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Review Article

Hypocomplementemic Urticarial Vasculitis (HUV) and Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS); Background, Pathogenesis, Diagnosis, Laboratory Testing, Management and Treatment

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Abstract

Hypocomplementemic Urticarial Vasculitis (HUV) is defined as patients diagnosed with Urticarial Vasculitis (UV) and hypocomplementemia who have not met the threshold criteria of systemic involvement. Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS) is defined as an autoimmune disorder of six or more month's duration of urticarial with hypocomplementemia along with systemic findings. Hypocomplementemic Urticarial Vasculitis is a rare disease. The incidence and prevalence regarding this disease is still under investigation.

Pathophysiology: HUVS has not been fully described and remains controversial. The various theories include vascular damage, anti C1q antibodies, the link between HUVS and overlapping diseases such as collagen tissue disease. There are also possible mechanisms involving vascular damage to include immune complex (Type III hypersensitivity), T-lymphocyte response and anti-C1q antibody.

Diagnosis: Critical for the diagnosing of HUV and HUVS requires a skin biopsy demonstrating leukocytoclastic vasculitis. However, the clinician should suspect this diagnosis as biopsies of garden variety urticarial are not clinically indicated.

Laboratory: Lab testing is also essential to making the diagnosis. Measuring C3, C4 or CH50 in UV and its subsets allows the physician to categorize the disease ie (NUV vs HUV). Other pertinent tests include: CBC with differential, renal function and liver enzyme tests, C3, C4, C1q and CH50

Treatment and management: The use of glucocorticoids combined with dapsone, colchicine or hydroxychloroquine to aid in their systemic disease have proven to be beneficial during the initial stages in patients who have mild to moderate disease. Biological include Anakinra, Canakinumab and Rituximab and Rilonacept shown benefit with advance disease.

ABBREVIATION

HUV: Hypcomplementemic Urticarial Vasculitis; HUVS: Hypocomplementemic Urticarial Vasculitis Syndrome; NUV: Normocomplementemic Urticarial Vasculitis; CIU: Chronic Idiopathic Urticaria; EGPA: Eosinophilic Granulomatosis with Polyangiitis; UV: Urticarial Vasculitis; SLE: Systemic Lupus Erythematous

BACKGROUND

One of the many entities that providers and especially allergy and dermatology specialists evaluate in their practice includes acute and chronic urticaria [1]. Included in this group are patients that may present with urticarial vasculitis (UV) as well as associated disorders of normocomplementemic urticarial vasculitis (NUV), hypocomplementemic urticarial vasculitis (HUV), hypocomplementemic urticarial syndrome (HUVS) [2-4].

The purpose of this article is to provide the reader with updated information used to evaluate diagnosis and treat patients suspected of having Hypocomplementemic Urticarial Vasculitis (HUV) and Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS).

Hypocomplementemic Urticarial Vasculitis is a rare entity, the incidence and prevalence regarding this disease has yet to be determined. This uncertainty has remained unchanged since the 1970's as controversy within the medical literature related to classifying and nomenclature of the various manifestations to include the cutaneous, systemic, serologic features and etiology continues to evolve [5,6].

In 1977 Mathison et al., reported on two patients who were diagnosed with chronic idiopathic urticaria (CIU) afflicted with immune cutaneous vasculitis and hypocomplementemia. This group wanted to understand how complement abnormalities in patients who suffer from chronic urticarial or angioedema affect the mechanism of complement activation. They performed a prospective study on complement profiles in 72 consecutive patients with CIU. In addition to the two patients they also found an additional 10 patients who presented with CIU and hypocomplementemia. These 12 participants were then screened using plasma total complement hemolytic activity (CH50). Those with abnormalities were found to have complement activation by both the classic and alternate pathway (Table 1). Mathison et al., investigation also demonstrated majority of the subjects had circulating immune complex with classic pathway activation. Finally they noted that hypocomplementemia may give further insight into the pathophysiologic mechanism in a segment of chronic urticarial patients [7].

Since then there have been numerous case reports, studies and investigations finding patients having CIU vasculitis with hypocomplementemia. Some of these studies have also revealed these patients having glomerulonephtritis, SLE (systemic lupus erythematosus) and other associated diseases [7-12]. Increasingly through the years, it was becoming evident that criteria needed to implemented and redefine and classify the vasculitides. Employing the criteria set forth in the 2012 revised International Chapel Hill Consensus Conference the nomenclature of vasculitides including urticarial vasculitis were revised and adopted [13]. UV has currently been characterized as two subtypes based on complement levels: Normocomplementemic UV (NUV) and Hypocomplementemic UV (HUV). During this International Chapel Hill Consensus Conference in 2012, HUV was also classified as anti-C1q vasculitis [5,13].

Jachet et al., reports patients who present with hypocomplementemia urticarial vasculitis (HUV), extensively and most commonly involve the following organ systems: it includes musculoskeletal (82% of the time) ocular (56%), pulmonary (19%), gastrointestinal (18%), kidney (14%), ENT (7%), neurological (4%) [5]. Furthermore, 100% of patients had chronic urticarial, 51% had angioedema, 35% had purpura, 14% had livedo reticularis and 56% with constitutional symptoms to include asthenia, fever and weight loss [5].

Additionally, when a patient has low complement levels it portends severity of disease with systemic involvement. In the absence of hypocomplementemia these patients tend to have a milder disease and are referred as normocomplementemic urticarial vasculitis [14].

UV has been described asbotha clinical feature of another diagnosis and at other times as a distinct entity [3]. Additionally, complement levels in addition to the presence or absence of specific systemic findings aid in separating UV from HUV and HUVS [2,5].

HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS (HUV)

Classified as patients who have been diagnosed with UV and hypocomplementemia who have not met the threshold criteria of systemic involvement. Rather, these patients only have cutaneous manifestations [15]. Additionally, Jachet et al., reports a total of 55% of these patients had detectable Anti-C1q antibodies [5]. Important to note people who have HUV will present with typical cutaneous vasculitic lesions along with low complement levels and increased C1q autoantibodies [2] (Table 2).

Table 1: Clinical Details, Complement Profiles,and Immune Complexes in 12 Patients with Chronic Idiopathic Urticaria*.

Classic or Alternative Pathway Components/Activity									
Subjects	**Age in years**	**Sex**	**Months of Disease**	**CH50**	**C3H50**	**C3**	**C5**	**C6**	**C9**
Normal ŧSubjects				65-107 U/ml	3750-4250 U/ml	100-190 mg/ml	4.2-14.0 mg/ml	5.0-7.0 mg/ml	1.8-2.8 mg/ml
Group A									
1Ł	37	F	28-58	0-43	0-2000	20-80	2.2-5.0		1.2-1.8
2	42	F	72	21	1300	60	2.5	4.0	2.0
3	45	F	16	55	2870	110	4.5	3.9	3.0
4	35	M	8	55	2970	100	4.8	4.5	2.8
Group B									
5	51	F	24	30	2450	70	4.2	3.8	3.0
6	28	M	6	38	2870	115	5.2	1.5	1.5
7	26	M	12	52	2470	95	4.8	4.2	1.2
8	31	F	4	53	2390	100	3.0	2.4	3.0
9	19	M	18	60	3300	120	3.8	2.9	3.8
Group C									
10	48	M	7	53	2280	98	3.6	2.8	1.5
11	28	F	36	60	2930	82	4.0	3.5	2.0
12	24	M	24	65	3100	103	3.1	4.0	3.1

Table 2: Adapted from: Hamad, Ahmad et al., Annals of Allergy, Asthma &Immunology, 2016 Volume 118, Issue 4, 394 – 398.

Disease associations	Chronic Urticaria	NUV	HUV	HUVS
Urticarial lesions	Last few hours, pruritic	Last > 24hrs, burning or pruritic, induration, pigmentation	Last > 24hrs, burning or pruritic, induration, pigmentation	Last > 24hrs, burning or pruritic, induration, pigmentation
Fever and acute-phase response	No	No	Positive or negative	Positive or negative
Joint	None	None	Arthalgias or arthritis	Arthalgias or arthritis
Asthma or lung disease	None	None	Asthma like disease	COPD, pleurisy, laryngeal edema
Bone pain or bone remodeling	Negative	Negative	Negative	Negative
Lymphadenopathy	Negative	Negative	Negative	Positive or negative
Gastroentestinal disease	Negative	Nausea, vomiting, diarrhea, abdominal pain	Nausea, vomiting, diarrhea, abdominal pain	
Heart disease	Negative		Negative	Ischemic heart disease, serositis, tamponade and valvular disease
Ocular disease	Angioedema	Angioedema	Angioedema	Uveitis, choroidopathy, Episcleritis
Neurologic disease	Negative	Negative	Negative	Myopathy, seizures, transverse myelitis, mononeuritis, pseudotumorcerebri
Renal disease	Negative	Negative	Negative	Glomerulonephritis, hematuria and proteinuria
Complement abnormalties	Negative	Negative	Low C1q, low C3/4, anti-C1q antibody	Low C1q, low C3/4/CH50,, anti-C1q antibody
Serum protein electrophoresis	Normal	Normal	Polyclonal	Polyclonal
Skin Biopsy	Typical urticarial changes	Vasculitis is seen: Pathologic findings include fibrinoid changes in blood vessel, eosinophilic infiltration, leukocytoclastic vasculitis, erythrocyte extravasation, neutrophilic infiltration and dermal edema.	Vasculitis is seen: Pathologic findings include fibrinoid changes in blood vessel, eosinophilic infiltration, leukocytoclastic vasculitis, erythrocyte extravasation, neutrophilic infiltration and dermal edema.	Vasculitis is seen: Pathologic findings include fibrinoid changes in blood vessel, eosinophilic infiltration, leukocytoclastic vasculitis, erythrocyte extravasation, neutrophilic infiltration and dermal edema.

Abbreviation: HUV: Hypcomplementemic Urticarial Vasculitis, HUVS: Hypocomplementemic Urticarial Vasculitis Syndrome, NUV: Normocomplementemic Urticarial Vasculitis

Associated symptoms in patients with HUV include gastrointestinal pain, rheumatological symptoms of arthralgias and arthritis and asthma symptoms may represent extracutaneous manifestations. Hamad et al., points out this overlap can be missed diagnosed for systemic lupus erythematosus (SLE), however antinuclear antibodies are less likely to be found on laboratory studies [2].

HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS SYNDROME (HUVS)

Classified as an autoimmune disorder of six or more months duration of urticarial with hypocomplementemia along with systemic findings as noted above [16] (Table 2).

Jachet et al., also reports that HUV in the 57 patients their group evaluated in a retrospective study found that 75% had isolated HUV. Also, 25% had an associated systemic disease and 68% had systemic HUV [5].

HUVS is a more severe systemic subtype of UV. HUVS is more commonly seen in women and results in cardiopulmonary, neurological and renal disease as well as serositis. Complications of HUVS include arthritis, cardiopathy to include and not limited to pericarditis and valvular stenosis. IgG4-related disease has also been associated with HUVS and is a new and evolving entity [2].

Wakamatsu et al., in 2011 reported a woman who had clinical symptoms of recurring gastrointestinal pain, purpuric urticarial lesions along with labs revealing her to be hypocomplementemic and skin biopsies revealing leukocytoclastic vasculitis. Lab and pathology studies revealed the patient to have IgG4 level in excess of 1,000 mg/dl along with skin biopsy revealing IgG4 deposition in her skin. Additionally, her lymph nodes contained IgG4-positive cells and this finding suggests association between IgG4-related disease and HUVS [17]. Tokura et al., in 2014 notes that use of rituximab may be a treatment for both the HUVS and IgG-related disease [18].

In 2016 Takao et al., reported on a woman who had hypocomplementemic urticarial vasculitis with IgG4-related disease her level was 637 mg/dl (normal range: 4.8-105 mg/dl) in a total serum IgG of 2,176 mg/dl. The patient also had systemic involvement to include salivary gland swelling, lymphadenopathy with infiltration of IgG4-producing plasma cells, renal involvement causing interstitial nephritis and thyroid nodule [19]. Somichsen et al., in 2016 noted that DNAS1L3 mutations have been found in one case of a person with HUVS [20].

PATHOPHYSIOLOGY

Buck et al., in 2012 reported the pathophysiology of HUVS has not been fully described and remains controversial. The various theories include vascular damage, anti C1q antibodies, the link between HUVS and overlapping diseases such as collagen tissue disease. There are also possible mechanisms involving vascular damage to include immune complex (Type III hypersensitivity), T-lymphocyte response and anti-C1q antibody [21].

It has been hypothesized IL-1 may play a role in pathogenesis of UV. This is based on both theoretical observations and also features of UV that are found in auto inflammatory disorders where IL-1 may be implicated as contributing to UV. Also using IL-1 inhibitors such as anakinra (IL-1 antagonist) and canakinumab (monoclonal antibody against IL-1**β**) that is a long acting fully humanized monoclonal anti-IL-1 beta antibody, reported to successfully treat UV [22,23].

Other factors contributing to HUVS developing in patients include genetic factors; in a study with 2 families who had autosomal-recessive HUVS found that mutations in DNASE1L3 were associated with a familial form of HUVS and HUVS associated with SLE [24].

In 2016 Hamad et al., reported that in genetically predisposed patients exposed to certain environmental antigens or self-antigen, immune complex formation and vessel wall deposits produced by complement activation herald the pathophysiologic features of UV. Additionally, C1q auto antibodies may be instrumental in immune complex formation. Complement activation results in C3a and C5 a production in turn causes mast cells to activate resulting in degranulation then leading to urticarial cutaneous lesions. Using the Gell Coombs classification, UV is classified as a Type III hypersensitivity reaction [2,3].

DIAGNOSIS

Critical for the diagnosing of HUV and HUVS requires a skin biopsy. However, the clinician should suspect this diagnosis as biopsies of garden variety urticarial are not clinically indicated. The features that help differentiate Chronic Idiopathic Urticaria from HUV and HUVS include CIU is mainly pruritic, lasts between 8 and 24 hours, and there are no residual effects. In HUV and HUVS the urticarial lesions last greater than 24 hours, burning or pruritic with pigmentation and in duration, thus these lesions warrant biopsy. On biopsy the pathology will likely reveal certain clues to suggest HUV and HUVS and this includes: leukocytoclastic vasculitis, eosinophilia and neutrophilin filtration. It may also reveal erythrocytes that are extravagated, dermal edema to include fibrotic changes of the blood vessel endothelium [2-4].

Hamad et al., reports employing Immunofluorescence is likely to reveal immunoglobulin or complement component deposition (C1q, C3 or C4) to include fibrinogen. Whereas Direct Immunofluorescence may show basement membrane and/or per vascular zone deposits of immunoglobulins, complement or fibrin using this staining technique. Hamad et al., state if the pathology does not reveal leukocytoclastic vasculitis and there is continued concern for HUVS then subsequent biopsy of a new lesion is then justified and warranted [2].

LABORATORY TESTING

Lab testing is also essential to making the diagnosis. Measuring C3, C4 or CH50 in UV and its subsets allows the physician to categorize the disease as previously mentioned (NUV vs HUV). Lab testing also provides critical prognostic information of the disease and is useful in monitoring thus allowing the physician when necessary to make needed changes to the treatment plan. The lab testing for UV is performed to assess for systemic disease rather than it being diagnostic. Pertinent tests include: CBC with differential, renal function test, liver enzyme tests, C3, C4, C1q and CH50 as well as urinalysis to determine if patient has presence of glomerulonephritis, these studies include evaluation for proteinuria, erythrocytes or leukocytes (2,7,21). Additionally, Hamad and Buck recommend testing for Hep B surface antigen, Hepatitis C, ANA panel, dsDNA, ANCA (PR3 and MPO-ANCA), Anti-Ro, La, Sm and RNP antibodies rheumatoid factor and anti-cyclic citrullinated peptide, cyroglobulins and cryofibrinogens to evaluate other causes [2,21].

Hamad et al., also cites there are several autoantibodies can be found in patients with HUV and HUVS that are directed against C1q, interleukin (IL) 1, IgE, high affinity IgE receptors and thyroid microsomal antigens [2,3,21]. C1q is the most studied and best characterized. C1q acts to dispose of apoptotic cells and its cellular remnants. Antibodies to C1q have also been implicated in proliferative lupus nephritis as well as UV (100% of the time). These antibodies have also been found in Felty syndrome, rheumatoid arthritis, Sjogren syndrome, IgA nephropathy and membranoproliferative glomerulonephritis [2].

Hamad et al., note that 5% of healthy population may express these antibodies. In a patient with UV the lab finding of C1q auto antibodies signals and is highly suspicious for HUV and HUVS.

MANAGEMENT AND TREATMENT

In moderate disease prednisone and colchicine may be effective to gain control of the disease [25,26]. It is also of utmost importance that patients be carefully monitored for rising levels of paraprotein (also known as monoclonal gammopathy). Monitoring of paraproteins can be accomplished with an SPEP. Inflammatory markers such as CRP and ESR are also obtained to assess for signs of inflammation. Additional monitoring is needed to assess for possible complications to include amyloidosis, SLE, Sjogrens Syndrome, COPD/Asthma, serum sickness, renal, end organ damage and lymphoproliferative diseases is critical. Treatment and intervention includes using prednisone and colchicine can be effective to gain control of the disease [25,26]. The use of glucocorticoids combined with dapsone, colchicine or hydroxychloroquine to aid in their systemic disease have proven

Table 3: Adopted from Ghazanfar MN et al. Dermatological Medicine, vol. 2015, Article ID 576893, 3 pages, 2015. doi:10.1155/2015/576893.

Author	Year	Case	Omalizumab Dose	Omalizumab Effectiveness
Del Pozo et al [33]	2012	51 y/o female diagnosed with SLE and UV. Patient was initially treated with oral steroids, antihistamines and azathioprine	Dose not known. Investigators used weight and IgE levels	Improved significantly with resolution of lesions. She experienced no hives, nor pain
Varricchi et al. [34]	2012	44 y/o female diagnosed with asthma, EGPA and UV. Oral steroids, antihistamines, azathioprine and cyclosporine proved ineffective	300 mg SC every 2 weeks	Symptoms Improved significantly
Diez et al. [35]	2013	3 women with chronic spontaneous urticarial with autoimmune and pressure component with vasculitis. Using antihistamines, cyclosporine and leukotriene receptor antagonists yielded no improvement	150 mg SC every 4 weeks (2 patients) and 300 mg SC every 4 weeks (1 patient)	Full remission of symptoms in all patients
Sussman et al [36]	2014	One subject with nondisclosed gender nor age who had urticarial vasculitis	150 mg SC every 4 weeks.	Full remission of symptoms. Details were not provided.
Ghazanfar, et al [32]	2015	68 y/o male who developed UV. Initially treated with oral prednisolone taper and then developed recurrence with tapering dose. Then treated with dapsone with no significant improvement. Then switched to omaluzimab	300 mg SC every 4 weeks	After 1 month complete remission and. Treatment started 12/2014 and by 07/2015 continued to be treated with omaluzimab.

Abbreviation: EGPA: Eosinophilic Granulomatosis with Polyangiitis SC: subcutaneous, SLE:Systemic Lupus Erythematous, UV: Urticarial Vasculitis.

to be beneficial during the initial stages in patients who have mild to moderate disease [25,26]. Usually glucocorticoids and dapsone are used in combination and patients need to be evaluated for G6PD deficiency if dapsone is going to be used. [25,26].

Additionally, biological agents that interrupt the IL-1 pathway may also be of benefit. These include anakinra (monoclonal recombinant IL-1 receptor antagonist protein [22]. Canakinumab (monoclonal antibody against IL-1β) has also been shown to be beneficial [23]. Rituximab (monoclonal antagonist directed against the CD20 molecule on B lymphocytes) and rilonacept (a dimeric fusion protein that acts as a decoy Il-1 receptor binding up IL-1) have been shown to be of benefit [2].

Mycophenolatemofetil has also been shown to be beneficial [27], methotrexate used as steroid sparing is also effective [28]. Azathioprine in combination with prednisone has shown to have significant improvement in patients with nephropathy and well as skin involvement in patients with HUVS [9,10]. Cyclosporine has also been effective in treating HUVS especially in patients suffering from pulmonary and renal involvement and used to taper patients off glucocorticoids [11,12].

In 2017 Aurich et al., reported that to the best of their knowledge their group is the first to publish using omalizumab to treat a patient with HUVS and was found to be ineffective. Their patient with HUVS along with cutaneous involvement did not improve with antihistamines, mycophenolatemofetil, cyclosporine oromalizumab. Aurich et al., theorize the pathogenesis of urticarial cutaneous lesions seen in HUVS may have different biochemical characteristics vs chronic spontaneous urticarial [29].

In past trials using omalizumab to treat chronic urticaria, omalizumab have been shown to be effective and is safe [30,31]. To date there continues to be no prospective clinical investigations using omalizumab to treat urticarial vasculitis (UV). There have been 5 case reports citing omalizumab might have benefit for urticaral vasculitis [32]. Details of these case reports are shown in Table 3. The challenge for investigators is to elucidate the mechanism of action for omalizumab in treating CIU, let alone UV or HUV has yet to be determined. However based on various case reports omalizumab does appear to have a beneficial effect in UV.

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