

# Hypocomplementemic Urticarial Vasculitis with Crescentic Glomerulonephritis, Interstitial Nephritis and Small Vessel Vasculopathy: Case Report and Mini-Review

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## Abstract

Hypocomplementemic urticarial vasculitis (HUV) is the rare immune complex vasculitis, affecting small vessels and associated with anti-C1q antibodies, presenting with urticaria and hypocomplementemia. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common in HUV. HUV may present as an idiopathic disease or be a part of systemic autoimmune or autoinflammatory condition, like systemic lupus erythematosus, arthritis-hives-angioedema (AHA) syndrome, cryoglobulinemic vasculitis, Schnitzler syndrome, Cogan's syndrome and Muckle–Wells syndrome. Renal involvement includes proteinuria, sometimes of nephrotic range, hematuria and usually moderately impaired kidney function. Various pathology variants were found in patients with HUV: mesangial proliferative, membranoproliferative, focal proliferative, membranous, minimal change, crescentic and severe sclerosing proliferative glomerulonephritis. Interstitial nephritis and C1q-associated small vessel vasculopathy are poorly described. Here we present a case of HUV with combined renal damage - crescentic glomerulonephritis, interstitial nephritis and small vessel vasculopathy, successfully treated with immunosuppressant's, and discuss the differential diagnostics of HUV.

**Keywords:** Small vessel vasculitis; Hypocomplementemia; Anti-C1q antibodies; Kidneys

## Background

Urticarial vasculitides are discriminated into normocomplementemic urticarial vasculitis (NUV) and hypocomplementemic urticarial vasculitis (HUV). Both can be associated with systemic symptoms like angioedema, arthralgias, abdominal or chest pain, fever, pulmonary disease, renal disease, episcleritis, uveitis, and Raynaud phenomenon [1]. However, only HUV, the rare immune complex small vessel vasculitis (SVV), was included to the current classification in the “2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides” [2]. According to this nomenclature consensus HUV is vasculitis, accompanied by urticaria and hypocomplementemia, affecting small vessels and associated with anti-C1q antibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common in HUV. This nomenclature identifies variety of other SVV, namely ANCA-associated, cryoglobulinemic, and Ig-A vasculitides, and anti-GBM disease, and also variable vessel vasculitis (VAV) - Behcet's disease and Cogan's syndrome, both less frequently affecting kidneys.

On the other hand, literature search shows that term HUV is used along with the term hypocomplementemic urticarial vasculitis syndrome (HUVS) [3-7]. HUVS is also referred as McDuffie syndrome, as it was first described by McDuffie at all in 1973 [8].

Some authors consider HUV and HUVS as different entities [7]: 1) HUV may present as idiopathic or secondary, which is often associated with a systemic inflammatory disease and characterized by certain overlapping features of Systemic lupus erythematosus (SLE) including low serum complement, autoantibodies, and facial dermatitis. 2) HUVS is a rare, distinct, and potentially severe form with multiorgan involvement. Its etiology and link with other diseases are still unknown. It is characterized by persistent urticarial skin lesions, leukocytoclastic vasculitis, and a variety of systemic manifestations, including severe angioedema, laryngeal edema, ocular inflammation, arthritis, arthralgia, obstructive lung disease, recurrent abdominal pain, and glomerulonephritis. HUVS hardly can be regarded as a particular form of SLE, as anti-nuclear antibodies (ANA) are absent in the number of reported cases.

Suggested differentials are as follows [7]: 1) Muckle-Wells syndrome - genetic mutation responsible for protein cryopyrin coding, presents with urticarial, deafness, and renal amyloidosis. 2) Cogan's syndrome - results from antibody formation against rheovirus-III infection, presents with interstitial keratitis and hearing loss. 3) Schnitzler syndrome - presents with urticaria and monoclonal IgM gammopathy along with lymphadenopathy, arthralgia and fever, 4) AHA-syndrome - poorly understood entity presenting with arthritis, hives, and angioedema, 5) SLE, 6) Mixed cryoglobulinemias and 7) Sharp syndrome (mixed connective-tissue disease).

Other authors indicate that HUVS presents as the most severe part of urticarial vasculitis continuum [5]: 1) The mild form of disease with distinct urticarial exanthema and slight or absent systemic manifestations without hypocomplementemia - NUV, 2) Various

special forms: AHA syndrome, Schnitzler syndrome, Cogan's syndrome, Muckle-Wells syndrome and 3) Life-threatening systemic vasculitis with hypocomplementemia and only mild urticarial skin lesions – HUVS.

Anyway, all authors refer to diagnostic criteria, suggested by Schwartz and McDuffie in 1982 [9]:

### Major criteria

Chronic urticarial exanthema, Hypocomplementemia.

### Minor criteria

Leukocytoclastic vasculitis, Arthralgia and arthritis, Uveitis or episcleritis (or conjunctivitis), Glomerulonephritis, Abdominal pain, Positive C1q antibody.

Renal involvement is described as usually mild, but dialysis may be required [10]. The most frequent clinical findings are proteinuria, sometimes of nephrotic range, and hematuria [3]. In the review, published in 1994 [11] and including data from 18 kidney biopsies, the following various pathology variants were described: mesangial proliferative, membranoproliferative, focal proliferative, membranous, minimal change, and severe sclerosing proliferative glomerulonephritis. Crescentic glomerulonephritis was also found at least in three patients with HUVS [12-14]. Some authors indicate, that the pattern of renal changes in HUVS is apparently indistinguishable from SLE nephropathy [4], based on the observation that approximately 30% 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 [15]. However, not all patients with HUVS meet diagnostic criteria for SLE.

Treatment for HUVS is controversial, antihistamines, hydroxychloroquine, colchicine glucocorticoids, methotrexate, azathioprine, cyclophosphamide, micophenolate mofetil, cyclosporine and rituximab are used depending on the disease severity, plasmapheresis and intravenous immunoglobuline had been proposed for cases with crescentic glomerulonephritis [6,7,15].

Here we present a case of hypocomplementemic urticarial vasculitis with unusual renal involvement.

## Case Report

Caucasian female 52 years old admitted to the ER of our clinic March 5 2016.

### Main complains

Abdominal pain, nausea, decreased appetite, weight loss.

### Previous medical history

8 pregnancies: 6 miscarriages (consanguine marriage) and 2 successful deliveries of healthy babies. Age 24 – single episode of renal colic with spontaneous lithecbole. Since age 30 – gradual hearing loss, diagnosed with bilateral sensorineural deafness, currently using earphones. She is taking antidepressants for many years, and denies food allergy, alcohol intake, tobacco smoking, jaundice, tuberculosis, diabetes and arterial hypertension.

### Family history

Unremarkable, no consanguine marriages in the family.

### History of present illness

September 2015 she developed unexplained urticarial rash, mostly on her arms and chest, slightly itching, which resolved spontaneously. Since that time urticaria recurred with irregular intervals. Same time she developed intermittent eye redness and smarting eyes. Her appetite decreased and she lost about 10 kilos of weigh. A day before admission she felt abdominal pain and nausea and arrived to the ER.

### At admission

Conscious, alert, oriented, slightly depressed. Body temperature 36.7°C, RR 16 per minute, pulse regular 68 per minute, BP 130/80 mm Hg. Obese (BMI 32). Skin dry, clear, normally colored, no edema. Eyes clear. HEENT and neck otherwise normal. Single palpable left axillary lymph node. Joints: no swelling, movements not restricted. No breast nodularity. Lungs: clear. Heart: regular rate and rhythm, no murmur. Tongue dry, clean. Abdomen soft, non-tender, painful in epigastria and right upper quadrant, bowel sounds normal. Liver, spleen and kidneys not felt. Urination and stools normal.

Work-up in the ER found moderate sideropenic anemia (Hb 8.7 g/dL, serum iron 7.9 µmol/L), mild elevation of AP, AsAt, AlAT, GGT and CK, serum creatinine 205 µmol/L and blood urea 12.4 mmol/L. Other blood count and blood chemistry parameters were normal. Urinalysis showed SG 1020, proteinuria 0.5 g/l and microhematuria 40-50 RBC/hpf. Plain chest and abdomen X-ray - unremarkable. Abdomen, kidneys and pelvis ultrasound found only multiple small gallstones. Esophagogastroduodenoscopy showed mild gastritis, colonoscopy – nothing but dolichosigmoid.

### Diagnosis at admission

She was diagnosed with calculous cholecystitis and CKD, referred to surgery and started on crystalloid IV infusions, spasmolytic's and antiemetic's.

### Further course and work-up

Few days later her abdomen pain and nausea resolved, her liver enzymes normalized, creatinine decreased to 179 µmol/L, other routine labs did not changed much, but she complained recurrence of skin rash (Figure 1), eye redness and lacrimation.

Dermatologist diagnosed recurrent urticaria and recommended antihistamine's and ordered IgE test.

Ophthalmologist diagnosed recurrent iridocyclitis and prescribed eye drops.

ENT specialist confirmed chronic sensorineural deafness.

Infections screening: RPR-test for Treponema Pallidum, HBsAg, anti-HCV and anti-HIV-antibodies negative, tuberculin skin test – all negative.

C-reactive protein: 2.8 mg/L (normal range 0-6)

Hormones: T3, T4, TSH and PTH – otherwise normal.

Immunoglobulin E: 20.6 U/mL – normal.

Urine culture: negative.



**Figure 1:** Urticarial rash on the chest and shoulder.

Thyroid gland and peripheral lymph nodes ultrasound: thyroid gland normal, multiple neck, axillary and inguinal lymph nodes, enlarged maximum to 47-66 mm (left axillary).

Hematologist suspected lymphoproliferative diseases or metastatic lymphadenopathy, performed bone marrow biopsy and recommended lymph node biopsy.

Bone marrow smear and bone marrow biopsy with immunohistochemistry ruled out lymphoproliferative disease.

Left axillary lymph node biopsy with immunohistochemistry showed nothing but follicular hyperplasia.

Nephrologist suspected systemic or autoinflammatory disease, ordered additional tests, and patient was referred to nephrology for kidney biopsy.

### Further work-up in nephrology unit

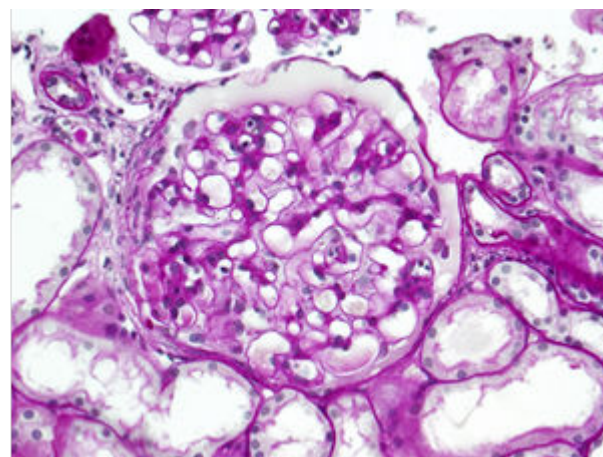
**Autoimmune and paraproteinemia screening:** pANCA, cANCA, rheumatoid factor, IgA and IgM within normal range, serum and urine immunoelectrophoresis did not found monoclonal secretion, cryoglobulines ++ (re-test negative), anti-ds-DNA antibodies 24.3 U/mL (normal range  $\leq 20$ ), ANA - 1/320 (normal range  $\leq 1/160$ ), IgG 24.0 g/L (normal range 7-16), IgG4 subclass 3.8% (normal range 4.0-5.0%), C3 complement 0.63 g/L (normal range 0.9-1.8), C4 complement 0.073 g/L (normal range 0.1-0.4), anti-C1q antibodies > 100 U/ml.

### Kidney Biopsy

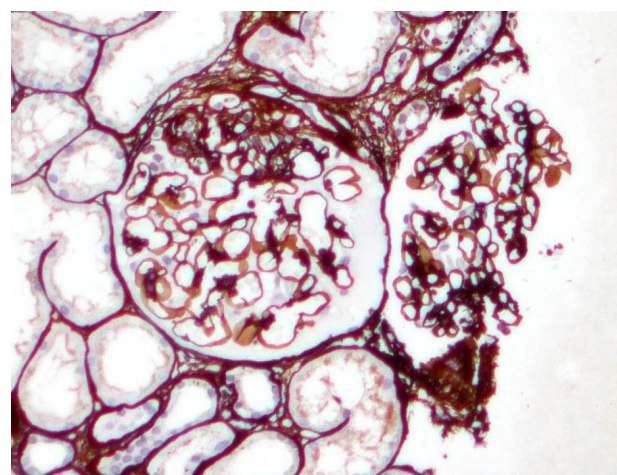
#### Light microscopy

Sections of formalin fixed paraffin-embedded tissue were stained with H&E, Masson's trichrome, periodic acid-Schiff, Jones' silver and Congo red. 25 glomeruli were found, 4 (16%) of them totally sclerosed, the rest slightly enlarged, capillary walls single-contour. Mild diffuse mesangial widening due to mesangial matrix expansion, and mild focal

and segmental mesangial hypercellularity (Figure 2). Glomerular basement membrane is thin, regularly impregnated by silver stain. 3 (12%) glomeruli with segmental nonspecific sclerosis and synechie formation. 6 (24%) glomeruli contain segmental fibrous crescents (Figure 3). Tubular brush border is almost well preserved, tubular lumens contain seldom RBC and protein casts. Mild focal tubular atrophy with thickening and shrinking of tubular basement membrane (20%). Mild focal interstitial fibrosis (20%). Arteriolar and small arteries walls moderately thickened due to muscle layer hypertrophy and irregular insudative changes. Moderate intimal fibrosis of middle arteries walls. Congo red staining was negative.



**Figure 2:** Light Microscopy (PAS x200) Mild segmental mesangial widening with slight hypercellularity; sporadic endocapillary mononuclears.



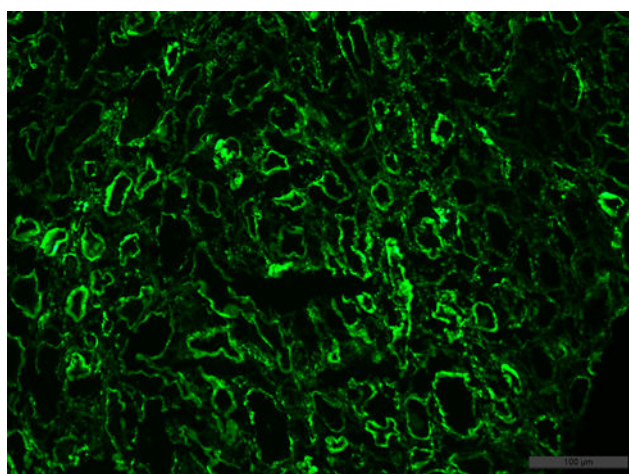
**Figure 3:** Light Microscopy (Jones' silver x100) Segmental fibrous crescent in upper glomerulus and non-specific segmental sclerosis in the lower glomerulus.

Immunofluorescence on unfixed cryo-sections with fluorescein conjugated anti IgA, IgG, IgM, C1q, C3, fibrinogen,  $\lambda$  and  $\kappa$  light chains antibodies showed diffuse granular expression of IgG, C3, C1q and  $\lambda$  light chains (+) in tubular basement membranes (Figure 4).

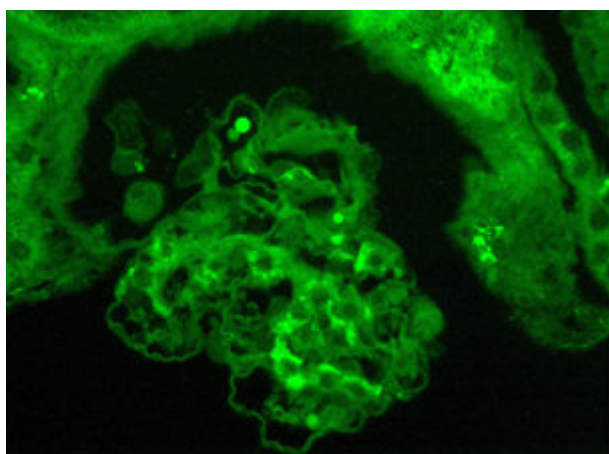
Immunofluorescence on formalin fixed/paraffin embedded sections with FITC-conjugated anti IgA, IgG, IgM, C1q, C3, fibrinogen,  $\lambda$  and  $\kappa$  light chains antibodies showed diffuse granular mesangial and hilar areas expression of IgG, C3, C1q,  $\lambda$  and  $\kappa$  light chains (++) and diffuse granular expression of C1q (++) in the arterioles and small arteries walls (Figures 5-7).

#### Pathologist's conclusion

Pathology findings were summarized as diffuse immune complex glomerulopathy with mild mesangial hypercellularity, fibrous crescents and secondary global and segmental glomerulosclerosis, immune complex tubulointerstitial nephritis and mild interstitial fibrosis, and diffuse small vessel vasculopathy with C1q expression, compatible with the hypocomplementemic urticarial vasculitis diagnosis.



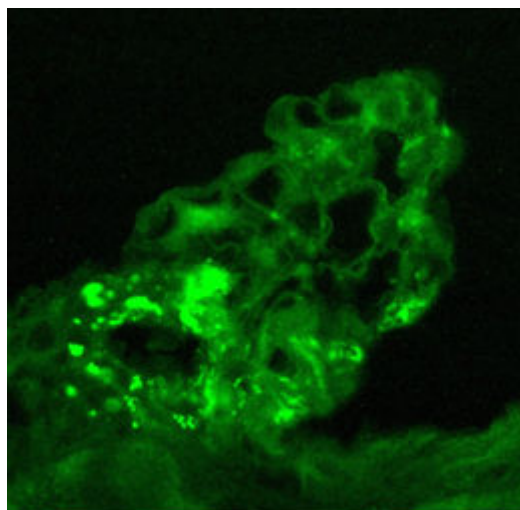
**Figure 4:** Immunofluorescence (x 200) Moderate granular expression of C1q in tubular basement membranes.



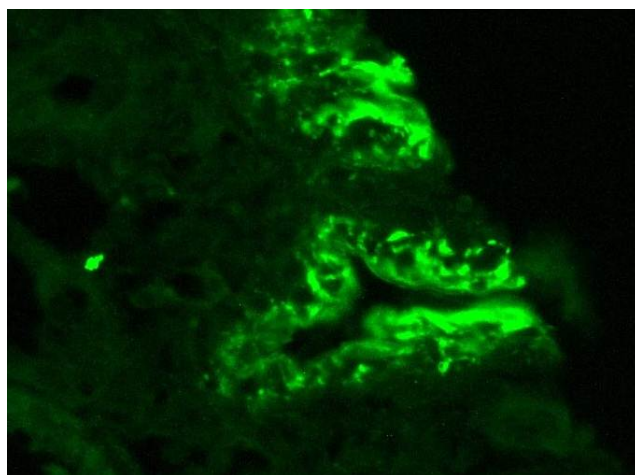
**Figure 5:** Immunofluorescence (x 200) Moderate granular mesangial expression of C1q.

#### Final Diagnosis, Treatment and Follow-up

Patient was diagnosed with HUV and started on two methylprednisone "pulses" 250 mg each, followed by oral prednisone 30 mg/day, her urticaria and iridocyclitis rapidly resolved, and her serum creatinine decreased to 140  $\mu\text{mol/L}$ . She was treated with steroids only in outpatient setting for 2 months, her urticaria did not recur, she had no proteinuria and hematuria either, and her serum creatinine was 136  $\mu\text{mol/L}$ .



**Figure 6:** Immunofluorescence (x 200) Moderate granular expression of C1q in the glomerular hilar area.



**Figure 7:** Immunofluorescence (x 200) Moderate granular expression of C1q in the small artery wall.

Azathioprine 100 mg/day was added, and prednisone was slowly tapered to 20 mg/day. At the latest follow-up visit in August 2016 she was doing well, no signs of skin or eye relapses, her anemia was compensated (Hd 12,0 g/dL), urinalysis became normal, and her serum creatinine 123  $\mu\text{mol/L}$ . She was advised to continue prednisone 20 mg/day and azathioprine 100 mg/day.

## Discussion

At the first nephrologist consult, given skin, eye, ears and kidney signs and symptoms, which were not compatible to the history of single episode of renal colic, systemic autoimmune or autoinflammatory disease was suspected. Combination of chronic recurrent skin rash, ocular inflammation, deafness and urinary symptoms with decreased renal function, suggested differential diagnostics between SLE, AHA-syndrome, ANCA-associated vasculitis, cryoglobulinemic vasculitis, Schnitzler syndrome, Cogan's syndrome, Muckle–Wells syndrome and HUV.

AHA-syndrome was ruled out based on the absence of arthritis/arthralgia, Cogan's syndrome due to the absence of keratitis (despite hearing loss). The results of autoimmune and paraproteinemia screening allowed ruling out also ANCA-associated vasculitis and Schnitzler syndrome, and showed very low C3 and C4 complement levels, high titers of anti-C1q-antibodies, along with mild elevation of ANA and anti-DNA antibodies. Those were suggestive for HUV, either idiopathic or as a part of systemic disease.

In order to prove the diagnosis kidney biopsy was performed and showed deposition of C1q in all compartments of renal parenchyma. Other immune findings were IgG, C3 and  $\lambda$  and  $\kappa$  light chains in the mesangium and tubular basement membranes, but not in small arteries walls. No IgA and IgM deposits were found either.

Based on the presence of two major (chronic urticaria and hypocomplementemia) and four minor (ocular inflammation, abdominal pain, glomerulonephritis and positive anti-C1q-antibodies) criteria HUV was diagnosed. Muckle–Wells syndrome was not confirmed, as there was no proof for renal amyloidosis in the pathology findings. The patient did not meet SLE diagnostic criteria, and kidney biopsy data were not compatible with the diagnosis of lupus-nephritis. Finally the diagnosis of cryoglobulinemic vasculitis, which was supported by positive cryoglobulines serum test, also was not confirmed, as the re-test for cryoglobulines was negative and kidney pathology did not show characteristic features of the cryoglobulinemic nephritis.

All those lead us to the diagnosis of idiopathic HUV. For this particular case and generally for the idiopathic variants we stand for the term HUV, used in the 2012 Nomenclature of Vasculitides [2]. The term HUVS probably better should be used in the context of systemic diseases with the characteristic features of HUV.

Of interest, renal damage in our patient was presented predominantly by impaired kidney function with very moderate urinary abnormalities, and kidney biopsy showed not only C1q-driven crescentic glomerulonephritis, which was described earlier [12,13], but also interstitial nephritis and small vessel renal vasculitis. That was proven by the features of tubulointerstitial nephritis and small vessel vasculopathy with predominance of C1q in tubular basement membranes and small vessels walls. That pathology pattern is rarely described; we found only one description of crescentic glomerulonephritis, accompanied by interstitial and small vessel deposition of C1q in the patient with overlapping SLE and HUVS [14].

Treatment with moderate dose steroids followed by azathioprine allowed achieving remission of skin and eye symptoms, resolution of urine abnormalities and improvement of kidney function.

## Conclusions

HUV should be considered in patients, presenting with systemic features and skin, eye, ears and kidney involvement, those patients need testing for wide spectrum of autoimmune markers, including anti-C1q antibodies and also kidney biopsy. Once patients meet the diagnostic criteria for HUV, that demand differential diagnostics with variety of autoimmune and autoinflammatory diseases, in order to discriminate idiopathic HUV from HUVS as a part of SLE, AHA-syndrome, cryoglobulinemic vasculitis, Schnitzler syndrome, Cogan's syndrome and Muckle–Wells syndrome. Immunosuppressive treatment for HUV allows achieving remission of extra-renal manifestations and kidney disease.

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