

INVITED ARTICLE

Urticaria mimickers in children

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ABSTRACT: Acute urticaria is a self-limited cutaneous condition marked by transient, erythematous, and pruritic wheals. It is a hypersensitivity response that is often secondary to infection, medications, or food allergies in children. In contrast, the urticarial “mimickers” described in this review article are often seen in the context of fever and extracutaneous manifestations in pediatric patients. The differential diagnosis ranges from benign and self-limited hypersensitivity responses to multisystem inflammatory diseases. Establishing the correct diagnosis of an urticarial rash in a pediatric patient is necessary to both prevent an unnecessary work up for self-limited conditions and to appropriately recognize and evaluate multisystem inflammatory disorders. Herein, we describe two cases to illustrate the clinical manifestations, laboratory findings, histopathology and differential diagnoses for several mimickers of acute urticaria including: urticaria multiforme, serum sickness like reaction, Henoch-Schönlein purpura, acute hemorrhagic edema of infancy, systemic onset juvenile idiopathic arthritis, cryopyrin associated periodic syndromes, and urticarial vasculitis.

KEYWORDS: acute hemorrhagic edema of infancy, cryopyrin-related disorders, serum-sickness-like reaction, systemic onset juvenile idiopathic arthritis, urticaria multiforme

Case 1

An 18-month-old girl presented to the dermatology clinic with 2 days of rash and subjective fevers. Nine days prior, she had presented to pediatric urgent care with fever, rhinorrhea and irritability. She was diagnosed with recurrent otitis media and prescribed a 10-day course of amoxicillin-clavulanate. Her fever improved on amoxicillin-clavulanate, but while on a camping trip with her parents, she developed an itchy rash. On examination in the dermatology clinic, she was well appearing with normal vital signs and rhinorrhea.

Skin examination revealed large erythematous, urticarial plaques with dusky to ecchymotic centers distributed on her face, ears, trunk and extremities. She had hand and foot swelling and was hesitant to walk. (FIG. 1a–c)

Based on the timing of onset of the rash 9 days after initiation of exposure to amoxicillin-clavulanate, the morphologic features of her eruption, and the presence of hand and foot swelling with pain with ambulation, she was diagnosed with serum sickness-like reaction (SSLR). Other diagnoses on the differential included urticaria multiforme, and acute hemorrhagic edema of infancy. No diagnostic tests were performed. On follow-up 1 week later, she was walking, energetic and the rash had resolved except for slight hyperpigmentation in the areas that had previously been ecchymotic.

Serum Sickness-Like Reaction (SSLR)

SSLR should be considered in the differential diagnosis of a young child with fever, acral edema,

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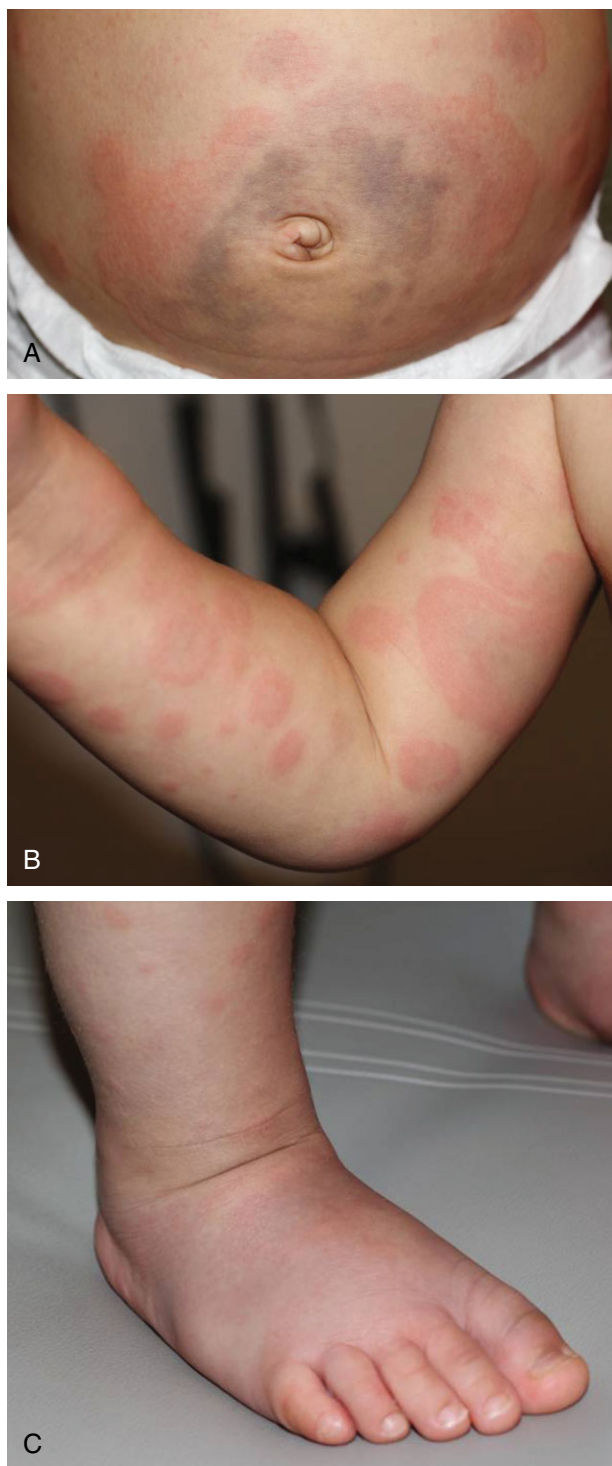


FIG. 1. Annular and polycyclic lesions with central ecchymosis on the A; abdomen and B; arm of a febrile toddler; C; foot swelling.

arthralgias, and a rash. Some authorities consider this condition to be clinically related to urticaria multiforme, which is described in detail below. Both SSLR and urticaria multiforme have similar

clinical morphologies, marked by urticarial plaques with a hemorrhagic pattern, and are self-limited conditions with favorable long-term prognoses. However, SSLR is a hypersensitivity reaction that is often secondary to a medication and may have a more severe clinical phenotype than urticaria multiforme. Additionally, the rash of SSLR tends to have a delayed onset following antigen exposure, in contrast to urticaria multiforme, which may present acutely (1,2).

SSLR is clinically similar to classic serum sickness, but pathogenically distinct and is therefore termed serum sickness “like.” Classic serum sickness is a type III hypersensitivity reaction that was first described in 1905 as a self-limited illness that developed in some patients following injection with equine diphtheria antitoxin (3). This was subsequently determined to be the result of the generation of host antibodies directed against horse serum proteins and immune complex deposition in tissues, with resultant activation of the complement system, and hypocomplementemia.

While SSLR is clinically similar to serum sickness, the pathogenesis is poorly understood. Unlike classic serum sickness, patients with SSLR do not have detectable circulating immune complexes or hypocomplementemia. One study demonstrated that cefaclor metabolites had direct toxic effects on lymphocytes derived from patients with a history of cefaclor induced SSLR, suggesting that SSLR may result from defects in the metabolism of reactive intermediates rather than the result of an immune mediated hypersensitivity reaction (4).

In contrast to urticaria multiforme, where the rash presents 1–3 days following an acute viral illness (5), SSLR presents with fever, rash and arthritis 7–21 days after antigen exposure, which is also the typical time frame in which classic serum sickness reactions present. Patients with SSLR may have more pronounced extracutaneous manifestations compared to those with urticaria multiforme, which may include: fever, malaise, lymphadenopathy, abdominal pain, nausea, vomiting, diarrhea, myalgias, headaches and a self-limited symmetric arthritis (6).

Associated triggers of SSLR include medications and infections. Cefaclor is the most commonly implicated medication resulting in SSLR. However, other β -lactam antibiotics, anti-cancer agents, anti-convulsants, antidepressants, anti-dysrhythmics, anti-hypertensives, and anti-inflammatory agents have been implicated (7). More recently, patients treated with various biologic agents including rituximab, infliximab, efalizumab, and natalizumab have been reported (8–11). Preceding

infections including streptococcal, and certain viral infections particularly those with associated circulating cryoglobulins such as hepatitis B and C are associated with the development of SSLR (6).

In an otherwise well-appearing child where there is a high suspicion for SSLR, laboratory tests and skin biopsies are not necessary. If ordered, laboratory findings include leukocytosis, as well as elevated acute phase reactants including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and proteinuria. Histopathology most commonly shows histologic features similar to urticaria including a perivascular and mid-dermal inflammatory infiltrate with admixed neutrophils, eosinophils and lymphocytes without neutrophilic debris or vascular fibrinoid necrosis, although leukocytoclastic vasculitis, has been reported (2,12,13). Treatment for SSLR usually requires only supportive measures.

Urticaria multiforme

Urticaria multiforme is in the differential diagnosis of an otherwise well-appearing patient with urticarial plaques, with an associated bruise-like or hemorrhagic pattern (FIG. 2). Urticaria multiforme was initially termed acute annular urticaria (14). The term “urticaria multiforme” was proposed in 2007 to reflect a complex cutaneous hypersensitivity reaction that is often preceded by a viral infection and has overlapping morphologic features with simple urticaria. However, in contrast to urticaria, urticaria multiforme presents as polycyclic to annular urticarial lesions with areas that are bruise-like, similar to SSLR. The dusky center within an annular, erythematous, urticarial plaque may be confused with erythema multiforme (5).

Urticaria multiforme occurs most often in children between 4 months and 4 years of age. However, children as young as 10 weeks and as old as 17 have been reported (5,14). Symptoms that precede the development of this rash include a fever of 1–3 days duration with or without other symptoms suggestive of a viral illness including cough, otitis media, rhinorrhea, and diarrhea (5,15).

Diagnostic criteria for urticaria multiforme includes: (i) annular to polycyclic urticarial lesions with transient ecchymotic skin changes, (ii) duration of individual lesions lasting less than 24 hours, (iii) angioedema or acral edema, (iv) dermatographism, (v) modest elevation of acute phase reactants, (vi) and a favorable response to antihistamines. Unlike erythema multiforme, there are no true target lesions, skin necrosis, mucous membrane involvement or blistering. While children



FIG. 2. An infant with polycyclic plaques with central duskiness of urticaria multiforme.

may have significant lower extremity edema and difficulty walking, this should not be confused with arthritis or arthralgias, which are not features of urticaria multiforme. There may be modest leukocytosis and elevation of acute phase reactants such CRP or ESR; however, elevations in these biomarkers are not typically at the level seen in patients with rheumatologic disorders, systemic infections or Kawasaki's disease.

Urticaria multiforme is a histamine-dependent allergic hypersensitivity reaction that is characterized by erythema and dermal edema. It is pathogenically similar to urticaria although morphologically distinct. For unknown reasons, the hemorrhagic morphology within urticarial lesions is commonly seen in children. In a prospective study identifying features of urticaria in children between 1 and 36 months of age, the characteristic hemorrhagic pattern now recognized as urticaria multiforme approached 50% (15). Angioedema, which is a coexistent clinical feature of urticaria multiforme, was present in 60% of all cases.

Strikingly, the vast majority of cases of acute urticaria in this setting were preceded by a respiratory or gastrointestinal viral infection including adenovirus, respiratory syncytial virus, rotavirus and enterovirus isolated from nasal or stool viral cultures. Less commonly, a preceding bacterial or parasitic infection from *Escherichia coli* and *Giardia lamblia* were also observed. Food and drug hypersensitivity, however, was uncommon (15). These observations suggest that urticaria multiforme is a cutaneous hypersensitivity reaction to microbial antigens with distinct morphology and exclusively seen in infants and children.

Patients with urticaria multiforme are often well appearing and respond favorably to combination antihistamines and antipyretics as needed (5). A practical approach to antihistamines in this condition includes a non-sedating antihistamine such as loratadine or cetirizine in the morning and a sedating antihistamine such as diphenhydramine or hydroxyzine at bedtime. Treatment is often used for several days to weeks until symptoms resolve.

Acute hemorrhagic edema of infancy and Henoch-Schönlein purpura (HSP)

Acute hemorrhagic edema of infancy (AHEI), also known as Finkelstein's or Seidlamayer's disease, is a cutaneous small vessel leukocytoclastic vasculitis that typically affects infants between 6 and 24 months of age, although it has been reported in children as young 2 months and as old as 60 months. There is often a history of a preceding or concurrent upper respiratory or diarrheal illness. Additionally, AHEI has been reported to develop within 2 weeks of administration of vaccines including diphtheria, pertussis and tetanus, with or without poliomyelitis; measles, mumps and rubella with or without varicella; and Haemophilus influenzae type B, measles, tuberculosis and smallpox (16).

The typical presentation for AHEI is that of a well-appearing child under 24 months who develops asymptomatic round, red to purpuric plaques predominately over the cheeks, ears and extremities. These develop within a 24–48-hour period and expand giving them a target-like or cockade appearance with a darker, occasionally necrotic or bullous center (FIG. 3). There is a male predilection occurring with male to female ratio of almost 2:1. In addition to the characteristic cutaneous findings, there may be facial and distal extremity edema. Fever is typically low grade, extracutaneous manifestations are uncommon, and resolution of



FIG. 3. Fixed, targetoid, urticarial plaques with central purpura and necrosis on an infant with acute hemorrhagic edema of infancy.

the dermatosis occurs over a few days to several weeks (17).

While urticarial lesions are typically not seen in AHEI, this condition should be considered in the differential diagnosis for infants with a low-grade fever and purpura with distinct targetoid or cockade appearance. Patients with AHEI are often strikingly well appearing, which may seem out of proportion to the extent of their cutaneous findings. Laboratory values are often normal. There may be slight leukocytosis and thrombocytosis. However, acute phase reactants including ESR and CRP are normal or only minimally elevated. Urinalysis, renal and liver function tests are often normal (17).

AHEI is considered to be a related entity to HSP, the most common multisystem vasculitis of childhood. Clinical features of HSP include palpable, non-thrombocytopenic purpura on the lower extremities and buttock, abdominal pain, arthritis, and nephritis. Lower extremity edema occurs in approximately half of patients; however, upper extremity and scrotal edema has also been reported. Like AHEI, HSP is more common in boys than girls, with a male to female ratio of 1.8:1. However, it more commonly occurs in older children between the ages of 5 and 15 years but can occur in infants and adults as well.

Extracutaneous manifestations of HSP include arthritis, gastrointestinal (GI), and renal disease. The arthritis in HSP is usually oligoarticular, and affects the large joints of the lower extremities. GI symptoms commonly include abdominal pain, nausea and vomiting, which occurs in one half to three quarters of patients. GI bleeding is reported in approximately 20% of patients; and intussusception, while rare, is also associated with HSP. Renal disease manifests as mild proteinuria or hematuria. However, significant renal insufficiency may develop in 2–3% of patients. In contrast to the arthritis and abdominal pain, renal disease is generally detected after the purpuric phase and therefore serial evaluation of renal function following the resolution of purpura is essential. The incidence and severity of renal disease appears to increase with patient age, duration of purpura, and severity of abdominal symptoms. Laboratory findings may reveal leukocytosis, elevation of acute phase reactants and serial urinalyses with microscopy should be followed to rule out renal insufficiency. Because HSP is self-limited, treatment is not always necessary. Supportive care with non-steroidal anti-inflammatory medications, rest, and pain relief is generally appropriate. In cases with significant abdominal or joint pain, systemic corticosteroids may alleviate gastrointestinal symptoms and arthritis but may not be sufficient to halt renal insufficiency (18).

Some authorities consider AHEI to be a variant of HSP (17). While these conditions have distinct clinical morphologies, both are reactive small vessel leukocytoclastic vasculitides that is seen in children following a viral illness. The notion that both HSP and AHEI are related entities is supported by observations wherein overlapping clinical morphologies are reported in the same patient (16,19). Both conditions predominately affect males in a 2:1 ratio. Furthermore, a report of two siblings, a 16-month-old who developed AHEI and her 43-month-old sibling developed HSP which were presumably hypersensitivity reactions to the same upper respiratory viral infection suggests an age-dependent variability on the clinical presentation of a reactive leukocytoclastic vasculitis (20).

There are sufficient differences between HSP and AHEI to suggest that these are distinct entities. AHEI predominately affects infants and young children, whereas HSP is typically seen in older children and adults. Extracutaneous manifestations in AHEI are rare but may be a prominent feature of HSP leading to different potential long-term prognoses between these conditions. Finally, on direct immunofluorescence, immunoglobulin A deposi-

tion can be detected in the cutaneous vessel walls in both lesional and non-lesional skin in approximately 75% of cases of HSP, whereas this is less often seen with AHEI. These observations suggest that while AHEI and HSP may be related entities, they are clinically distinct vasculitides.

Case 2

A 9-year-old girl presented to dermatology clinic for an evaluation of urticaria since 1 week of age. The skin lesions would come and go daily, on all parts of her body. She tried topical steroids and oral antihistamines with no relief. Additional medical history included migraine headaches, sensorineural hearing loss and occasional ankle pain. Skin examination was remarkable for diffuse erythematous macules and papules ranging from 5 mm to 3 cm, with occasional annular lesions. (FIG. 4) A skin biopsy was consistent with neutrophilic urticaria.

Based on the constellation of neutrophilic urticaria since infancy, sensorineural hearing loss and headaches, a cryopyrin-related disorder was suspected. Genetic testing was positive for a mutation in cold induced auto inflammatory syndrome 1 (CIAS1). She was started on anakinra with excellent control of her inflammatory symptoms.



FIG. 4. Small urticarial papules and arcuate plaques on a child with a cryopyrin-associated disorder.

Cryopyrin-associated periodic syndromes (CAPS)

CAPS are a group of autosomal dominant inherited disorders and include familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID) which is also known as chronic infantile neurologic, cutaneous and arthritic (CINCA) syndrome (21).

Although these were initially believed to be distinct diseases, it is now recognized that all cryopyrin-associated disorders share a common genetic defect in *CIAS1*, which encodes cryopyrin. This defect results in the gain of function of cryopyrin and ultimately leads to the increased secretion of the proinflammatory cytokine interleukin (IL)-1 β . Given the common genetic defect among CAPS, current paradigm suggests that the above disorders lay in phenotypic spectrum of disease severity where FCAS is the mildest form and NOMID/CINCA is the most severe (21–23).

Presentation of CAPS often occurs in the neonatal period or early infancy although children as old as 10 years of age have been reported. Clinical manifestations of FCAS include fever, a non-pruritic urticarial rash, arthralgias and conjunctival injection following cold exposure. Cold exposure times required to promote disease activity may vary from 5 minutes to 3 hours. Less commonly symptoms including drowsiness, headache and thirst have been described. The rash of FCAS typically lasts about 12 hours but may range from 30 minutes to 72 hours and is typically associated with a burning sensation. Laboratory values after cold exposure may reveal neutrophilia as well as elevation of acute phase reactants including ESR and CRP.

In contrast to FCAS, the clinical findings of MWS do not depend on cold exposure. Patients present within the first few years of life with a fever, a non-pruritic urticarial rash, and arthralgias that may last for 1–3 days. Joint involvement may range from arthralgias to severe destructive polyarthropathy. A progressive, high frequency, sensorineural deafness due to chronic inflammation of the cochlea begins in childhood and often results in complete deafness by adolescence. Secondary amyloidosis is a prominent feature of MWS affecting 25% of patients. It initially presents as proteinuria and can result in chronic renal insufficiency. Laboratory findings may reveal a generalized leukocytosis and elevated acute phase reactants. Under conditions of progressive secondary amyloidosis, proteinuria may be noted in a urinalysis, in addition to

elevated serum creatinine and amyloid A levels (23).

Finally, the most severe form of CAPS is NOMID/CINCA. Systemic innate inflammation primarily affects the skin, eyes, joints, and central nervous system. These patients typically present within the first few weeks of life with fever, arthralgias or a destructive polyarthritis involving the knees, ankles, elbows and wrists, and a non-pruritic rash marked by pink figurate erythematous papules and plaques. Additionally, central nervous system manifestations including headache, vomiting, aseptic meningitis, spastic diplegia, seizures, impaired cognitive function and papilledema are also seen. Conjunctivitis and uveitis may also be seen as in other cryopyrin-related disorders. Like patients with MWS, these patients may also develop sensorineural deafness and secondary amyloidosis with subsequent renal impairment and peripheral neuropathy. Patients with NOMID/CINCA have elevated acute phase reactants, generalized leukocytosis with neutrophilia and pathogenic neutrophilic infiltration in affected organ systems. In the skin, this is characterized by a perivascular and perieccrine neutrophilic infiltrate (24).

The basic genetic defect in the above disorders is a missense mutation in *CIAS1* that encodes the protein cryopyrin, which is an essential scaffolding protein of the NLRP3 inflammasome and is involved in IL-1 β regulation. The gain of function mutation of *CIAS1* ultimately results in increased systemic levels of IL-1 β and dysregulated inflammation.

Treatment for CAPS is therefore targeted at IL-1 blockade. Three therapies directed against this cytokine have been developed for clinical use. These include: (i) Anakinra, an IL-1 receptor antagonist, (ii) Riloncept, a fusion protein consisting of the ligand binding domain of IL-1-receptor-1 fused to the Fc portion of IgG1, and (iii) Canakinumab, an anti-IL-1 β monoclonal antibody (25). These therapies lead to rapid resolution of clinical signs systemic inflammation in most cases (26–30).

Systemic onset juvenile idiopathic arthritis (SoJIA)

The differential diagnosis for pediatric patients with an evanescent rash and evident multisystem inflammation includes SoJIA. SoJIA has overlapping clinical features with the cryopyrin-associated periodic syndromes, which is in part due to dysregulated activation of innate immune function in both conditions.

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of inflammatory arthritides that is present in patients under 16 years old with at least a 6-week duration of arthritis of unknown cause. Well-characterized categories within the spectrum of JIA include: (i) SoJIA, (ii) Rheumatoid-factor positive polyarthritis and (iii) Spondyloarthropathies including psoriatic arthritis and enthesitis-related arthritis (31).

SoJIA constitutes 10 to 20% of all cases of JIA but causes two-thirds of the mortality associated with JIA. It may present at any age up to 16, but the peak age of presentation is 1–6 years old. It has no gender predilection unlike other forms of JIA (6,31).

SoJIA is described as an inflammatory arthritis associated with daily fevers of at least 2 weeks duration in a child younger than 16 years of age with an inflammatory arthritis that must have been present for at least 6 weeks duration. In contrast to other forms of JIA where articular features are the predominant clinical finding, the diagnosis of SoJIA requires one extra-articular feature including: hepatomegaly, splenomegaly, lymphadenopathy, serositis or a non-fixed, evanescent rash. The disease is also seen in adults where it is known as adult-onset Still's disease (32,33).

The rash of SoJIA is a non-fixed erythematous dermatosis that is pruritic, urticarial and associated with linear dermatographism. Atypical cutaneous findings including confluent and persistent lesions, splinter hemorrhages and periorbital edema have also been described. Unlike SSLR and urticaria multiforme, the bruise-like morphology is not characteristic of this condition. Both the rash and arthritis correlate with fever spikes where the rash may be barely noticeable in the morning, but becomes extensive with associated arthritis in the afternoon and evening during febrile episodes (34).

Macrophage activating syndrome (MAS) is a rare but feared complication of SoJIA. MAS is due to the excessive activation of peripheral T-cells and macrophages, resulting in overwhelming systemic inflammation marked by hepatosplenomegaly, lymphadenopathy, persistent fevers, and coagulopathy. While there is currently no clear consensus on the precise diagnostic criteria for MAS, a recent international consensus survey among 505 pediatric rheumatologists has suggested that important clinical features and biomarkers include: a falling leukocyte and platelet count, hyperferritinemia, evidence of macrophage hemophagocytosis in bone marrow, increased liver enzymes, persistent and continuous fever over 38°C, falling ESR, hypofibrinogenemia and hypertriglyceridemia (35).

SoJIA is a polygenic auto-inflammatory syndrome associated with dysregulated production of the proinflammatory cytokines: IL-1, IL-6, IL-17, and tumor necrosis alpha (31). Previous studies have suggested a significant pathogenic role for IL-6 in the disease process, which is supported by the effectiveness of treatment with tocilizumab, an anti-IL-6 receptor antibody. Additionally, the observation that IL-1 blockade being largely effective for another subset of patients with SoJIA, suggests that at least two subpopulations of patients with SoJIA exist whereby manifestations of disease are largely mediated by IL-6 or IL-1. IL-1 dysregulation is also seen in patients with cryopyrin-associated syndromes, which partially explains the overlapping clinical phenotypes among these disease entities. Patients responsive to IL-1 blockade tend to have higher peripheral neutrophil counts and fewer joints affected than those responsive to IL-6 antagonism (36–38).

Urticarial vasculitis (UV)

Urticarial lesions in a patient with systemic inflammation are also seen in patients with UV. UV is a leukocytoclastic vasculitis that may present with a constellation of symptoms including a generalized urticarial-appearing eruption, fevers and arthralgias. Other manifestations may include angioedema, abdominal or chest pain, nephritis, uveitis or obstructive lung disease. It is, however, rarely reported in children (39).

Cutaneous manifestations include wheals with a generalized distribution and may be associated with petechiae, purpura or post-inflammatory hyperpigmentation. The lesions are typically fixed for more than 24 hours, which clinically distinguishes it from urticaria, urticaria multiforme, serum sickness like reaction, and the evanescent rashes of SoJIA and cryopyrin associated disorders. The urticarial dermatosis of UV is typically described as burning or stinging and is often non-pruritic.

UV is a type III hypersensitivity reaction mediated by antigen-antibody complexes deposited on vascular endothelium resulting in inflammation and vasculitis. It may be precipitated by infections, medications or neoplasms. Post-infectious UV has been associated with Hepatitis B, Hepatitis C and Epstein Barr virus. Drug-induced UV has been reported by the use of angiotensin converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs, penicillins, sulfonamides, fluoxetine, potassium iodide, and thiazides.

Patients with UV may be hypocomplementemic or normocomplementemic. Extracutaneous manifestations may be seen in either group of patients although is more frequently encountered in patients with hypocomplementemia. Approximately 50% patients with hypocomplementemic UV will develop or have coexistent systemic lupus erythematosus (SLE).

Evaluation for patients with suspected UV includes serum complements including antibodies for C1q. Depending on the clinical context, further evaluation for connective tissue diseases including SLE may be indicated. The histologic features of UV reveal a small vessel leukocytoclastic vasculitis and direct immunofluorescence shows fibrin, complement and immunoglobulin deposition in a granular pattern perivascularly (40,41).

As noted above, UV is rare in children and management is directed toward the patient's clinical presentation and underlying disease process. For mild disease with only cutaneous involvement, non-steroidal anti-inflammatory and antihistamines may be sufficient. For a refractory disease, colchicine, dapsone or hydroxychloroquine may be options; and for patients with multisystem disease, oral corticosteroids may be indicated.

Conclusions

The diagnostic entities discussed above are important to keep in mind when evaluating a child with an urticarial eruption. The morphology and histology of the rash, inflammatory biomarkers and the extracutaneous manifestations of the disease process may distinguish those conditions that are self-limited and require supportive measures only from multisystem disease processes. Prolonged duration and severe systemic findings like arthritis, fever and neurologic symptoms are signals that the child may have a systemic inflammatory disorder such as a cryopyrin-associated disorder, SoJIA or urticarial vasculitis that requires laboratory studies, skin biopsy and systemic medication. Striking annular and polycyclic urticarial lesions with central duskeness or ecchymosis in a well-appearing child are likely signs self-limited conditions such as SSLR, urticaria multiforme or AHEI. The decision to pursue a laboratory work-up or skin biopsy in such cases depends on the general clinical appearance of the child, morphology of the rash and the severity of associated symptoms, but is not necessary in every case. Close follow-up is recommended to monitor for resolution of the eruption and other symptoms.

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