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Urticaria multiforme in a 3-year-old child and review of the literature.

Abelha L., Sousa Fernandes S., Bonifazi E.*, Costa Azevedo A.
Pediatrics Department, Alto Minho Local Health Unit, Viana do Castelo, Portugal
*Pediatric Dermatology, University of Bari, Bari, Italy

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Summary Urticaria multiforme is a variant of parainfectious urticaria characterized by annular aspects, ecchymotic sequelae, acral edema without pitting. These aspects may give rise to some problems of differential diagnosis with other conditions, especially erythema multiforme and neonatal hemorrhagic edema. In literature it is most often described with the questionable name of urticaria multiforme, but also with other terms such as annular, giant, ecchymotic urticaria that emphasize its different morphological aspects. A clinical case in a 3-year-old child was described and a complete review of the literature was performed.

Keywords Urticaria, erythema multiforme, infections, child.

Acute urticaria, which is characterized by one or more erythematous-whealing lesions that occur daily for less than six weeks, is a frequent and easily diagnosed condition, especially when the lesions are not very numerous, so that their ephemeral nature and their regression without sequelae can be easily appreciated. In infants, acute urticaria is often parainfectious, due to the greater frequency of infections in this period of life. Another characteristic of acute urticaria in infants is its scarce or absent subjective symptoms. It should also be remembered that at this age of life, vasodilation linked to urticaria can often be associated with extravasation of red blood cells, as well as plasma, so that after the regression of the wheals over hours, superficial ecchymoses that reproduce their shape may persist (1).

The name urticaria multiforme* is usually reserved for acute, febrile conditions of acute urticaria, characterized by rapidly extending centrifugal pomphoid lesions, with a clear or ecchymotic center and acral edema of the distal extremities and face.

Although the clinical manifestations of urticaria multiforme are impressive, its prognosis is benign with spontaneous resolution in a few days, usually without recurrences. A case is described in a three-year-old child and a complete review of the literature is made.

*The English term urticaria multiforme recalls the similarity of this form with erythema multiforme, but it does not seem really correct because the Latin adjective multiforme is of neuter gender and it is rightly agreed with erythema. If agreed with urticaria, which is of feminine gender, it should be multiformis. However, the term urticaria multiformis already exists in literature and is attributed to a syndrome characterized by papulopomphoid and bullous lesions caused by sandfly bites (Burns DA. Diseases Caused by Arthropods and Other Noxious Animals in Rook's Textbook of Dermatology 7th ed. Burns T, Breathnach S, Cox N, Griffiths C eds. 33.7).

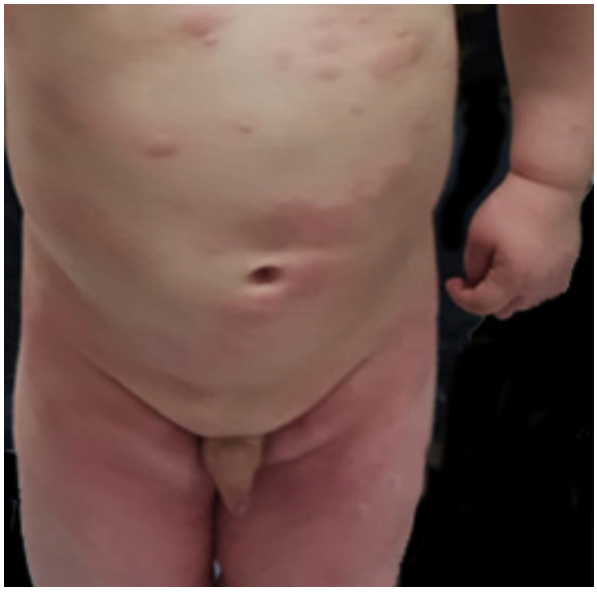

Fig. 1

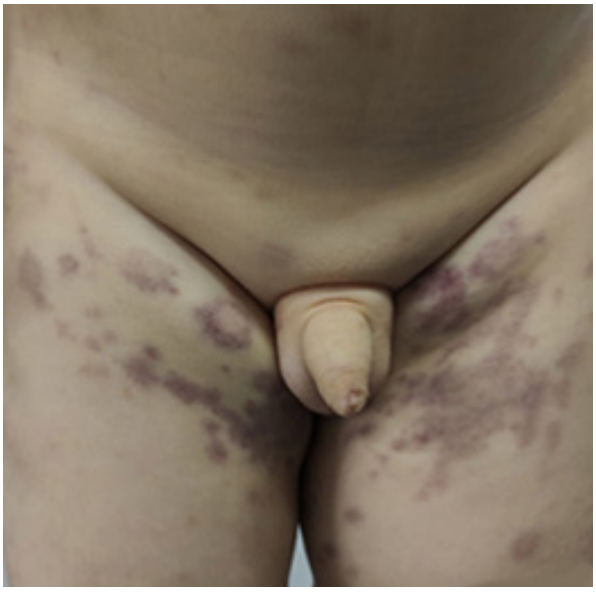

Fig. 2

Fig. 1, 2: Urticaria multiforme: erythema and wheals prevalent on the trunk and thighs (Fig. 1). In Fig. 2 ecchymotic outcomes in the same locations in the child of Fig. 1.

Methods

The review was performed after typing in PubMed and Google the keywords "urticaria multiforme", "annular urticaria", "giant urticaria". We identified 25 works, of which 1 with 34 cases (2), one with 20 (3), one with 18 (4), 1 with 5 (5) and one with 2 cases (6); the other 20 papers (7-31) instead referred to single cases. Of the 99 cases in total, age, sex, presence of itching, fever, annularity, acral edema, ecchymotic outcomes were recorded; inflammation indices (blood count, CRP) and histological examination were also evaluated.

Case report

A 3-year-old boy, with no relevant medical history, previous allergies, or regular use of medications, presented to the pediatric emergency department with progressive skin lesions. The rash began 2 days before the examination and was preceded by a brief episode of cough, fever, and rhinorrhea, all of which resolved spontaneously. Initially, the lesions were well-defined, confluent erythemas and wheals (Fig. 1), scattered over the entire skin area, but predominantly on the trunk and thighs. The child was evaluated by his family physician and diagnosed with parainfectious urticaria, for which he was prescribed a 5-day course of oral corticosteroids and antihistamines. The rash pattern progressively changed, and the lesions became purple and bruise-like, some petechial (Fig. 2). There was no history of topical application, sun exposure, insect bites, or contact with animals. Aside from the skin findings, the remainder of the physical examination was normal. During his stay in the emergency department, he presented with arthralgia. Laboratory evaluations, including a complete blood count, electrolyte panel, urinalysis, and coagulation tests, were all normal. A diagnosis of urticaria multiforme was made and the child was discharged with instructions for clinical follow-up. At 1-week follow-up, the skin lesions had completely regressed.

Results of the literature review

As seen in table 1, the age ranges from 40 days to 18 years with a mean of 2.3 years. For the 34 cases of Tamayo-Sanchezet al. (2) the age of the

individual cases is not specified, but the authors state that the age ranges from 4 months to 4 years. The only case in the literature older than 18 years of age, a 56-year-old woman with giant, annular, febrile urticaria with a clear, non-ecchymotic center, was not calculated in the statiscal average.

There were 53 males and 46 females.

Fever was present in 78 cases, absent in 17, unspecified in 4. In 2 cases, fever and urticaria multiforme were linked to COVID 19 infection (24, 31).

Itching was present in 56 cases, absent in 29, unspecified in 14.

Table 1: Clinical and laboratory data in 99 cases of urticarial multiforme of the literature.

Mean age	2.3 years (40 days-18 years)
Sex	53 M, 46 F
Fever	present in 78 cases
Itching	present in 56 cases
Annularity	present in 55 cases
Central ecchymotic area	present in 68 cases
Edema	present in 41 cases
Leukocytosis	present in 3 cases
C-reactive protein	increased in 4 cases
Histological exam	performed in 7 cases

The annularity of the lesions was present in 55 cases, absent in 6, unspecified in 38. A central ecchymotic area was present in 68 cases, absent in 13 cases. Shah et al. (4) stated that in some of their 18 cases a central ecchymotic area was present.

Leukocytosis was present in 3, absent in 42, unspecified in 17. Furthermore Shah et al. (4) stated that in 17/18 cases it was not always present and Kan et al. (3) stated that in their 20 cases the white blood cells were slightly increased.

C-reactive protein was increased in 4 cases, normal in 38, unspecified in 37. Kan et al. (3) stated that in their 20 cases it was negative or slightly positive.

Histological examination was performed in 7 cases and showed a dermal infiltrate containing eosinophils in all cases, lymphocytes in 3, histiocytes in 2.

Discussion

In infants, acute urticaria is more often than in adults parainfectious, febrile, slightly or not at all itchy, and its objective manifestations are often generalized, circinnate, rapidly extending in a centrifugal direction with central resolution. Sometimes in the resolution area a purplish color is evident linked to a blood suffusion. It is likely that infection and fever, which are more frequent in children, contribute to determining these characteristic objective manifestations.

Urticaria multiforme is the term coined by Shah et al. (4) to summarize the peculiarities of these cases of infant urticaria. The term urticaria multiforme emphasizes the similarity with erythema multiforme, while the terms annular, giant, ecchymotic, which are sometimes used in literature for this particular form of urticaria, emphasize other characteristics, such as the circinnate appearance, the extension and the presence of a central ecchymotic area.

The observation of the case described in the current work led us to verify the frequency of the different aspects of urticaria multiforme in the literature and their variable association.

Age is a determining factor in urticaria multiforme; in fact, of the 99 cases reviewed, only 1 (28) occurs in patients older than 18 years and the average age is 2.3 years. The incidence peak at this age is probably linked to the greater frequency of infectious episodes and vaccinations that are often found in the history of these patients.

It is also interesting to note that fever is the most frequent characteristic among those investigated, being present in 78 cases, absent in 14 and not documented in 7. It is likely that fever and the resulting vasodilation are a factor favoring blood extravasation.

The latter is present in 68 cases, in all cases of Tamayo-Sanchez et al. (2), Kahn et al. (3) and Sempau et al. (5). Shah et al. (4) say that ecchymoses are present in some cases without specifying how many. Note that ecchymoses are not present in all lesions (16). Guerrier et al. (18) show a case in which there are ecchymoses in the first eruption, which are instead absent in subsequent eruptions. Rubio-Granda et al. (23) present a case in which urticaria is associated with

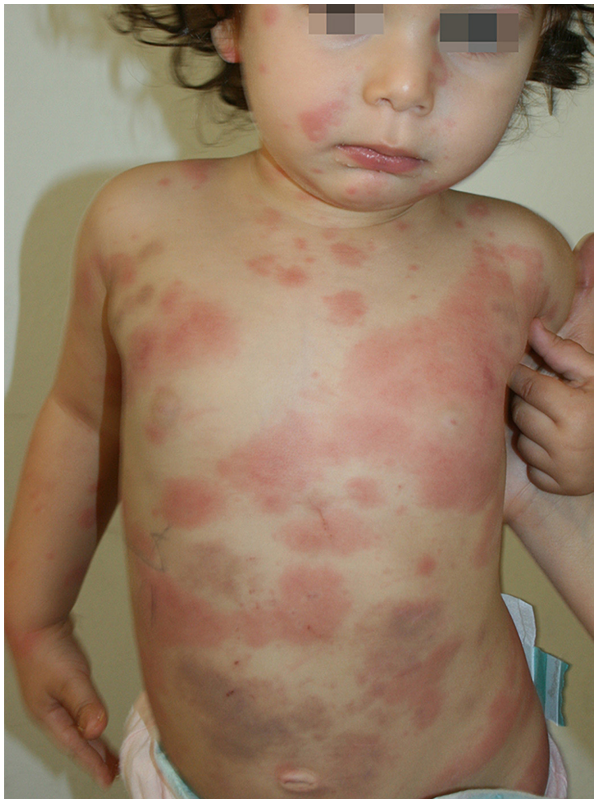

Fig. 3

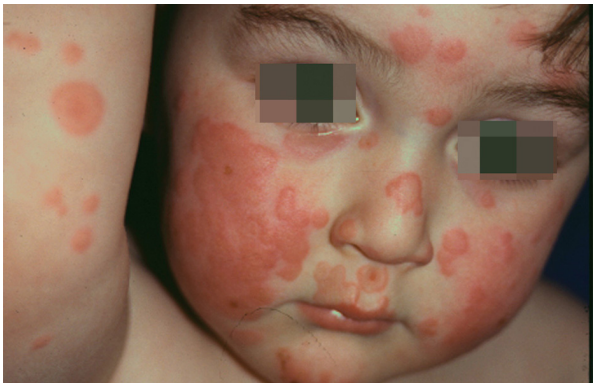

Fig. 4

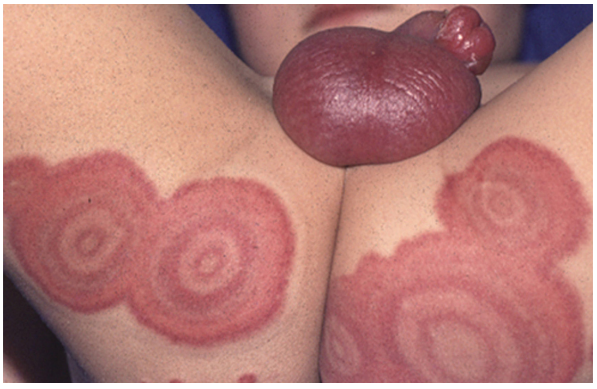

Fig. 5

Fig. 3, 4, 5: In urticaria multiforme (Fig. 3) the erythematous-pomphoid lesions are ephemeral and followed by ecchymotic sequelae. In erythema multiforme (Fig. 4) and in neonatal hemorrhagic edema (Fig. 5) the lesions remain fixed for several days.

petechiae and thrombocytopenia. Shah et al. (4) recall that the ecchymotic appearance is frequent in children in the first 3 years of life affected by acute urticaria, even non-multiforme, as supported by several authors (1, 30, 31).

While Tamayo-Sanchez et al. believe that the annularity is the most important characteristic, so much so that they speak of annular urticaria (2), Kan et al. (3) speak of urticaria multiforme but do not specify whether the lesions are annular. Shah et al. (4) focus on itching, acral edema and infectious manifestations, but do not mention annularity.

Acral edema is present in 41 cases. Shah et al. (4) find it in 13 of his 18 cases, Tamayo-Sanchez et al. (2) in 13/34 cases and Sempau et al. (5) in 5/5 cases. Kan et al. (3) do not mention the presence of acral edema in their 20 cases of urticaria.

Itching is present in 56 cases, in particular in 17 of the 18 cases of Shah et al. (4) and in 12 of the 20 cases of Kan et al. (3). Tamayo-Sanchez et al. (2) find itching in 17/34 cases or rather specify that itching is reported in 17 cases, but that in no case are there objective signs of scratching. The absence of itching even in these severe forms of urticaria multiforme should not be surprising, because it is known that urticaria in the first years of life is often not accompanied by itching (1).

Laboratory tests, when performed, do not show significant alterations, except for a slight increase in white blood cells and C-reactive protein. Histological examination is mentioned in only 7 of the 99 cases and shows a perivascular lymphocytic infiltrate in the dermis, often eosinophils, sometimes histiocytes or neutrophils. In this regard, it is strange that in none of the biopsied cases is the presence of extravasated red blood cells in the dermis highlighted, despite the presence of ecchymosis.

Parainfectious urticaria, which is more frequent in infants, often recurs. It is interesting to note that in none of the reviewed cases is the

appearance of recurrence in urticaria multiforme mentioned, not even in works with large case studies collected over very long time periods (2, 3, 4, 5). The absence of recurrences has never been emphasized in the literature.

Almost all the works that refer to urticaria multiforme talk about its differential diagnosis from other diseases, especially from erythema multiforme. The latter, in the minor variant, which most resembles urticaria multiforme (Fig. 3), has the same frequency in children, but the lesions are acrolocated (face, ears, hands, knees), symmetrical, fixed for days, and rosette-shaped (Fig. 4). Furthermore, they are often recurrent, because it often represents a reaction to the Herpes simplex virus.

Urticaria multiforme must also be differentiated from another acute condition characteristic of infants, neonatal hemorrhagic edema (Fig. 5). It is a leukocytoclastic vasculitis similar to anaphylactoid purpura that manifests with acrolocated lesions, prevalent on the face, symmetrical, erythematous-purpuric, often rosette-shaped, in any case fixed. It may be associated with intestinal vasculitis, renal vasculitis and testicular torsion; it is non-recurrent. Differential diagnosis is easier from anaphylactoid purpura, vasculitic urticaria, serum sickness and other serum sickness-like reactions, circinnate erythemas, neonatal lupus erythematosus, and Kawasaki disease.

The prognosis of urticaria multiforme, despite the apparent severity of the symptoms, is excellent. It regresses in about ten days and does not recur. Antihistamine therapy is usually sufficient.

Ultimately, urticaria multiforme is a severe form of parainfectious urticaria, in which characteristics such as fever, annularity, very extensive lesions, acral edema, ecchymotic outcomes are more accentuated and can all be present in the same case or variously associated.

Conclusion

The current work was presented to remind doctors of the existence of this rare clinically impressive disease, but with an excellent prognosis.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Address to:
Luciana Abelha, MD
Unidade Local de Saúde do Alto Minho – Serviço de Pediatria
Strada di Santa Luzia, 50
4904-858 – Viana do Castelo, Portogallo
e-mail: lucianacristinabelha@gmail.com

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