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REVIEW ARTICLE

"Urticaria Multiforme": A Case Series and Review of Acute Annular Urticarial Hypersensitivity Syndromes in Children

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ABSTRACT

Acute annular urticaria is a common and benign cutaneous hypersensitivity reaction seen in children that manifests with characteristic annular, arcuate, and polycyclic urticarial lesions in association with acral edema. It is mistaken most often for erythema multiforme and, occasionally, for a serum-sickness–like reaction. Although these 3 entities may present in a similar manner, specific clinical features help to distinguish them, and it is important for the clinician to be able to differentiate among them. We present herein a series of 18 patients who were given a diagnosis of acute annular urticaria and review the clinical distinctions between acute annular urticaria, serum-sickness–like reactions, and erythema multiforme. Because of the frequency of its clinical confusion with erythema multiforme, we propose the term "urticaria multiforme" as a more apt description to highlight the distinctive clinical features of this urticaria variant.

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ACUTE ANNULAR URTICARIA, an acute urticarial hypersensitivity syndrome, is a morphologic subtype of urticaria characterized by the acute onset of blanchable annular, arcuate, and polycyclic erythematous wheals[1] (Fig 1). Associated angioedema of the face, hands, and feet is often encountered in affected patients (Fig 2). Dermatographism, the production of transient erythema and edema ("wheal and flare") at sites of skin trauma, is common in this context and may manifest in linear or geometric patterns (Fig 3). Acute annular urticaria is reportedly more common in children 4 months to 4 years of age.[1] Systemic symptoms are usually limited to fever of short duration (1–3 days) with or without other symptoms suggestive of a concomitant illness such as diarrhea or cough, and children are nontoxic in appearance. The eruption is self-limited, and episodes usually resolve within 8 to 10 days.

Although the clinical findings in a patient with acute annular urticaria are distinctive, the condition is often misdiagnosed as erythema multiforme or, less commonly, a serum-sickness–like reaction. Confusion arises when the urticarial lesions of annular urticaria display a dusky, ecchymotic center, which can be mistaken for the target lesion of erythema multiforme, or when the presence of fever and/or edema of the hands and feet misleads the clinician to diagnose a serum-sickness–like reaction. Although the clinical distinctions between annular urticaria and erythema multiforme have been highlighted previously, confusion still exists.[2,3] To emphasize the distinctive clinical and morphologic manifestations of acute annular urticaria that can aid the clinician in differentiating acute annular urticaria from erythema multiforme, we propose the new term "urticaria multiforme." We suspect that urticaria multiforme is underrecognized as a result of the paucity of reported cases in the literature and the lack of a clear, concise summary of the clinical features that distinguish urticaria multiforme from these other clinical entities. Here we describe our experience with 18 patients who were given a diagnosis of urticaria multiforme, many of whom were referred for consultation out of concerns for erythema multiforme, and delineate the important clinical features that distinguish between these 3 conditions.

METHODS

A retrospective chart review of patients seen in consultation in both the inpatient and outpatient settings by the pediatric dermatology service at the Children's Hospital of Philadelphia over a 4½-year period from August 2001 to April 2006 was approved by the Children's Hospital of Philadelphia Institutional Review Board. Patients given a diagnosis of acute annular urticaria or urticaria multiforme were identified. Information obtained from the review of patient records included patient age and gender, antecedent symptoms including fever, documentation of recent immunizations, medication history, results of any diagnostic testing performed during the evaluation, and physical examination with a focus on the cutaneous examination and the presence or absence of angioedema and dermatographism.

Diagnostic criteria used in the diagnosis of urticaria multiforme are outlined in Table 1.

RESULTS

Eighteen patients between 10 weeks and 17 years of age were given a final diagnosis of acute annular urticaria or urticaria multiforme (Table 2). Data on the prevalence of pertinent associated symptoms are presented in Table 3. The most common initial referring diagnosis was either "rash" or "erythema multiforme." At the initial evaluation, most patients presented with 1 to 6 days of symptoms. A majority of the patients (12 of 18 [67%]) reported an antecedent upper respiratory infection, otitis media, or viral symptoms; fever was present in 8 patients (44%).

Although not performed for all patients, the results of complete blood counts were normal for all children except one who had an elevated white blood count and evidence of concomitant *Mycoplasma* infection (patient 1). The only other documented infections included 1

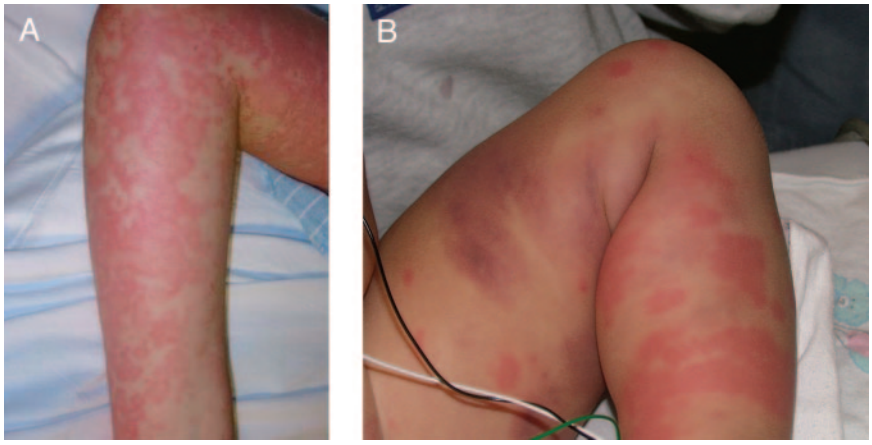

FIGURE 1
Urticaria multiforme. A, Transient polycyclic and annular wheals. B, Urticarial lesions may sometimes appear dusky, resembling erythema multiforme, but there are no true target lesions and no blistering or necrosis.

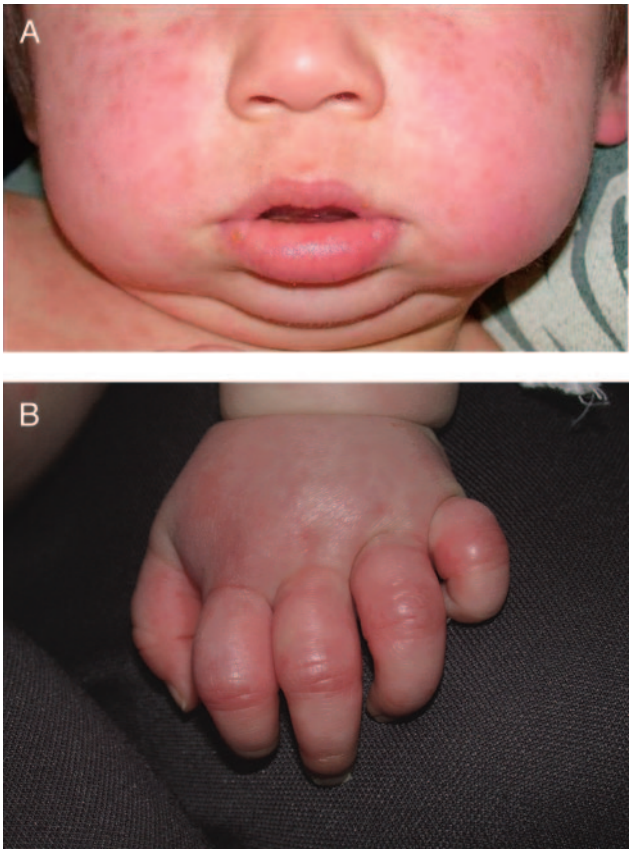

FIGURE 2
Urticaria multiforme. Acral edema of the face (A), hands (B), and feet is common.

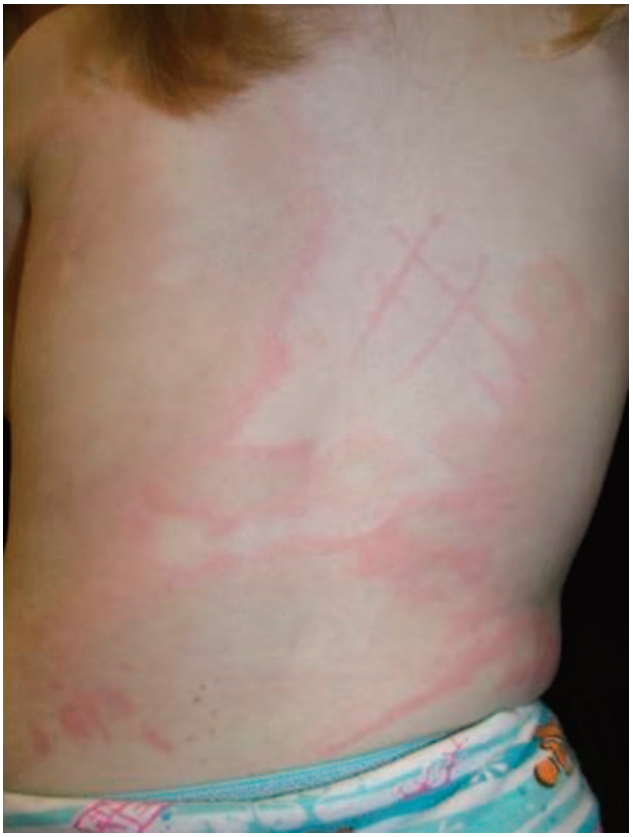

FIGURE 3
Urticaria multiforme. Dermatographism, characterized by localized erythema and edema ("wheal and flare") and occurring at sites of skin trauma such as that induced by scratching, is common.

patient with streptococcal pharyngitis (patient 15) and 1 patient with adenovirus gastroenteritis (patient 3). Other laboratory evaluations, including Lyme serologies, Epstein-Barr virus serologies, erythrocyte sedimentation rate, and blood cultures, were obtained in selected patients, and their results were negative. Two patients (11%) had received routine childhood vaccinations before the onset of symptoms (Varivax in patient 11 and unspecified routine immunizations in patient 17). Synagis had been administered to 1 patient (patient 4) 36 hours before the onset of symptoms. Concurrent or recent antibiotic use was documented in 8 (44%) of 18 patients.

Typical features of urticaria and angioedema were observed in a majority of the patients. Pruritus was nearly universal and was reported in 17 (94%) of 18 patients. Hand and/or foot edema was seen in 11 (61%) of 18, and facial edema was seen in 11 (61%) of 18 patients; overall, either hand and/or foot edema or facial edema was reported in 13 patients (72%). Although not evaluated in all patients, dermatographism could be demonstrated in 8 patients (44%). None of the patients manifested true target lesions, skin necrosis or blistering, mucous membrane involvement, arthralgias, or arthritis.

The majority of patients with urticaria multiforme required combinations of systemic antihistamines, usually a combination of cetirizine, diphenhydramine, or hydroxyzine with or without ranitidine, to achieve satisfactory symptomatic relief. Three patients had been

TABLE 1 **Diagnostic Criteria for Urticaria Multiforme**

Typical annular and polycyclic morphology and configuration to urticarial lesions
Transient, ecchymotic skin changes may be present
Absence of true target lesions and/or skin necrosis or blistering
Absence of mucous membrane involvement with blisters or erosions
Duration of individual lesions of <24 h
Dermatographism
Angioedema but not arthralgias or arthritis
Angioedema typically involves the hands and/or feet but may also involve the periocular or oral mucosa; children with significant edema of the feet may find walking difficult, which should not be confused with arthritis or arthralgias
Favorable response to antihistamines
May require combination therapy with a long-acting antihistamine such as cetirizine in conjunction with a short-acting agent such as diphenhydramine or cetirizine in conjunction with ranitidine
Modest but not-significant elevations in acute-phase reactants may be present
White blood cell count, erythrocyte sedimentation rate, or C-reactive protein level may be mildly elevated but does not demonstrate the elevations typically seen in patients with rheumatologic disorders, serious systemic infections, or Kawasaki disease

TABLE 2 **Urticaria Multiforme: Patient Characteristics**

Patient No.	Age	Gender	Antecedent Symptoms	Antecedent Infection	Antecedent Medication Use	Fever	Facial and/or Acral Edema
1	17 y	Male	OM, bronchitis	Mycoplasma	Amoxicillin		+
2	13 mo	Female	Rhinorrhea	—	Nitrofurantoin (prophylaxis)	+	+
3	2 y	Male	—	Adenovirus (stool)	—	+	
4	11 wk	Male	—	—	Palivizumab (Synagis)	+	
5	9 mo	Female	OM	—	Augmentin	+	+
6	3 y	Male	Viral syndrome	—	—		+
7	15 mo	Male	OM, URI	—	Mesalamine, 6-mercaptopurine, omeprazole		+
8	2 y	Male	OM	—	Amoxicillin	+	+
9	15 mo	Male	—	—	—		
10	7 y	Female	URI	—	Topiramate, cefprozil		
11	12 mo	Female	—	—	Amoxicillin, immunizations (Varivax)	+	
12	10 wk	Male	—	—	—		+
13	2 y	Female	—	—	—		+
14	13 mo	Male	URI, diarrhea	—	—		+
15	8 y	Male	Pharyngitis	Streptococcal pharyngitis	Amoxicillin	+	+
16	17 mo	Male	URI	—	Albuterol		+
17	8 mo	Female	URI, OM	—	Amoxicillin, immunizations (unknown)	+	+
18	18 mo	Male	URI	—	—		+

OM indicates otitis media; URI, upper respiratory infection; —, none.

TABLE 3 **Prevalence of Clinical Features Associated With Urticaria Multiforme**

Symptom	Prevalence, *n/N* (%)
Pruritis	17/18 (94)
Angioedema	
Hands, feet	11/18 (61)
Face	11/18 (61)
Angioedema of hands and feet or face	13/18 (72)
Dermatographism	8/18 (44)
Fever	8/18 (44)
Symptoms suggestive of recent viral or bacterial illness	12/18 (67)
Recent antibiotic use	8/18 (44)
Recent immunizations	2/18 (11)

started on systemic glucocorticoids by their primary care provider before their evaluation by the dermatology service. Systemic glucocorticoids were promptly discontinued in 2 patients. In 1 patient with a history of previous allergic hypersensitivity reactions that required systemic glucocorticoids, corticosteroids were tapered slowly over 1 week. Patient 6 had been admitted with a presumptive diagnosis of Kawasaki disease because of fever, rash, and peripheral edema and had received several doses of aspirin. We were consulted before initiation of intravenous immunoglobulin, because each dose of aspirin was accompanied by an exacerbation of the "polymorphous rash" in association with features of facial and peripheral angioedema. Aspirin is a known histamine-releasing agent and can exacerbate urticaria. Discontinuation of aspirin and administration of combination antihistamine therapy resulted in prompt resolution of the child's clinical findings. Additional evaluation did not support a diagnosis of Kawasaki disease, and the child did not receive intravenous immunoglobulin. In all patients for whom follow-up was obtained, symptoms and signs remitted within 2 to 12 days.

DISCUSSION

Urticaria multiforme, also known as acute annular urticaria or acute urticarial hypersensitivity syndrome, represents an allergic hypersensitivity reaction mediated predominantly by histamine and characterized by transient cutaneous erythema and dermal edema. It may be immunoglobulin E dependent or independent.

Urticaria multiforme is a distinctive morphologic form of urticaria that is often misdiagnosed as erythema multiforme or a serum-sickness–like reaction. Urticaria multiforme is a common presentation of urticaria in infants and children. Most patients in our series who were diagnosed with urticaria multiforme were infants or preschool-aged children between 2 months and 3 years of age (15 of 18 patients [83%]), with the youngest patient presenting at 10 weeks of age and the oldest at 17 years of age.

The diagnosis is typically made on clinical grounds and should not require skin biopsy. The individual lesions of urticaria multiforme, like typical lesions of urticaria, are evanescent, initially appearing as small urticarial macules, papules, or plaques, but they expand rapidly to form annular, arcuate, and polycyclic wheals that subsequently fade within hours. Centrally, lesions may display either central clearing or a dusky, ecchymotic, hemorrhagic hue, which has been reported to occur more commonly in infants with acute urticaria (up to 49% of infants aged 1–36 months).[4–6] This dusky hemorrhagic hue resembles ecchymosis or purpura but

TABLE 4 Distinguishing Features of Urticaria Multiforme, Erythema Multiforme, and Serum-Sickness–Like Reactions

Feature	Urticaria Multiforme	Erythema Multiforme	Serum-sickness–Like Reactions
Appearance of individual lesions	Annular and polycyclic wheals with central clearing or ecchymotic centers	Classis target lesion with annular lesions with purpuric or dusky, violaceous center (may blister), middle ring of pallor and edema, outer ring of erythema or blisters	Polycyclic urticarial wheals with central clearing; may appear purpuric
Location	Trunk, extremities, face	Involvement of palms, soles common	Trunk, extremities, face, lateral borders of hands and feet
Duration of individual lesions	<24 h	Days to weeks	Days to weeks
Fixed lesions	No	Yes	Yes
Total duration of rash	2–12 d	2–3 wk	1–6 wk
Mucous membrane involvement	Oral edema common, no erosions or blisters	May see oral erosions or blisters of lips, buccal mucosa, and tongue; rarely involves conjunctivae, nasal, or urogenital mucosa; usually involving only a single site	Oral edema common, no erosions or blisters
Facial or acral edema	Common	Rare	Common
Dermatographism	Yes	No	No
Fever	Occasionally, low-grade	Occasionally, low-grade	Prominent, high-grade
Associated symptoms	Pruritus	Mild pruritis or burning	Myalgias, arthralgias, lymphadenopathy
Common triggers	Antibiotics, immunizations, viral illness	Herpes simplex virus, other viral illness	Antibiotics
Treatment	Discontinue any new or unnecessary antibiotics or medications; combinations of H1 and H2 antihistamines may be helpful; systemic steroids can be helpful in more recalcitrant cases	Supportive care; early institution of systemic steroids can sometimes be helpful	Discontinue any new antibiotics or medications; H1 and H2 antihistamines; supportive care; consider systemic corticosteroids

FIGURE 4
Erythema multiforme. Classic acral bull's-eye target lesions with central necrosis are shown.

rapidly resolves with antihistamine or systemic corticosteroid therapy. Associated angioedema of the face, hands, and feet represents subcutaneous vascular leak with resultant dermal edema and has been reported to occur in 37% to 60% of patients with acute urticaria. This angioedema is self-limiting and has not been associated with laryngoedema.[4–6] In our series, the presence of facial and/or acral edema was common and was documented in more than two thirds (72%) of the patients. Pruritus is also commonly seen in urticaria, with a reported prevalence of 60% to 89%, although excoriations are uncommon.[4,5] Pruritus was an almost universal finding associated with urticaria multiforme that was seen in 94% of the patients in this study. Fever was much less common and was seen in only 44% of the patients in this study.

Many children with urticaria have a history of an antecedent viral or bacterial infection or recent use of a systemic medication, often an antibiotic. However, exhaustive diagnostic evaluations for an infectious etiology are generally not helpful, and focused testing based on specific symptoms is advised. In our study, a history of an antecedent upper respiratory tract infection, otitis media, or viral symptoms was reported in a majority (67%) of the patients, although in only 3 patients was an associated infection identified (adenovirus in 1 patient, group A β-hemolytic *Streptococcus* in 1 patient, and *Mycoplasma* infection in 1 patient).

Medications that have been reported in association with acute urticaria include systemic antibiotics and antipyretics. Antibiotics commonly associated with acute urticaria include amoxicillin, cephalosporins, and macrolides.[4,5] Recent or concurrent antibiotic use was documented in 44% of the patients in our study. Among antipyretics, aspirin and acetaminophen are historically those most commonly linked to urticarial reactions, with

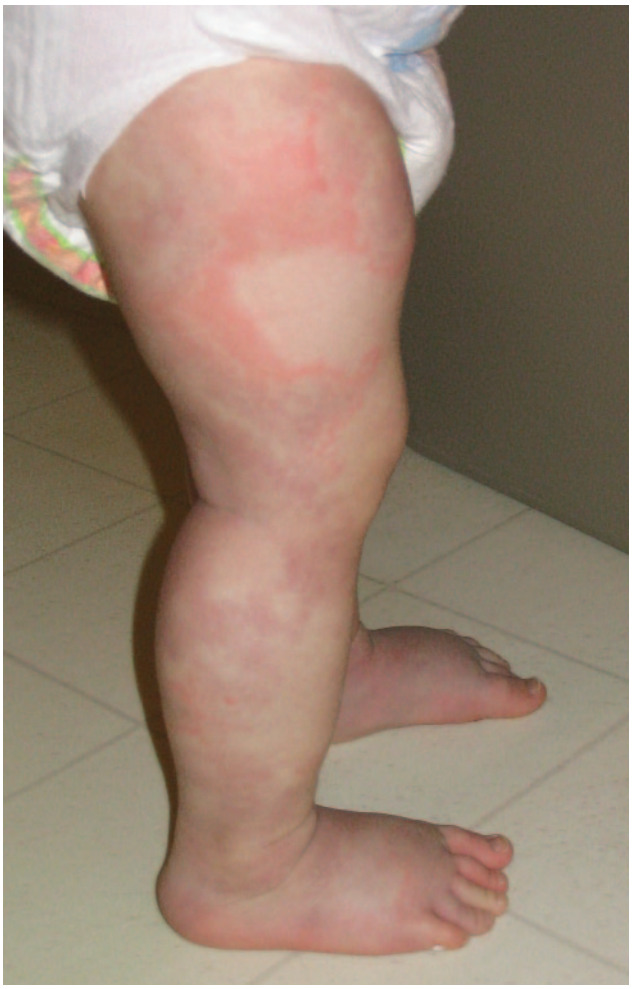

FIGURE 5
Serum-sickness–like reaction. A polycyclic urticarial eruption seen in association with acral edema and systemic symptoms, including fever and arthralgias, is shown.

only rare reports of urticaria seen in association with nonsteroidal antiinflammatory drugs such as ibuprofen.[5] Food allergy has not been reported in association with acute annular urticaria in children.[7]

Children with urticaria frequently show an incomplete response to oral antihistamines and may require combination therapy. Patients with urticaria multiforme seem to benefit from the administration of systemic antihistamines, usually both an H1 antihistamine (eg, diphenhydramine) and an H2 antihistamine (eg, ranitidine). Systemic corticosteroids are rarely required except in the most severe cases, and we tend to avoid systemic corticosteroid administration when underlying infection is suspected unless patients remain symptomatic despite combination antihistamine therapy.

Urticarial multiforme is commonly misdiagnosed as either erythema multiforme or a serum-sickness–like reaction. Important clues in the history and clinical examination that help to differentiate between these 3 entities are outlined in Table 4. An important distinction is the fleeting duration of the lesions of urticaria multiforme, which usually last minutes to hours as opposed to the fixed lesions of erythema multiforme and serum-sickness–like reactions, which typically last from days to weeks. The presence of dermatographism, a transient, induced wheal-and-flare reaction that may be elicited by rubbing or scratching of the skin and which represents a mast cell–mediated cutaneous dermal hypersensitivity reaction to pressure, is common in children with urticaria multiforme but is not usually observed in erythema multiforme or serum-sickness–like reactions. Infants and children with urticaria multiforme also commonly manifest angioedema of the face, hands, and feet, which is not a feature of either erythema multiforme or serum-sickness–like reactions.

Erythema multiforme represents a cutaneous cytotoxic hypersensitivity reaction. Classically, erythema multiforme manifests as so-called "target" lesions characterized by a central dusky zone of epidermal necrosis, which may blossom into frank blisters, surrounded by an inner ring of pale edema and an outer ring of erythema (the classic "bull's-eye" lesion) (Fig 4). Although true target lesions are not seen in urticaria multiforme, on some occasions the lesions of urticaria multiforme may appear somewhat dusky or ecchymotic in the center but do not develop frank necrosis, central or peripheral blistering, or crusting. These ecchymotic changes are evanescent and resolve within 24 hours. Herpes simplex virus is the most common etiology associated with erythema multiforme, although other systemic infections such as *Mycoplasma pneumoniae* and medications such as antibiotics have also been implicated as triggers of erythema multiforme.[8,9] Herpes simplex virus has not been identified as a causative agent in urticaria multiforme. Like urticaria multiforme, erythema multiforme is self-limiting and generally requires only symptomatic treatment.

In children with fever, urticaria multiforme may resemble a serum-sickness–like reaction. Both conditions can manifest with polycyclic urticarial eruptions and angioedema. True serum sickness is a systemic type III hypersensitivity reaction mediated by immunocomplex

TABLE 5 **Principal Differential Diagnostic Considerations for Urticaria Multiforme**

Urticaria variants
Erythema multiforme
Serum sickness and serum-sickness–like reactions
Viral exanthem
Erythema marginatum
Lupus erythematosus (neonatal, subacute cutaneous)
NOMID (neonatal multisystem inflammatory disorder)
Kawasaki disease
Urticarial vasculitis and other vasculitides
Juvenile rheumatoid arthritis
Figurate erythema (eg, erythema annulare centrifugum)
Lyme disease (secondary)

deposition and complement activation within blood vessels.[10] It classically occurs 1 to 3 weeks after administration of animal serum or foreign proteins, is dose and frequency dependent, and resolves spontaneously without permanent sequelae within days to weeks. The characteristic cutaneous findings are fixed, polycyclic urticarial lesions, angioedema, and a serpiginous purpuric eruption on the lateral borders of the hands and feet (Fig 5). Systemic manifestations include vasculitis, nephritis with hematuria and albuminuria, arthralgias and/or arthritis, myalgias, and lymphadenopathy. True serum sickness is very rare in children, because administration of animal serum or medications containing protein components occurs infrequently.

Serum-sickness–like reactions are much more common and are characterized by fever, arthralgias, lymphadenopathy, urticaria, and angioedema. Immunocomplex formation and systemic involvement such as nephritis and vasculitis do not occur. Serum-sickness–like reactions in children have been reported most commonly in association with medications such as cefaclor, but have also been linked to buproprion, griseofulvin, minocycline, amoxicillin, sulfamethoxazole-trimethoprim, penicillin, flucloxacillin, cefprozil, and carbamazepine.[11–17] There are also postlicensure reports of serum-sickness–like reactions to the heptavalent conjugate pneumococcal vaccine.[18] The treatment of serum-sickness–like reactions includes discontinuation of the offending agent, administration of systemic antihistamines, and administration of a 2- to 3-week course of systemic steroids for more severe symptomatic cases.

Clinicians who care for children should be able to recognize urticaria multiforme and differentiate this condition from erythema multiforme and serum-sickness–like reactions. A directed history and physical examination can reliably distinguish these conditions, which will help avoid unnecessary diagnostic testing and allow for appropriate treatment. Early in the course of the disease, it may be difficult to differentiate urticaria multiforme from its clinical mimics. As the course of the disease progresses, the correct diagnosis typically becomes clear. The transient nature of the urticarial lesions, the presence of dermatographism and acral angioedema in patients with urticaria multiforme, and a favorable response to combination antihistamine therapy with an H1-antihistamine and an H2-antihistamine within 24 to 48 hours will often aid in the correct diagnosis. The use of systemic corticosteroids should be reserved for more severe symptomatic cases. For children in whom an urticarial eruption persists or is associated with other systemic findings such as arthralgias, persistent fevers, or abnormalities on routine laboratory evaluation, other diseases should be considered in the differential diagnosis. Other important differential diagnostic considerations are listed in Table 5.

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The Fig 5 image is courtesy of Lisa Zaoutis, MD.

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