Urticarial Vasculitis in an Infant

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Urticarial vasculitis (UV), a subtype of leukocytoclastic vasculitis, is a small vessel necrotizing vasculitis characterized by urticarial lesions and decreased serum complement. Primarily a disease of adult women, this immune complex disorder is seldom reported in children. Pathologic examination of skin lesions in patients with UV reveals leukocytoclastic vasculitis. UV is a frequent finding, particularly involving early components of the classical complement cascade C1q and C2 to C4. We report a 9-month-old male infant who presented with chronic urticaria of 7 months' duration that was unresponsive to conventional therapies for urticaria. His lesions appeared as erythematous wheals followed by the development of purpuric papules and resolving with ecchymoses and postinflammatory hyperpigmentation. Laboratory studies and skin biopsy results were consistent with UV.

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Case Report

An otherwise healthy 9-month-old male infant presented with a 7-month history of chronic recurrent urticaria. The patient's symptoms began at 2 months of age with the acute onset of fever (39.9°C), malaise, diarrhea, and a rash. During the following months, his rash appeared intermittently, beginning on the trunk and often extending to involve the entire body. The exacerbations continued despite chronic treatment with H1 blockers (ie, hydroxyzine, diphenhydramine hydrochloride, cetirizine), occasional courses of oral glucocorticosteroids for less than 1 week, and brief improvement following epinephrine injection.

After months of evaluation and treatment, his condition failed to improve and the patient was referred to dermatology. Physical examination revealed a healthy 9-month-old infant of normal length and weight, having attained the expected developmental milestones. He was a term infant born to nonconsanguineous parents. In addition to his skin lesions, his medical history included gastroesophageal reflux disease for which he was taking famotidine. Family history included a maternal grandfather who died suddenly at 31 years of age from an autoimmune membranoproliferative glomerulonephritis (as determined by postmortem renal biopsy), a maternal great-aunt with Berger disease, and another maternal great-aunt with discoid lupus erythematosus. Also, the patient's mother had a history of childhood alopecia areata. Recent laboratory analysis of the mother's blood revealed the following elevated liver function tests of unclear etiology: aspartate aminotransferase, 106 U/L (reference range, 3–35 U/L); alanine aminotransferase, 175 U/L (reference range, 3–40 U/L); lactate dehydrogenase, 392 U/L (reference range, 100–250 U/L), with negative hepatitis A and B serologies. Screening for cardiolipin antibody and antinuclear antibody was negative, and complement levels (including C3 and C4) were within reference range.

Cutaneous examination of the infant revealed multiple dusky, erythematous to violaceous, urticarial wheals concentrated on the back (Figure 1) and extending to involve the extremities, some scattered purpuric papules, ecchymotic plaques, and mild dermatographism. The parents reported that these flares lasted from 72 to 96 hours on average. Gastrointestinal and constitutional symptoms were absent. Examination of the eyes, mucosa, and joints was unremarkable.

Initial laboratory evaluations included a normal complete blood count, liver function tests, urinalysis, creatinine, and thyroid-stimulating hormone. Further analysis revealed low serum complement levels including a C2 less than 1.3 mg/dL (reference range, 1.6–3.5 mg/dL), C3 of 30 mg/dL (reference range, 90–180 mg/dL), C4 of 6 mg/dL (reference range, 16–47 mg/dL), CH50 of 13 U/mL (reference range, 26–58 U/mL), and C1q of 4.1 mg/dL (reference range, 5.0–8.6 mg/dL). Immunoglobulin (Ig) G antibody against C1q was negative as

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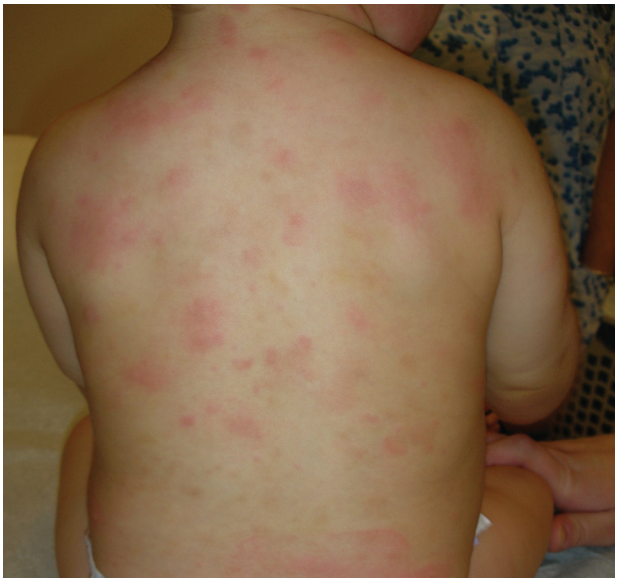

Figure 1. Patient's back at 10 months of age with raised erythematous wheals.

measured by enzyme-linked immunosorbent assay. Tryptase, erythrocyte sedimentation rate, antinuclear antibody (titer <1:40), and thyroglobulin antibody all were within reference range, while thyroid peroxidase antibody was elevated at 47 IU/mL (reference, <35 IU/mL). Because our patient's initial presentation suggested a viral infection, hepatitis B and C serologies were obtained; both were negative. Antibodies for dsDNA, c-ANCA (antineutrophil cytoplasmic antibody), p-ANCA, rapid plasma reagin, anti-Sm (Smith), and Sjögren syndrome antigens SS-A and SS-B also were negative. C1 esterase inhibitor levels were within reference range, and a test for cryoglobulins was negative. A chest radiograph was unremarkable.

A 4-mm punch biopsy specimen from the midline lower back was examined histologically. There was a superficial and deep perivascular and interstitial infiltrate containing prominent neutrophils, eosinophils, and lymphocytes (Figures 2 and 3), as well as fibrinoid degeneration of small blood vessel walls. Leukocytoclasis was present but to a lesser degree than is usually observed in classic leukocytoclastic vasculitis. A punch biopsy taken from perilesional skin was submitted for direct immunofluorescence and revealed deposits of C3, IgM, IgA, and, focally, fibrinogen around vessels of the superficial plexus. These results are consistent with urticarial vasculitis (UV).

The patient currently is being maintained on 4-mL hydroxyzine hydrochloride syrup twice daily and 4-mg montelukast sodium once daily. He continues to experience flares that are temporarily relieved by short 4- to 5-day courses of oral glucocorticosteroids. His mother recalls that her son's initial flares seemed to coincide with his immunization schedule; however, recent immunizations have been uneventful. According to the patient's allergist, skin flares often coincided with a missed dose of montelukast sodium.

We recently referred the patient to a nephrologist for consultation after his mother noted blood in his urine. Repeat urinalysis showed a pH of 5.5, specific gravity of 1.010, trace protein, and small hemolyzed occult hematuria. Microscopic evaluation revealed 3 to 4 eumorphic red blood cells per high-power field, without evidence of casts or white blood cells. A subsequent urinalysis was normal. Aside from his cutaneous flares, the patient is otherwise healthy and thriving. We will continue to closely monitor him for the development of renal or other systemic complications in the future.

Comment

This case of hypocomplementemic UV is notable for its presentation in a male infant beginning at 2 months of age, which is considerably younger than any patient with UV previously described in the literature. Children are seldom affected by this syndrome; a review of the literature found one report of normocomplementemic UV in an infant[1] and few reports of UV in children.[2-7] Among patients with chronic urticaria, the prevalence of UV has been estimated at 5% to 10%[8-11]; of those patients with UV, the majority are women, with onset typically occurring at a median age of 43 years.[12,13]

Although our patient showed no signs of renal disease, several previously reported cases of children with UV describe the development of renal disease years after initial presentation. Cadnapaphornchai et al[2] described a 12-year-old girl originally diagnosed with juvenile rheumatoid arthritis at 3 years of age. At 4 years of age, she developed an intermittent purpuric rash and was diagnosed with Henoch-Schönlein purpura (HSP). It was not until 8 years later while being evaluated for the development of hematuria and proteinuria that she was found to have UV. Renal biopsy revealed membranoproliferative glomerulonephritis and the patient was started on oral dapsone 100 mg daily, with good results. Waldo et al[3] described a 16-year-old boy with a less fortunate outcome. His UV developed at 2 years of age, with the onset of hematuria and proteinuria 10 years later. Renal biopsy revealed mesangial proliferation with membranoproliferative features. Unfortunately, he did not respond to steroid and cytotoxic therapy and ultimately progressed to end-stage renal disease.[3] Martini et al[4] reported 2 pediatric patients with UV.

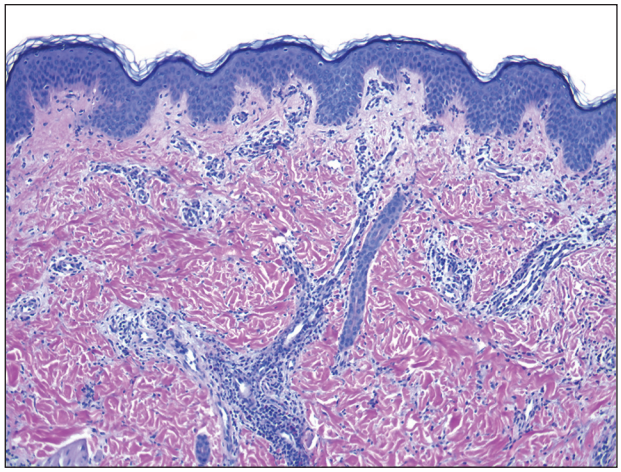

Figure 2. Superficial and deep perivascular and interstitial infiltrate (H&E, original magnification ×100).

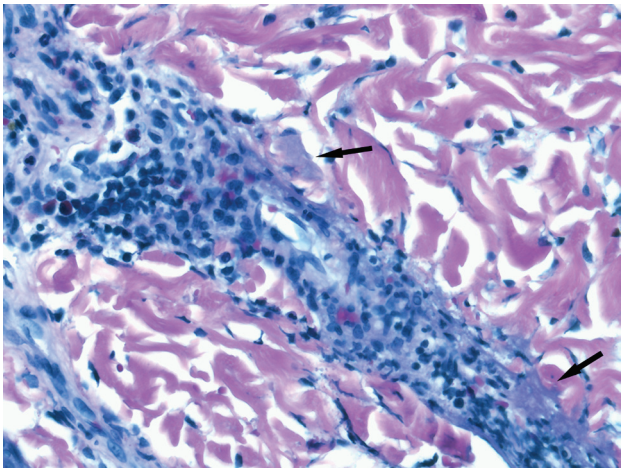

Figure 3. Perivascular infiltrate with eosinophils and extravasated fibrin (arrows). A hint of leukocytoclasis also was present (H&E, original magnification ×400).

One patient ultimately developed pulmonary hemorrhage, presumably due to UV, in the absence of renal disease. The other patient, who presented at 6 years of age with urticarial lesions, eventually developed proteinuria and hematuria at 10 years of age. Subsequent renal biopsy revealed fibrous crescents involving 50% of the glomeruli, with the remainder showing mesangial proliferation. Immunofluorescent studies revealed deposits of immunoglobulin and complement in the mesangium and subendothelial space. At the time the report was published, the patient had progressed to end-stage renal disease requiring hemodialysis and was awaiting renal transplant.[4] Renard et al[5] described a boy with UV who, after years of cutaneous manifestations, developed a rapidly progressive glomerulonephritis requiring repeated steroid and cyclosporine therapy.

HSP, the most common systemic vasculitis in children, shares many characteristics with UV. Direct immunofluorescence of a skin biopsy taken from our patient showed immunoglobulin and complement deposition in and around vessels of the superficial plexus. These results are similar to other children and adults with UV[6,7,14] and also are consistent with a diagnosis of HSP. However, a few important traits help distinguish UV from HSP in the pediatric population. Unlike patients with UV, those with HSP seldom present with hypocomplementemia.[15,16] Furthermore, HSP tends to be an acute self-limited illness. Our patient and the other children reported with UV have experienced chronic symptoms, often persisting over many years. Of the minority of patients with HSP who do go on to develop renal impairment, 80% develop it within 4 weeks of onset of symptoms.[17] This pattern is not seen in pediatric patients with UV.

Patients with idiopathic UV often are stratified on the basis of serum complement results. Those with decreased C3, C4, and/or CH50 are more likely than normocomplementemic patients to experience multisystem involvement, often affecting the kidneys, respiratory tract, gastrointestinal tract, joints, and eyes. Arthralgias and arthritis, the most common extracutaneous manifestations of UV, were absent in our patient. Also of note, laboratory studies did not reveal IgG antibodies against C1q. These anti-C1q antibodies are required for the diagnosis of hypocomplementemic UV syndrome, as defined by Wisnieski.[11] Hypocomplementemic UV syndrome, formerly thought to be a subtype of systemic lupus erythematosus (SLE), is now recognized as a distinct autoimmune disease. Unlike patients with SLE, all patients with hypocomplementemic UV syndrome exhibit UV as well as anti-C1q antibodies. The latter were lacking in our patient and also were absent in the 12-year-old girl with hypocomplementemic UV described by Cadnapaphornchai et al.[2]

While the causes of acute urticaria occasionally can be identified, the factors contributing to chronic urticaria often prove more difficult to pinpoint. Our patient's family history, including a maternal grandfather, maternal great-aunts, and mother with autoimmune disease, suggests that his vasculitis could be autoimmune in nature. Of note, his thyroid peroxidase antibody level was moderately elevated. This antibody, historically referred to as antimicrosomal antibody, has emerged as a marker for autoimmune thyroid disease. A link between chronic urticaria and autoimmune thyroid disease has been

described,[18] with studies documenting improvement or resolution of urticarial hives concomitant with thyroid replacement therapy.[19,20] However, it remains unclear if a link between UV and autoimmune thyroid pathology exists.

Although some cases of UV are benign, many have been linked to substantial morbidity. Hypocomplementemia in the setting of chronic urticaria often signals an underlying and potentially serious illness. Many patients diagnosed with idiopathic hypocomplementemic UV eventually prove to have an underlying disease such as SLE, Sjögren syndrome, or cryoglobulinemia.[11] Other patients may go on to develop hypocomplementemic UV syndrome. As evidenced by the 4 pediatric patients with hypocomplementemic UV previously described, renal and pulmonary disease can be particularly severe in the pediatric population.[5] Although our patient currently exhibits no signs of extracutaneous disease, his presentation, coupled with his family history of autoimmune disease, warrants close monitoring in the future. In young patients with chronic urticaria, the possibility of hypocomplementemic UV and associated morbidity should be carefully evaluated.

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