Hypocomplementemic Urticarial Vasculitis Syndrome

A Case Report and Literature Review

[a]ANDREW BUCK, DO; [b]JIM CHRISTENSEN, MD; [a]MORGAN McCARTY, DO

[a]Valley Hospital Medical Center, Las Vegas, Nevada; [b]Allergist and Immunologist, Private Practice, Las Vegas, Nevada

ABSTRACT

Hypocomplementemic urticarial vasculitis syndrome, as opposed to urticarial vasculitis or urticarial vasculitis syndrome, is a rare disease process where the exact pathophysiology remains unknown. This article discusses the case of a 34-year-old Hispanic man with an ongoing history of chronic urticaria comprising episodes induced by low ambient temperatures, emotional stress, and spontaneous occurrences. This article serves as a consolidated reference for specialists to comprehensively review the plethora of systemic manifestations that may accompany urticarial vasculitis and highlights new systemic complications reported in association with this disease which are also observed in this case.
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Hypocomplementemic urticarial vasculitis syndrome (HUVS), or McDuffie syndrome, is a rare disease process that was first described by McDuffie et al[1] in 1973. Four patients presented with recurrent urticarial lesions and decreased serum complement. Incidence for chronic urticaria hospital admissions ranges from 2 to 20 percent diagnosed with urticarial vasculitis (UV).[2] The major manifestations of HUVS are chronic, nonpruritic, urticarial vasculitic lesions that persist more than 24 hours or recur at short intervals. Debate surrounds the pathophysiology of HUVS; however, low serum complement measurements in patients indicate the activation of the classical pathway, with low C1q, C4, and variably decreased C3 levels. Serum C1q precipitins were identified and later confirmed to be the autoantibodies against C1q (anti-C1q autoAbs).[3–11] Diagnosis is confirmed by skin biopsy revealing leukocytoclastic vasculitis (LCV) as a pathogenic correlate. Although HUVS is rare, practitioners should be mindful to include HUVS in their arsenal of differentials given the extensive overlap across a spectrum of subspecialties in medicine.[2]

Chronic urticaria often causes suspicion for a diagnosis of a systemic disease, particularly when UV is present. UV is one of the small-vessel vasculitides involving the postcapillary venules.[12] UV presents clinically as a persistent urticarial skin lesion and histopathologically as LCV. UV is classified as an immune complex-mediated or type III hypersensitivity reaction.[4] UV has been associated with connective tissue diseases, such as systemic lupus erythematosus (SLE) Sjogren's syndrome, immunoglobulin (Ig) M paraproteinemia (Schnitzler syndrome), serum sickness, infections (hepatitis B, infectious mononucleosis), and drug sensitivity.[4]

Urticarial vasculitis: Three distinct syndromes. *Normocomplementemic Urticarial Vasculitis (NUV).* NUV is typically a self-limited subset of hypersensitivity vasculitis, generally idiopathic, and benign. NUV can be viewed as a manifestation of cutaneous leukocytoclastic angitis. Chronic cases of NUV must be distinguished carefully from neutrophilic urticaria, which is a persistent form of urticaria unassociated with vasculitis.[13]

Hypocomplementemic urticarial vasculitis (HUV). Two categories of primary or idiopathic, usually not associated with systemic disease until recently, and secondary that is more likely to be a chronic disorder, often associated with a systemic inflammatory disease.[14] The latter is characterized by certain overlapping features of SLE including low serum complement, autoantibodies, and an interface dermatitis characterized by immunoreactant deposition (complement and immunoglobulins) at the

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ADDRESS CORRESPONDENCE TO: Morgan McCarty, DO; E-mail: morganmccarty@gmail.com

dermal-epidermal junction in a pattern essentially equal to the lupus band test.[13]

HUV Syndrome (HUVS). HUVS is a rare, distinct, and potentially severe form of UV with multiorgan involvement. Its etiology and link with other diseases are still unknown.[12] It is associated with an array of organ systems and characterized clinically by persistent urticarial skin lesions, LCV, and a variety of systemic manifestations, including severe angioedema, laryngeal edema, ocular inflammation, arthritis, arthralgia, obstructive lung disease, recurrent abdominal pain, and glomerulonephritis.[12,15] HUVS is considered by some to be an independent immunological disease from SLE, whereas many others propose just the opposite.[2] Due to the number of reported cases of HUV with absent classic anti-extractable nuclear antigen (ANA) commonly obtained in SLE, HUVS may arguably be separate from SLE.[3]

CASE REPORT

A 34-year-old Hispanic man was evaluated in August 2009 for an initial manifestation of urticarial-like flare that occurred in October 2008 following an emotional court case. The urticarial-like flare initially involved only the distal extremities. The wheals were nonpruritic, painless, mildly erythematous, and palpable, which remained for less than 20 minutes. The wheals resolved with residual red-brown macules. Recurrences of the lesions were associated with repeat emotional upsets, followed by arthralgia resulting in decreased range of motion of the hands and feet, myalgia, and diffuse angioedema. Two months prior to skin manifestations, the patient noted hand, wrist, and ankle joint swelling.

Roughly four months after the initial skin manifestations, flares also included association with exposure to cold temperatures. The urticarial-like lesions became pruritic, with dysesthesia of hands, feet, and especially shins. Wheals averaged 1.5cm and were irregular, semi-circular, and erythematous. The lesions resolved after a maximum of 15 minutes as nonblanching, red-purple macules with a central red hue. The patient soon discovered that a large portion of the lesions would nearly resolve immediately following outdoor exposure during the summer. Yet, not all lesions would completely resolve following exposure to heat. Residual hyperpigmentation would fade over two-week periods.

Many active lesions would fade in the evenings and during sleep, and then erratically reappear upon awakening, particularly during conditions with exposure to cold ambient air. Such an association was first noticed by the patient at the elbows and medial forearms, after resting them on a cold metal desk in his office. Flare episodes were irregular at first, then increased in frequency. Over time, urticarial involvement progressed to include the buttocks, lower back, and then trunk (anterior more than posterior), with sparing at the inner thigh, genitalia, gluteal cleft, and axillae. Facial involvement was the last region to be affected, notably at the bridge of the nose, ears, scattered about the cheeks and neck (anterior more than posterior), and supraorbital region with an accompanying dysesthesia. There was facial-sparing at the forehead, posterior-auricular, and philtrum (unlike the malar rash of SLE noted for sparing of the nasolabial fold). Angioedema was more prominent following significant flares, affecting the lips, periorbital tissue, cheeks, and hands more so than the feet. Common urticaria, as well as palpable purpura, also presented throughout these stages, and more numerously at the feet to mid-shin level with resolution within 10 to 15 minutes without residual hyperpigmentation.

The patient was asplenic following a motor vehicle accident in 1999, and underwent left ankle compound fracture repair. There was no personal history of autoimmune disease or hepatitis. The patient's mother had a history of rheumatoid arthritis. Otherwise, the family

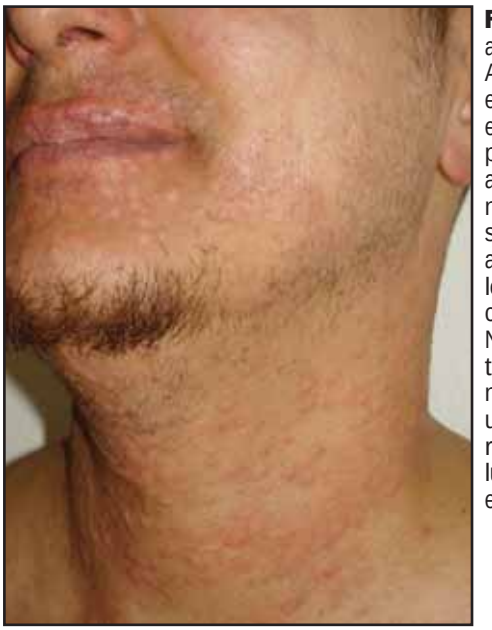

Figure 1. Left face and neck. Active raised, erythematous eruption of wheals, particularly affecting anterior neck, submandibular area and upper, lower, and cutaneous lips. Note the sparing of the philtrum but not nasolabial fold unlike the malar rash of systemic lupus erythematosus

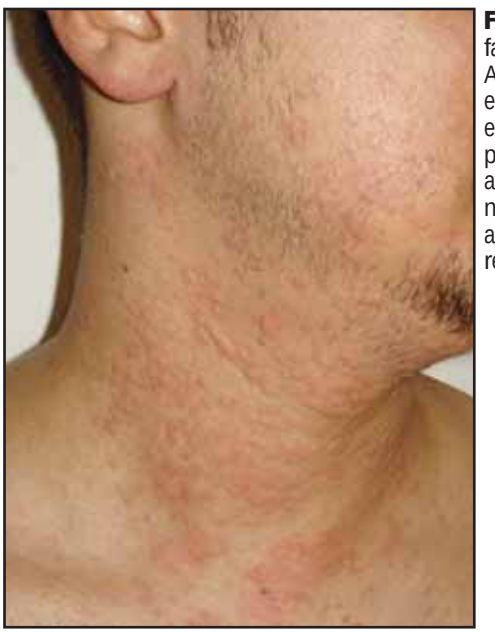

Figure 2. Right face and neck. Active raised, erythematous eruption of wheals, particularly affecting anterior neck, mandible, and submandibular regions

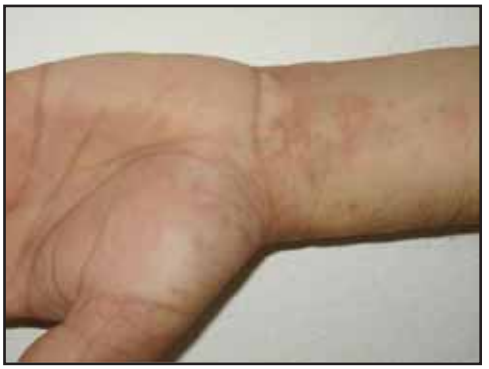

Figure 3. Anterior wrist and palm. Resolving erythematous wheals soon after flare; urticarial lesions sparing palms with post-inflammatory hyperpigmentation. Note concentration around volar wrist.

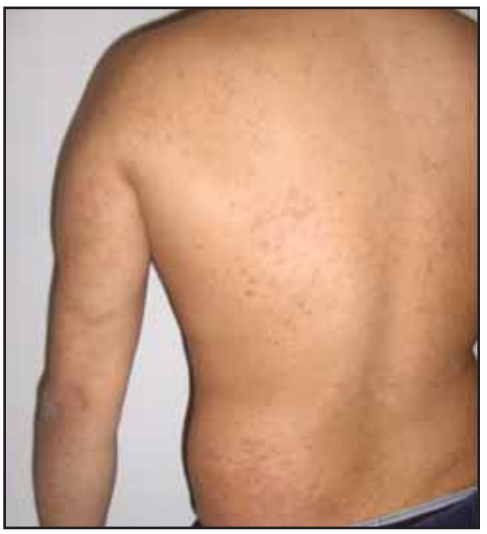

Figure 4. Right arm and back (soon after flare). Involvement of upper hips showing both recent resolving erythema. Concentration also at elbows and triceps region

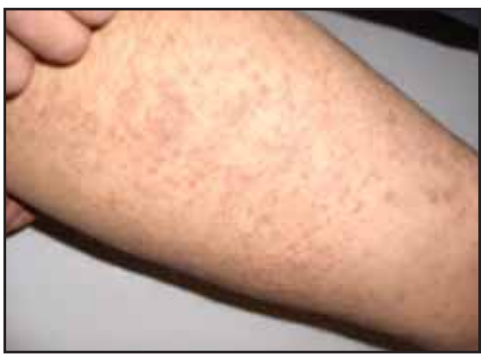

Figure 5. Left calf region. Resolving erythematous wheals soon after flare

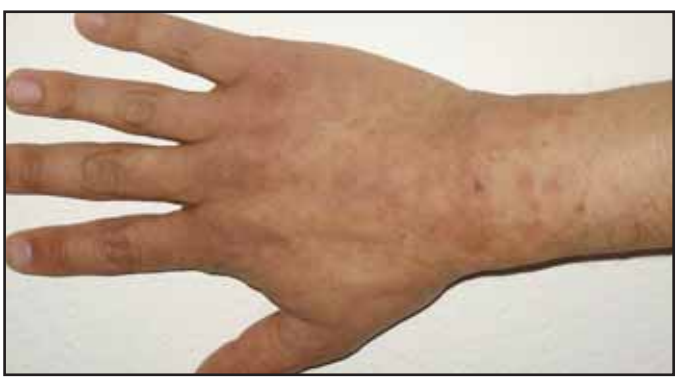

Figure 6. Dorsum right hand. Concentration around the metacarpophalangeal joints, less involvement over distal interphalangeal joint and proximal interphalangeal joint

history was only significant for hypertension and coronary artery disease. The patient had two healthy daughters and a history of social alcohol use, cessation of tobacco two years prior, marijuana use 25 years prior, and illicit drug experimentation in his 20s.

The patient admitted to initial weight loss of 20 pounds prior to steroid treatment and fatigue, especially with flares, and to worsening myalgia and arthralgia of all extremities and upper back. In August 2009, the patient complained of intermittent chest pain and mid-back pain causing shortness of breath that was temporary and without recurrence. Otherwise, the patient denied any abdominal pain, gastrointestinal abnormalities, nor hematuria at any time during the authors' examinations. He also denied a history of such urticarial-like lesions prior to his first episode in 2008.

Results from a total of four punch biopsies of urticarial-like lesions taken from the left arm, right mid-back, and two at the right forearm were consistent with neutrophilic dermatosis, UV, LCV, and HUVS, respectively. The patient was found to be hypocomplementemic on three occasions. In August 2009, serum complement level C3 was 26mg/dL (reference range 90–180mg/dL), serum complement level C4 was 7mg/dL (reference range 16–47mg/dL), and total complement activity (CH50) was less than 10 units/mL (reference range 31–66 units/mL). In September 2009, serum complement level C2 was less than 1.3mg/dL (reference range 1.6–35mg/dL), serum complement level C3 was 26mg/dL (reference range 90–180mg/dL), serum complement level C4 was 7mg/dL (reference range 16–47 mg/dL), and CH50 was less than 10units/mL (reference range 31–66 units/mL).

In August 2009, laboratory results also showed the patient to have C1 esterase inhibitor and respective antibody to be within normal limits. Then in November 2010, the C1 esterase inhibitor was found to be greater than 100-percent function, Raji-equivalent complement immune complex (CIC) elevation (detects quantification of total serum immune complexes) and solid phase C1q CIC negative. In September 2009, serum protein electrophoresis (SPEP) showed elevated gamma globulin and low beta globulin, and the antiphospholipid antibody panel was positive for beta2-glycoprotein I IgM antibody, antiphosphatidylserine antibody IgM, and cardiolipin antibody IgM. The patient's labs were negative for a coagulopathy, cryoglobulin, ANA, Smith antibodies, antiscleroderma-70 antibody, Sjogren's anti-SS-A and SS-B, antichromatin antibody, anti-Jo-1, anti-centromere B antibody, anti-neutrophil cytoplasmic antibody (ANCA) screen, and hepatitis panel. Complete blood counts, renal panels, anti-deoxyribonucleic acid (DNA) antibody, U1-ribonucleoprotein antibody, rheumatoid factor, erythrocyte sedimentation rate, and thyroid stimulating hormone were all within normal limits. Due to the patient's financial situation, no further diagnostic imaging was pursued.

Case treatment. The patient's primary physician began trials of cetirizine, montelukast, ranitidine, and fexofenadine with no symptomatic relief. Later, the patient's allergist began

prednisone 7.5mg daily, then 10mg daily two months later, which decreased flares mildly. Flares returned soon afterward and prednisone 60mg daily was tapered to 40mg daily, which controlled flares for four more months. Azathioprine 50mg three times per day was initiated approximately 10 months later and aided flares mildly. Azathioprine was then successfully replaced by cyclophosphamide 250mg daily. Flares were well controlled on this regimen of cyclophosphamide and prednisone for nearly two years. The patient was lost to follow up due to relocation. Of note, several months before the patient relocated, he complained of dysesthesia in a sock distribution of lower extremity consistent with peripheral neuropathy. Contact was made six months following re-location, and the patient reported dramatic decrease in flares. He is adherent to the medical regimen, he is away from the source of emotional stress, and has limited cold exposure.

DISEASE PRESENTATION

HUVS has been found to affect numerous organ systems.[2] The most common clinical, laboratory, and immunological features of HUVS and SLE are summarized in Tables 1 and 2. Constitutional symptoms (fever, malaise, fatigue) may arise though myalgia is the most common symptom. When distinguishing HUVS from SLE, note that chronic obstructive pulmonary disease (COPD) is not a common manifestation of SLE.[3]

Skin. In HUVS, the dominant clinical finding is recurrent urticaria.[1,16] Angioedema is found to occur in up to 50 percent of patients, frequently involving the lips, tongue, periorbital tissue, and hands, and can be the first sign of HUVS.[3,16] Most commonly, patients with HUVS present with generalized wheals lasting more than 24 hours that may resolve with postinflammatory hyperpigmentation.[12,17] UV is non-blanching and resolves with post-inflammatory hyperpigmentation or purpura, whereas common urticaria

TABLE 1. Clinical symptoms of hypocomplementemic urticarial vasculitis syndrome compared with systemic lupus erythematosus[12]

HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS SYNDROME (HUVS)		SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	
Symptom	**Frequency (%)**	**Symptom**	**Frequency (%)**
Urticaria-like skin lesions (with biopsy-consistent leukocytoclastic vasculitis)	100	Urticaria	<10
		Cutaneous symptoms (malar eruption, oral ulcer, photosensitivity)	80
Arthralgia and/or arthritis	100	Arthralgia and/or arthritis	95
Angioedema	72	Angioedema	<5
Chronic obstructive pulmonary disease	65	Restrictive pulmonary disease	24–30
Eye involvement	61	Eye involvement	15
Renal involvement	50	Renal involvement	36–50
Pericardial effusion	17	Pericarditis	30

TABLE 2. Laboratory investigations of hypocomplementemic urticarial vasculitis syndrome compared with systemic lupus erythematosus[12]

HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS SYNDROME (HUVS)		SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	
Laboratory investigation	**Frequency (%)**	**Laboratory investigation**	**Frequency (%)**
Anti-C1q antuoAb	100	Anti-C1q antuoAb	35
Low C1q	100	Hypocomplementemia	22–47
ANA	61–71	ANA	95
Raised ESR	60–70	Raised ESR	50
dsDNA Ab (transient)	17	dsDNA Ab	≥70
Anti-SS-A/SS-B Ab	16–17	Anti-SS-A/SS-B Ab	30–45
Hematological abnormalities	11	Hematological abnormalities	85
Rheumatoid factor	8	Rheumatoid factor	25–33

ANA=antinuclear antibodies; aanti-C1q autoAb=autoantibodies to C1q; dsDNA Ab=antibodies to native DNA; ESR=erythrocyte sedimentation rate; anti-SS-A/SS-B Ab=antibodies to SS-A/SS-B

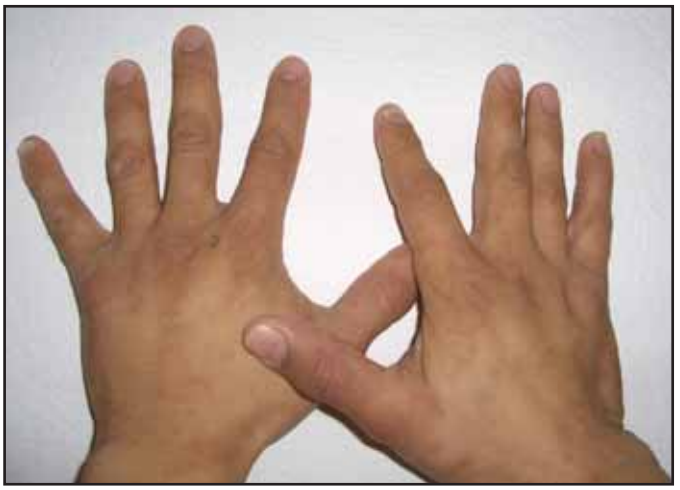

Figure 7. Dorsum hands. Resolving hyperpigmented macules less than one hour after active flare. Concentration around MCP joints, and less so over DIP, PIP, and wrists.

resolves without residual affects.[17] Raynaud's phenomenon may also occur.[18]

UV lesions are caused by leukocytoclastic vasculitis (LCV) in contrast to other forms of urticaria. UV wheals persist for more than 48 hours, but generally between 24 to 72 hours versus common urticaria where lesions resolve within 8 to 24 hours. UV lesions are found to cause dysesthesia and less commonly pruritis, which is more associated with common urticaria.[12] UV lesions have a predilection of arising anywhere and they tend to be centripetal, favoring the trunk and proximal extremities more than dependent regions, unlike common urticaria, which characteristically affects the lower extremities, as does palpable purpura.[13,17,19] The eruptions of HUV (as opposed to HUVS) are found to primarily affect the face, upper extremities, and trunk. They can also present on the palms and soles. With each exacerbation, urticarial lesions last 2 to 4 days then fade without scarring.[13] Angioedema may be found when a vasculitis involves deeper vessels. Immunohistochemistry demonstrates immunoglobulin and complement deposits in the vessel walls or on the endothelium. Such deposits also occur together with vasculitis in SLE, but in SLE patients they are typically found along the basal membrane (i.e,. the lupus band).[2,4]

Joints. Arthralgia and arthritis of various joints are the most frequent systemic manifestations of HUVS, occurring in up to 50 percent of cases. The joint pain wanders and is often transient. Typically, the elbows, wrists, knees, and ankles are involved. Joint deformities are possible, which include Jaccoud's arthropathy, in which case the cardiac valves are also affected, such as aortic and mitral valvulopathy.[20–22]

Kidneys. Renal involvement is usually mild, but dialysis may be required.[23] The frequently found proteinuria and hematuria with demonstration of acanthocytes (nephritic sediment) is seen histologically as membranous, membranoproliferative, or intra- and extracapillary glomerulonephritis. Nevertheless, renal biopsy is necessary only in proteinuria (>1g/day) or in acute or chronic progressive renal failure. The renal involvement seems to be more severe in children.[2,7,24,25] However, case reports of renal involvement progressing to end-stage renal disease have occurred and prompt the clinician to include this phenomena in the differential diagnosis for a patient presenting with HUVS.[15]

The pattern of renal changes with HUVS is apparently indistinguishable from SLE nephropathy.[16] Clinically detectable glomerulonephritis occurs in more than one third of the patients with SLE, and at autopsy, 75 percent have evidence of nephritis.[3] Approximately 30 percent of patients with SLE and glomerulonephritis have C1q precipitins in response to pre-existing double-stranded DNA and anti-double-stranded DNA immune complexes in the glomerular basement membrane.[4] Yet, in up to 50 percent of HUVS cases, renal involvement is present, with the majority manifesting in a benign manner.[15] In a 1994 literature review by Kobayashi et al,[27] 78 patients were reported from 1973 to 1990 with 18 biopsies performed, representing the following various histopathological types: mesagnial proliferative (8 cases), membranoproliferative (3 cases), focal proliferative (3 cases), membranous (2 cases), minimal change (1 case), and severe sclerosing proliferative glomerulonephritis (1 case). Wisnieski et al[3] reported another 18 HUVS patients having renal involvement in 50 percent. These investigators described renal manifestations ranging from minimal proteinuria to nephrotic syndrome with variable degrees of hematuria and glomerular involvement, including mesangial and membrano-proliferative glomerulonephritis. Yet, rarely was crescentic glomerulonephritis found to be associated with HUVS.[15]

Lungs. Lung involvement includes dyspnea, coughing, hemoptysis, pleural effusion, and COPD. Interestingly, COPD occurs in 50 percent of HUVS patients.[3,17] Apparently, the prevalence of C1q precipitins in HUVS is 80 to 100 percent and may be associated with a greater frequency of obstructive lung disease.[3,28–31] Emphysema has been found to occur in more than half of HUVS patients, and symptoms may be absent at presentation.[28,30,32] According to Jones et al,[33] HUVS-associated emphysema has an early onset (often before the age of 30) and may be clinically significant within two years of the diagnosis of UV. COPD is progressive in HUVS and is the most frequent cause of death.[2,5] Cigarette smoking and HUVS may act synergistically in the process of pulmonary elastinolysis, and though smoking markedly accelerates its development, HUVS-associated emphysema may occur even in nonsmokers.[32–35] Restrictive type pulmonary disease occurs in as many as 25 to 30 percent of SLE patients. Patients are also predisposed to pyogenic infections, including pneumonia.[1,2,4,5,32,28]

Gastrointestinal tract. About 30 percent of HUVS patients suffer gastrointestinal symptoms, such as pain, nausea, vomiting, diarrhea, ascites in connection with serositis, hepatomegaly, and splenomegaly.[2,8] Reports of adenocarcinoma are not uncommon.[36]

Ocular. As many as 30 percent of patients have ocular

inflammation, particularly of the uveal tract, but also conjunctivitis and episcleritis.[1,3,4]

Cardiac. Cardiac involvement presents in the form of valvular abnormalities (found in the presence of joint deformities) and congestive heart failure.[3,22]

Central nervous system. Although the central nervous system is rarely affected, neurological manifestations include seizure disorder, mononeuritis, cranial nerve palsies, axonal neuropathy, aseptic meningitis, pseudotumor cerebri, transverse myelitis, and peripheral neuropathy.[6,12,14,17,27]

Other. HUVS may also be associated with malignancies, particularly Hodgkin's and non-Hodgkin's lymphomas. HUVS may result in prolonged B lymphocyte stimulation, thus evolving into lymphoma, yet this mechanism is still not fully established.[37]

A recent case of primary HUV with neuropathy, though unusual, is a consideration for patients diagnosed with idiopathic HUV who may go undiagnosed when no other secondary cause for HUV is found.[38]

Imaging. An unusual radiographic pattern associated with HUVS, yet primarily reported with alpha-1 antitrypsin deficiency, is basilar hyperlucency.[25] Depending on which organs are affected, a complete workup of suspected organ systems is indicated.[2]

Laboratory data and other studies. Typical lab findings in HUVS include erythrocyte sedimentation rate acceleration, hypocomplementemia (with low serum complement level C1q, C3, C4), and C1q antibodies, antinuclear antibodies without anti-double-stranded DNA.[4] If renal involvement is suspected, detection should be performed by means of urinalysis with microscopy, protein quantification, and if applicable, protein analysis. Renal biopsy should be considered if a nephritic syndrome is found.[2]

Histology. UV lesions affect the capillary and postcapillary venules. Histopathological examination of the persistent urticarial lesions show perivascular neutrophilic (or, less commonly, lymphocytic) infiltrate with fibrinoid necrosis, evidence of LCV with injury to the endothelial cells of the postcapillary venules, and erythrocyte extravasation. Direct immunofluorescence study of HUVS lesions demonstrates both immune complex and complement deposition in a granular pattern in or around blood vessels in the upper dermis and a striking deposition of immunoglobulins and complement along the dermal-epidermal junction.[12,13,16,38]

In the proper setting, these findings (interface dermatitis as well as immunoreactant deposition within blood vessels) are diagnostic of hypocomplementemic UV. HUVS, in contrast, is a clinical diagnosis based on the presence of UV and the occurrence of typical features in extracutaneous organ systems.[13]

PATHOPHYSIOLOGY

The pathophysiology of HUVS is not clear and many have attempted to investigate this controversy. Among the theories are a range of proposed mechanisms and pathogenesis, particularly regarding vascular damage, anti-C1q antibodies, and the link between HUVS and other disease processes, such as collagen tissue diseases. The possible mechanisms of vascular damage include the following: immune complex, T-lymphocyte response, and anti-C1q antibody.[16]

Immune complex. The following humoral autoimmune complex cascade may be a possible pathological mechanism for urticaria, angioedema, and obstructive lung disease: C1q-precipitins (C1q-p also referred to as anti-C1qAb/C1q) comprising IgG autoantibodies that bind to the Fc portion, collagen-like regions, of the C1 molecule, which then form immune complexes, activates the complement system (C3a and C5a) by the classical pathway within and around blood vessels.[40,41] This cascade generates both anaphylatoxins (allowing mast cell degranulation) as well as upregulates chemokines and cytokines, which collectively contribute to increased vascular permeability, chemotaxis of inflammatory cells, and deposition of immune complexes that further exacerbate tissue destruction and edema.[16,42,43] Such events lead to the clinical findings of urticaria and or angioedema and lead to the histological findings of LCV; in terms of a Coombs and Gell type III reaction.[2,17,27]

The autoantibody IgG2 anti-C1q in patients with HUVS (100%) and SLE (35%) binds only to the collagen-like region of C1q, suggesting that HUVS and SLE autoantibodies to C1q bind to the same epitope(s).[39,44] However, there is evidence of distinct specificities of C1q-reactive IgG in the serum of SLE and HUVS. Western blot analysis has shown HUVS patients have binding to dimers of collagenous C1 fragments and C1q chains, for which SLE patients' serum were negative. Further evidence has shown HUVS patients to have specific zymogen (C1r-C1s) complexes in serum versus SLE patients who had high concentrations of C1 inhibitory complexes, C1r and C1s. Thus, different binding specificities of C1q-reactive IgG could be important with regard to pathogenetic mechanisms in SLE versus HUVS.[16,41]

The exact mechanism of HUVS associated with obstructive lung disease is currently unknown, yet it likely follows the detailed model provided above.[28] Anti-C1q autoantibodies have clearly been detected in pulmonary diseases and may likely be responsible for the lung involvement in HUVS.[2,6,26] Consider the following mechanism: C1q precipitins may bind to the collagen-like regions of pulmonary alveoli surfactant proteins; when paired with the vasculitis of pulmonary capillaries and venules, this may contribute to the development of obstructive lung disease.[34] Also, it has been found that neutrophil elastase is over expressed in the vasculitis lesions of HUVS, which may theoretically hydrolyze complement proteins and connective tissue components. It has also been proposed that collagen or a collagen-like molecule is the target of degradation by immune cells rather than by a specific antibody.[3,31,40] This purposed mechanism may contribute to the morbidity and mortality of COPD in HUVS patients.

T-lymphocyte response. C1q has been shown to be involved in the activation as well as the inhibition of T cells.

Immune complexes in the presence of C1q activate T cells.[45] Also, anti-C1q may interfere with the clearance of apoptotic cells, influencing induction and expression of autoimmunity.[46] Yet, it is unknown if T-cell activation involves immunoregulatory circuits in HUVS.[16] It has been found that apoptotic bodies of keratinocytes bind C1q.[47] And, numerous sources of evidence suggest apoptotic bodies derived from keratinocytes are immunogenic in SLE. Thus, the expression of neoepitopes on the C1q bound to apoptotic bodies might trigger an immune response.

Anti-C1q antibodies. Besides complement cascade activation, C1q has been found to have other biological functions including a modulating role on cellular functions within the adaptive immune response.[48] The complement system is also a target for autoantibodies.[16,46] Lienesch et al[49] investigated a population of patients with chronic hepatitis C virus (HCV) infection and hypothesized that anti-C1q antibody, detected with high frequency in SLE and HUVS, may have a direct pathogenic role in complement-mediated autoimmune diseases. Lienesch et al[49] found that 38 percent of HCV patients detected positive for anti-C1q Ab compared to two percent of healthy controls, and that levels were also significantly elevated in patients with SLE (61%), rheumatoid arthritis (20%), scleroderma (15%), Sjogren's syndrome (15%), and mixed connective tissue disease (15%). Other diseases that also have such antibodies in circulation include idiopathic membranoproliferative glomerulonephritis (which is not associated with UV) and Goodpasture's syndrome.[50,51] It is not clear if these antibodies have the equivalent C1q-binding specificity or clinical consequence.[16] For example, anti-C1q antibody in SLE patients do not bind to reduced C1q, but about 60 percent of HUVS anti-C1q Ab preparations do bind. Evidence suggests that the tertiary structure of the intact C1q collagen-like domain is required for the recognition of the anti-C1q antibodies in SLE, whereas HUVS precipitins bind epitopes on reduced and denatured C1q. Anti-C1q antibodies are found in a number of autoimmune diseases, and can be found in patients with SLE even when no vascular disease is present.[52–56] Anti-C1q antibody, though present in 95 to 100 percent of HUVS patients, are not specific, yet are considered a diagnostic marker for HUVS (it should be noted that authors vary regarding this statement, others state that anti-C1q antibody are a relatively specific marker for both HUVS and SLE).[2,16,28,53]

In the 1999 case study by Trendelenburg et al,[9] examination of four renal biopsy specimens of patients with HUVS indicated the presence of C1q antigen in glomeruli with significant anti-C1q fluorescence. Deposits of C1q along the tubular basement membranes has also been reported among SLE patients.[3] In SLE, anti-C1q autoantibody levels correlate with the severity of skin involvement and renal disease.[57] Whether the concentration of anti-C1q autoantibody or C1q antigen can predict the outcome of the disease remains unknown. SLE patients with glomerulonephritis have almost all anti-C1q autoantibodies at the time of a flare.[9,10,58] The pathogenesis of anti-C1q autoantibodies is not fully understood, and they are present in low concentrations in up to 10 percent of healthy individuals. These levels increase with age.[10,59,60] Trendelenburg et al[9] further stated that this might explain the close link between skin disease and the presence of anti-C1q autoantibodies in SLE and HUVS.

The debate continues as to whether HUVS is a rare subset or unusual type of SLE, or is a separate entity entirely.[5,12,15] Some studies state that the findings of HUVS are atypical of SLE, and that HUVS is to be regarded as a separate entity given the lack of classic serology in most cases. Furthermore, there seem to be different skin lesions and pathological states.[13,15] Some authors emphasize the possible progression of HUVS to SLE, while others state that HUVS is a precursor to SLE.[61,62] Aydogan et al[12] concluded that SLE and HUVS share clinical and lab features, have a similar clinical progression and treatment, are likely not separate entities, and probably fall into the same spectrum of autoimmune diseases. They also stated that their case represented HUVS as an exacerbation of acute SLE. Yet others argue that HUVS resembles SLE both clinically and immunologically, and that it is accepted as an SLE-associated syndrome.[12] A case of HUVS that occurred in a pair of twins suggests a potential role of abnormal genetic immunoregulation as part of the pathogenesis.[52]

EPIDEMIOLOGY/INCIDENCE

The prevalence of UV is 5 to 10 percent in patients with chronic urticaria, and less than five percent in patients with HUVS.[3,53] In a retrospective study performed at a single center, 18 percent of patients with biopsy-confirmed UV exhibited a hypocomplementemic form of the disease. The normocomplementemic form of UV is not strongly associated with SLE (2%).[5] Yet, approximately 2 to 20 percent of patients admitted for chronic urticaria are found to have UV.

According to the literature, the exact incidence and prevalence of HUVS is unknown, as it is a rare and severe systemic form of UV.[2,16] HUVS is present in 7 to 8 percent of SLE patients, and 54 percent of HUVS patients are diagnosed with SLE in follow-up period.[5,12] Given that approximately 250,000 Americans have SLE (according to a recent article from the National Arthritis Data Working Group), this would indicate that HUVS occurs in approximately 17,500 to 20,000 Americans.[63]

HUVS is found to primarily occur with young women, with a female to male ratio of 8:1.[30,32] It has a peak incidence found in the fifth decade of life, while UV is found to have its peak in the fourth decade.[2,4,32,64,65] In one published report, the average age of diagnosis for HUVS and NUV patients was 43 and 51 years, respectively, while the average age of HUVS presentation is 48.[4,5] In comparison, HUVS is rarely reported in the pediatric population.[15,26]

DIAGNOSIS

The diagnosis of UV is found by demonstration of LCV in dermal biopsy samples, which involves a leukocytoclastic reaction, vessel wall destruction, and deposits of fibrinogen.

Immunohistochemical analysis will show immune complexes and complement in blood vessels.[2,66]

Regarding the diagnosis of HUVS, in 1982 Schwartz et al[32] established a diagnostic criteria for HUVS.[17] Two major criteria (recurrent urticaria more than six months and hypocomplementemia) and at least two minor criteria (venulitis on skin biopsy, arthralgias or arthritis, glomerulonephritis, ocular inflammation, abdominal pain, and positive C1q-p test by immunodiffusion with decreased C1q level) are required for the diagnosis of HUVS. Other clinical findings associated with HUVS include obstructive lung disease, angioedema, and various neurological problems including transverse myelitis, and NUVS peripheral neuropathy.[14,16,67,68]

Criteria for exclusion include cryoglobulinemia (cryocrit, >1%), elevated titer of anti-double-stranded DNA antibody (dsDNA) or Sm antibodies, hepatitis B virus antigenemia, deficiency of C1 esterase levels or a congenital complement defect, and a high titer of ANA; however, 50 percent of patients may have ANA in their serum.[2,12,15] HUVS patients may however develop these other autoantibodies, such as anti-DNA, anti-Sm, antiendothelial cells, or anti-phospholipid antibodies, yet as stated above, a high titer may exclude them from diagnostic protocol, though the criteria for exactly what titer quantity is permitted has not been delineated.[52]

Complement measures with low C1q and C4 levels and variably decreased C3 levels indicate activation of the classical pathway.[16] Two principles of complement measurement can distinguish between hereditary deficiency and inflammatory influences. If CH50 is lower than 10 units/mL, this range is most indicative of a hereditary deficiency. The complement components C3 and C4 are acute phase reactants, and levels of these components will be reduced but less drastically during inflammatory episodes compared to hereditary deficency component measurements. Even CH50 may be increased during inflammation. Therefore, assessing hypocomplementemia requires serial evaluation during and following flare episodes.[17,16,44] Although some UV patients may have hypocomplementemia, not all meet requirements to be diagnosed with HUVS. These patients are referred to as having HUV, but not necessarily as having HUVS.[17]

Thus, according to McDuffie's diagnostic criteria,[1] the case report patient meets both major criteria for recurrent urticarial vasculitic skin lesions for more than six months and serum hypocomplementemia via three different lab confirmations.[3] In regard to minor criteria, skin biopsy showed LCV. The patient has had progressive arthralgia and arthritis since 2008, and serum C1q autoantibody was found to be elevated. No further workup has been performed in regards to glomerulonephritis, as renal panels have been within normal limits, and the patient has always denied abdominal pain. Signs and symptoms of ocular inflammation have been observed on more than one account, yet again, no further workup has been performed to rule out uveitis or episcleritis. Thus, minor criteria have been met as well, allowing a confident diagnose of HUVS.

DIFFERENTIAL DIAGNOSIS

Distinguishing between acute and chronic urticaria is the first step when presented with a possible UV case. Several types of urticaria exist including aquagenic, androgenic, pressure, cold-induced, and cholinergic. Many of these types of urticaria have been associated with UV as well.[42,43] Once the clinical difference is delineated, several other syndromes can be explored. The differential can be an exhausting endeavor. Focus will be placed on Muckle-Wells syndrome; Cogan syndrome; Schnitzler syndrome; arthritis, hives, and angioedema (AHA); SLE; mixed cryoglobulinemias; and Sharp syndrome.

Muckle-Wells syndrome stems from genetic mutation on chromosome 1q[44] responsible for protein cryopyrin coding. This syndrome is clinically distinguished from HUVS by progressive hearing loss and secondary amyloidosis, which may include renal involvement. Cogan syndrome occurs from antibody formation against rheovirus-III infection which reacts with inner ear and eye tissue causing hearing loss and visual disturbances. Schnitzler syndrome is an entity that presents with UV and monoclonal IgM gammopathy along with arthralgia and fever. AHA syndrome is a poorly understood entity; however, it can be distinguished from HUVS by the normal function of C1 esterase inhibitor. HUVS versus SLE is by far the most difficult diagnosis to differentiate. C1q antibodies may be positive in 30 percent of SLE cases. However, if double-stranded DNA antibodies are present in high titers, this may be the only distinguishing factor needed to differentiate the two disease entities. Similarly, clinical overlap with cryoglobulinemias exist. However, extremely high titers of cryoglobulin and cryoprecipitate will distinguish cryoglobulinemias. Mixed connective-tissue disease (Sharp syndrome) is differentiated by the presence of U1-RNP antibodies.[42,43]

TREATMENT

As with patients with UV, those whose serum complement levels remain normal during an attack will have a self-limited disease and require little therapy. The drug of choice for treatment of UV with only cutaneous lesions is an antihistamine. Monotherapy with antihistamines only serve to control the itching and are typically insufficient because they intervene late in the inflammation cascade, the immune complex formation is not controlled, and the course of the disease is not altered.[2,17]

There is no specific treatment for HUVS, though multiple therapies have been attempted, no consensus as to an effective therapeutic regimen has been established. Antihistamines may provide temporary relief, as was the case with the authors' patient, but as the disease advanced, the antihistamines were found to be ineffective. Nonsteroidal anti-inflammatory agents for symptomatic relief of joint pain may be helpful.[12] Life-threatening involvement of the lungs (i.e., COPD) or other organs may occur, which may require established treatments specific to such diseases, as well as periods of intense immunosuppression.[13] Thus, treatment decisions in HUVS must be individualized according to the patient's clinical

status.[68] Given the spectrum of disease from UV to the rare form of HUVS and then layered by the controversial aspect of HUVS' link to SLE, treatment options are proportionately diverse.

Some cases of HUVS respond to therapies commonly used in SLE treatment, such as low-dose prednisone, hydroxychloroquine, dapsone, or other immunomodulatory agents. Serious cases of HUVS, particularly those presenting with glomerulonephritis or other forms of serious organ involvement, may require high doses of glucocorticoids and cytotoxic agents. Cytotoxic agents of choice include the following: cyclophosphamide, cyclosporine A, azathioprine, mycophenolate mofetil, and methotrexate, alone or in combination with prednisolone, will control the disease if used long term. Other treatment options, colchicines and rituximab, may be considered if lesions are refractory.[3,4,15,28,32,36,38,68,70] Plasmapheresis and intravenous immunoglobulin (IVIG) have been proposed as valuable alternatives to be considered particularly in those cases with rapid deterioration of kidney function or crescentic glomerulonephritis.[15]

PROGNOSIS, RISK FACTORS, MORBIDITY, AND MORTALITY

Regarding UV, the prognosis is linked to the disorder with which it is associated. SLE, COPD, angioedema, and valvular abnormalities are all known to occur in association with UV and may strongly influence both quality and quantity of life.[13] In regards to the debated link between HUVS and SLE, it should be kept in mind that the overlap of the two disease processes may exhibit a relatively rapid progression and poor prognosis given that either disease can end fatally. Therefore, all patients diagnosed with HUVS should also be examined for SLE and possibly vice versa.[12]

Cigarette smoking itself appears to be a strong risk factor for developing lung disease with HUVS, which causes substantial morbidity and mortality in this disease.[3] While the decrease or absence of C1, C2, and C4 tend to favor the development of an autoimmune disease, HUVS studies regarding complement levels have indicated that the degree of hypocomplementemia, and not just the severity of clinical signs and symptoms, parallels the severity of the illness and thus a poorer prognosis.[2,13,15] It is also under question as to whether anti-C1q autoantibodies might have value in predicting outcome.[10]

DISCUSSION

Although the case follows diagnostic criteria for HUVS, the presentation of the case has two unusual components. The authors' patient experienced both cold-induced and possibly adrenergic-induced flares. Cold-induced urticarial vasculitis cases have previously been reported; however, no reports of UV induced by adrenergic-induced urticaria have been reported to the authors' knowledge. Although the standard adrenaline and norepinephrine-stimulating test eliciting similar lesional patterns of background vasoconstriction with pink macules was not performed on the patient, several reports of adrenergic urticaria from stressful situations have been reported.[71] The patient also likely exhibited features of peripheral neuropathy, which has only recently been reported.[14]

Based on the case presentation with varying complement level values and progression of symptoms noted in the patient, a proposed continuum of disease progression rather than restriction to primary or normocomplement categorization is suggested. Such a proposed mechanism suggests HUVS is a disease of progression, and that standardized monitoring of patients, even if they present with seemingly idiopathic or normocomplement HUV, may benefit from periodic monitoring for advancing disease.

Regarding the debate of the pathophysiology of HUVS and its overlapping relation to SLE, diagnostic criteria for SLE are not met in the authors' patient. The possible pathophysiology discussed persuade the view that HUVS and SLE originate from separate, but potentially overlapping, pathways allowing for possible coexistence of these two disease processes.

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