% of cases [2]. Skin necrosis and blistering, as well as mucous membrane involvement, arthralgias, and/or arthritis, are absent in UM. Pruritus frequently accompanies UM, but not erythema multiforme and urticarial vasculitis, where pain and burning are more commonly reported. While the lesions associated with erythema multiforme, serum-sickness-like reactions, or urticarial vasculitis last days to weeks, the skin changes of UM are transient and last less than 24 hours, similar to acute urticaria or juvenile idiopathic arthritis (Still's disease). Dermatographism commonly makes up part of the clinical picture in urticaria multiforme and urticaria, but it is classically absent in patients with erythema multiforme or serum-sickness-like reactions. Lesions characteristic of urticarial vasculitis and erythema multiforme can manifest with dusky, purpuric centers, while these skin lesions usually resolve with postinflammatory dyspigmentation, which is not seen in urticarial multiforme [7].

Many children have a history of viral infection or recent use of systemic medication, often antibiotics or antipyretics [8]. Lesions spontaneously resolve within 6 to 10 days without leaving residual pigmentation. The differential diagnosis of UM includes other annular lesions such as acute urticaria (which is usually associated with intense pruritus but not fever and lacks a central ecchymotic coloration), erythema multiforme, and urticarial vasculitis (where individual lesions typically persist for several days and leave residual lesions) [9.10]. Facial and acral edema can be differentiated from serum sickness-like reactions, which are drug-induced and typically (but not exclusively) associated with administering cefaclor and vaccines. Unlike UM, however, the lesions in serum sickness do not fluctuate daily and tend to be associated with general malaise, arthralgia, and enlarged lymph nodes. It is also important to distinguish UM from acute hemorrhagic edema of infancy, which occurs in children younger than 24 months, is associated with low-grade fever, and has minimal impact on general health. Unlike UM, acute hemorrhagic edema in infants presents as purpuric plaques that spread outward, forming ring-like, targetoid lesions, sometimes with necrotic or bullous centers, lasting several days and leaving residual pigmentation [9].

UM is frequently misdiagnosed as either erythema multiforme (EM) or a serum-sickness-like reaction due to the similarities in their clinical presentations. Both conditions can feature polycyclic urticarial eruptions and may involve angioedema, making differentiation challenging. However, key differences in lesion morphology, triggers, and the absence of systemic involvement in UM help distinguish it from these other conditions. Proper diagnosis is crucial to ensure appropriate management and avoid unnecessary testing or treatments [2].

An important distinguishing factor between urticaria multiforme (UM) and conditions like erythema multiforme (EM) or serum-sickness-like reactions is the transient nature of UM lesions. UM lesions typically last only minutes to hours, whereas the lesions in EM and serum-sickness-like reactions persist for days to weeks.

Another distinguishing feature is the presence of dermatographism in UM, a transient wheal-and-flare reaction that can be induced by scratching or rubbing the skin. This mast cell-mediated hypersensitivity response to pressure is commonly seen in children with UM but not in EM or serum-sickness-like reactions.

Additionally, infants and children with UM often exhibit angioedema in the face, hands, and feet, a feature not typically found in either EM or serum-sickness-like reactions. These differences in lesion duration, dermatographism, and associated angioedema are important clues for making the correct diagnosis.

EM is a cutaneous hypersensitivity reaction, typically presenting as "target" lesions with a central dusky area of epidermal necrosis, which can progress into blisters. These are surrounded by an inner ring of pale edema and an outer ring of erythema, resembling a "bull's eye." While urticaria multiforme (UM) does not exhibit true target lesions, its lesions may occasionally appear dusky or ecchymotic in the center without progressing to necrosis, blistering, or crusting. These ecchymotic changes resolve rapidly, usually within 24 hours. Unlike EM, herpes simplex virus is not a recognized trigger for UM [2].

Herpes simplex virus is the most common cause of EM, but other systemic infections, such as *Mycoplasma pneumoniae*, and medications, such as antibiotics, can also trigger it. In contrast, UM is not associated with these pathogens. Both conditions are self-limiting and typically require only symptomatic treatment.

UM may sometimes be confused with a serum-sickness-like reaction in children presenting with fever due to similar symptoms, such as polycyclic urticarial eruptions and angioedema. However, serum sickness is a systemic type III hypersensitivity reaction mediated by immune complexes. Serum sickness is a rare type III hypersensitivity reaction that typically occurs 1 to 3 weeks after administering animal serum or foreign proteins. It is dose-dependent and can resolve spontaneously within days to weeks without permanent sequelae. The

characteristic cutaneous features of serum sickness include fixed, polycyclic urticarial lesions, angioedema, and a serpiginous purpuric eruption, often appearing on the lateral borders of the hands and feet. Systemic symptoms may include vasculitis, nephritis (with hematuria and albuminuria), arthralgias, arthritis, myalgias, and lymphadenopathy. True serum sickness is uncommon in children today, primarily due to the infrequent administration of animal serum or protein-containing medications [2].

Serum-sickness-like reactions, however, are more common and are typically associated with fever, arthralgias, lymphadenopathy, urticaria, and angioedema. Unlike serum sickness, these reactions do not involve immunocomplex formation or systemic issues such as nephritis or vasculitis. Serum-sickness-like reactions in children are frequently linked to medications such as cefaclor, bupropion, griseofulvin, minocycline, amoxicillin, and others. Post-licensure reports have also associated these reactions with the heptavalent conjugate pneumococcal vaccine [2].

The diagnosis of urticaria multiforme can be made on history and physical examination grounds. Thus, detailed laboratory testing and/or skin biopsy are not routinely required in affected patients. While an elevation in acute phase reactants (ESR and/or CRP) may be seen in some patients, a completely normal CBC, ESR, blood and lesional bacterial cultures, stool sample, ASLO, and throat swabs may be found positive in many cases. Although unnecessary in the medical workup for a patient with urticaria multiforme, skin biopsies reported in the literature are indistinct from other subtypes of acute urticaria, which demonstrate dermal edema with a perivascular lymphocytic infiltrate with few intermingled eosinophils [7]. The histopathological spectrum of urticarial vasculitis ranges from minimal vascular damage associated with swollen endothelial cells and a sparse infiltrate of neutrophils, eosinophils, and lymphocytes to severe leukocytoclastic vasculitis. Nuclear debris or fibrinoid alteration of the microvasculature with or without extravasation of erythrocytes are the minimal essential criteria for a histopathological diagnosis of urticarial vasculitis. EM is characterized by distinct histopathology. Exocytosis and spongiosis are apparent in conjunction with varying degrees of epidermal necrosis. Necrotic keratinocytes are generally present at all epidermal levels with an edematous papillary dermis and dilated capillaries [7].

The treatment of urticaria multiforme is symptomatic, as the condition is self-limiting, with a duration of up to two weeks, as observed in our patients. All suspected causative medications should be discontinued. Most patients require systemic therapy with an H1 antihistamine, such as cetirizine, diphenhydramine, or hydroxyzine, with or without an H2 antihistamine, such as ranitidine, to achieve optimal symptomatic relief [2,11]. Combined therapy with oral antihistamines is effective in most cases, with symptoms resolving in most patients within 24 to 48 hours. Treatment with systemic corticosteroids should be reserved for the most severe cases that are resistant to combined antihistamine therapy. Local therapy with antipruritic agents, such as topical corticosteroids, calamine, pramoxine, or menthol, can also be used. Extensive laboratory evaluations for infectious etiology are not recommended, as these tests rarely provide clinically important information [2].

Since UM has a benign course but can have an alarming appearance, it may lead to a misdiagnosis and unnecessary diagnostic tests. While a broad range of differential diagnoses should be considered when evaluating any rash in the pediatric population, it is important for physicians to recognize the clinical picture of UM from its clinical mimics to optimize patient care. By conducting a thorough history and physical examination, the correct diagnosis can be made, and appropriate, effective treatment and management can be provided, avoiding unnecessary biopsies and laboratory evaluations.

Conflict of interest statement. None declared.

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