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SARS-CoV-2 Infection as a Stimulus to Upgrade from a Chronic Spontaneous Urticaria to an Hypocomplementemic Urticarial Vasculitis Syndrome

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Introduction

Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS, McDuffie syndrome) is a rare and immune-complex mediated small vessel vasculitis [1], part of the Urticarial Vasculitis (UV) spectrum disease, and consisting of hypocomplementemia, leukocytoclastic vasculitis, systemic involvement, and recurrent skin lesions resembling those of Chronic Spontaneous Urticaria (CSU) [2,3].

The epidemiology of HUVS is unknown due to its rarity; recent data evaluate an incidence of 0.5/100,000 inhabitants [4]. Interestingly, up to 27% of patients who initially present with typical spontaneous urticarial wheals later will be diagnosed with UV [2,5].

In most cases, HUVS is idiopathic, even though it can be related to viral infections, drug hypersensibility, malignancy or connective tissue diseases, mainly Systemic Lupus Erythematosus (SLE) [2,3]. Notably, HUVS and SLE share both pathophysiological and clinical aspects. Indeed, almost 10% of SLE patients present with HUVS, and more than 50% of HUVS patients are diagnosed with SLE over time [6].

HUVS typically manifests with recurrent, burning, and painful urticarial lesions lasting more than 24 with a residual ecchymotic hyperpigmentation after resolution [7,8]. Intermittent angioedema occurs in up to 50% of patients [9].

Typical systemic manifestations include arthralgias or arthritis, gastrointestinal, and constitutional symptoms. Kidney involvement occurs in up to 50% of HUVS patients [10]. Pulmonary damage is seen in almost 50% of the patients. About 30% of patients show ocular involvement [8]. Far rare are neurological and cardiac complications [11].

Main, although nonspecific, laboratory findings of HUVS are leukocytosis and/or anemia, increased Erythrocyte Sedimentation Rate (ESR), polyclonal hypergammaglobulinemia, and Rheumatoid Factor (RF) and Antinuclear Antibody (ANA) positivity in absence of anti-double-stranded DNA autoantibodies (anti-dsDNA). Complement consumption - low serum levels of C1, C1q, C4, C3, and CH50/100 - and anti-C1q antibody positivity are present in all the HUVS patients [8,9].

Skin biopsy represents the gold standard for the diagnosis of cutaneous vasculitis. The histological analysis of the urticarial lesion typically displays leukocytoclastic vasculitis. The neutrophilic-dominant infiltrate is associated with fibrinoid necrosis, interstitial erythrocyte extravasation and endothelial swelling. Rarely, a lymphocytic/eosinophilic infiltrate is found. The direct immunofluorescence test shows the deposition of immunoglobulins, immune complexes and complement in the vessel walls and along the dermal-epidermal junction [2,8,12].

HUVS can be diagnosed by applying Schwartz-Mc Duffie´s criteria (Table 1): At least two major and two minor criteria and the exclusion of a more plausible autoimmune disease are needed for the diagnosis of HUVS [9,13].

HUVS exclusion criteria include elevated cryoglobulinemia (cryocrit >1%), a high titer of ANA or anti-dsDNA antibody, anti-Smith antibody positivity, active hepatitis B virus infection, decreased C1 inhibitor level, or an inherited complement deficiency [8,14].

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Table 1: HUVS diagnostic criteria.

Major criteria	• Recurrent urticaria more than 6 months
	• Hypocomplementemia: Low levels of C1q, C3, and C4
Minor criteria	• Venulitis on skin biopsy
	• Arthralgias or arthritis
	• Glomerulonephritis
	• Ocular inflammation
	• Abdominal pain
	• Positive C1q-p test by immunodiffusion with decreased C1q level

In case of a chronic urticarial rash with systemic symptoms, it is mandatory to exclude other conditions that may resemble HUVS, including CSU, autoinflammatory syndromes, mast cell disorders, viral infections, and connective tissue diseases [2,15].

Regarding HUVS therapy, no drugs have yet been approved, and a treatment consensus is still missing. Currently, treatment options are tailored to the severity of systemic involvement. For severe disease, a high dose of Glucocorticoids (GCs) and cytotoxic agents are needed to control the potentially life-threatening condition. Afterwards, other immunosuppressive/immunomodulant drugs, including hydroxychloroquine, methotrexate, azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil, can be adopted. In the presence of refractory disease, plasmapheresis or intravenous immunoglobulins may be necessary. Antihistamines and nonsteroidal anti-inflammatory drugs mainly play a role in relieving symptoms, such as itch or constitutional complaints and arthralgias, respectively. Biological agents, including anti-IgE monoclonal antibodies, anti-CD20 or IL-1 inhibitors, seem to be promising for recalcitrant disease [11,14,16].

HUVS prognosis therefore derives from the speed of onset, organ involvement, delay in diagnosis, response to treatment, and comorbidities [8,11].

As anticipated, the proper diagnosis of HUVS is hard because of the challenging evaluation of skin lesions, which resemble those of CSU, thus difficult to assess. Furthermore, recent studies hypothesized the possibility of an overlap between CSU and UV over time; therefore, it is still debated whether UV is a disease entity in its own right or an aspect of the CSU spectrum. On the other hand, as mentioned before, HUVS and SLE may likewise overlap, to the point that it has been supposed that HUVS could be a precursor of SLE.

Herein, we present a case of a patient who first experienced a CSU that disruptively turned into an HUVS, both following a SARS-CoV-2 infection, and progressively showed SLE traits.

Case Presentation

In January 2022, four weeks after a paucisymptomatic SARS-CoV-2 infection, a middle-aged woman experienced a widespread urticaria, characterized by spontaneous, transient, and itchy wheals (Figure 1) and one episode of histaminergic labial angioedema. The clinical picture was suggestive for a post-infective acute urticaria, and she was treated with a conventional dose of oral anti-H1 Antihistamine (AH-1), unfortunately without a significant improvement.

Notably, the patient's previous medical history was notable for Hashimoto's thyroiditis, properly treated with levothyroxine.

In April 2022, more than 6 weeks later, urticaria was still present

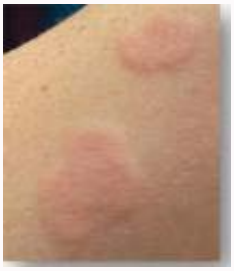

Figure 1: Widespread urticaria.

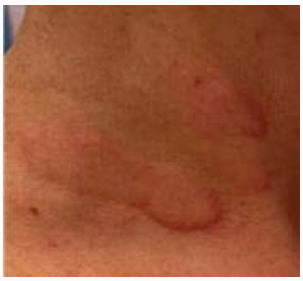

Figure 2: Ecchymotic residual hyperpigmentation.

despite AH-1 up-dosing; thus, the patient was referred to the Immunology and Allergy Unit of A.O. Mauriziano Hospital, where a first-line work-up panel (blood count, inflammatory markers, total IgE, basal serum tryptase, and TSH-reflex) was performed and systemic involvement was excluded. Tests for Chronic Inducible Urticaria (CIndU) were negative. Therefore, the diagnosis of CSU was made. As per guidelines, 300 mg omalizumab every four weeks was started, with advantages and subsequent complete remission.

In August 2022, the patient experienced another paucisymptomatic SARS-CoV-2 infection and one month later she started to present fever, abdominal pain, and migratory arthralgias - later diagnosed as arthritis. In addition, the urticarial lesions changed their features: Wheals became long-lasting, indurated, symmetrical, coalescent, and burning rather than itching with ecchymotic residual hyperpigmentation (Figure 2). Moreover, persistent facial angioedema was notable during the physical exam.

Because of the rapidly progressive changes in the clinical picture, a more detailed laboratory work-up panel was performed. The main detected findings were leukocytopenia (WBC 3150/mcl), anemia (Hb 11.5 g/dl), increased acute phase reactant levels (ESR 82 mm/h, CRP 12.8 mg/l), polyclonal hypergammaglobulinemia, and hypocomplementemia (C4 0.02 g/l, C3 0.27 g/l).

On the immunological side, a high titer of anti-C1q antibodies was detected. ANA, anti-Smith antibody, RF, anti-citrullinated protein, and anti-phospholipids antibodies were absent. In contrast, mild positivity for anti-Ro/SSA was revealed, and anti-dsDNA antibodies were positive by ELISA, but not confirmed by the *Crithidia luciliae* Indirect Immunofluorescence Test (CLIFT). Screening for infectious diseases (HBV, HCV, HIV, EBV, and CMV) was negative. Cryoglobulins were absent. Screening for malignancy resulted in negative too. No renal, cardiac, pulmonary, nervous, or hepatic involvement was detected.

To better define the urticarial lesions, a skin biopsy was performed, suggestive of leukocytoclastic vasculitis. The histological evaluation

confirmed the presence of neutrophil-dominant perivascular infiltrates with rare eosinophils, perivascular erythrocytes, endothelial swelling, and fibrin deposits. Direct immunofluorescence was positive.

Considering the clinical aspects of the urticarial lesions, histology, systemic involvement, and laboratory features, the diagnosis of HUVS was made, and other etiologies ruled out. The patient was promptly treated with oral prednisone (1 mg/kg daily for two weeks) in association with hydroxychloroquine 200 mg daily, without clinical improvement. Cyclosporin A at a dosage of 4 mg/kg was started, and prednisone slowly tapered to 5 mg/kg daily with achievement of clinical and laboratory slow recovery. To note, omalizumab and AH-1 were continued.

In January 2023, the laboratory work-up was repeated, and positivity for IgM anticardiolipin (aCL) was revealed and confirmed twelve weeks later, without any previous history of thrombosis or obstetric complications.

In March 2023, the patients experienced severe Cyclosporin A side effects, including high blood pressure, spotting and hypertrichosis. Hence, Cyclosporin A was stopped, and mycophenolate mofetil 2 g daily was started.

Since June 2023, the patient is asymptomatic: Skin lesions absent and laboratory values (liver and renal function, CRP, ESR, C3, C4 and C1q antibody) unremarkable, except for a mild anemia (Hb 11.5 g/dl). Considering the recovery of the patient, prednisone was further reduced and stopped without relapsing.

Discussion

Chronic urticarial lesions and angioedema are HUVS-dominant presenting signs, as for CSU; therefore, distinguishing them properly could be difficult [17]. Regarding this, recent studies showed no significant differences in clinical features between UV and CSU [18]; moreover, up to 25% of CSU patients report either long-lasting wheals or hyperpigmentation after wheal resolution [19], allowing the assumption of an overlap between CSU and UV.

Furthermore, it is known that the clinical presentation may change from CSU to UV or vice versa over time [19]. Therefore, it is still debated whether HUVS is a disease entity in its own right or an aspect of the CSU spectrum.

As in this case, the patient first experienced a common CSU that disruptively turned into a severe HUVS. Interestingly, both CSU and HUVS occurred following SARS-CoV-2 infection. In this regard, we reasonably hypothesize that SARS-CoV-2 has been the trigger in both diseases. Indeed, it is well known that SARS-CoV-2 is related to urticarial rash [19], and the first case report of UV due to COVID-19 was recently described [16,20,21]. Therefore, we wondered whether the diagnosis of CSU was an isolated clinical condition or the initial phase of a more severe form of urticarial vasculitis, which manifested itself several months later prompted by a viral infection [22].

Regarding HUVS and SLE, some authors have hypothesized that HUVS could be a precursor of SLE [6] due to their shared features. Our patient showed some clinical characteristics of SLE, including constitutional symptoms, arthritis, and urticarial rash. Regarding laboratory values, complement consumption, anti-SSA and aCL positivity, and the elevation of acute phase reactants could have led to the diagnosis of SLE. Nevertheless, the absence of ANA and anti-dsDNA and other SLE typical clinical aspects allowed us to rule out SLE diagnosis, according to ACR classification criteria [19].

Conclusion

We described the first case of HUVS induced by SARS-CoV-2 infection. The diagnostic approach to urticarial lesions is still challenging, especially in cases of systemic involvement and inadequate response to CSU standard-of-care. HUVS is a rare but severe disease that should be quickly investigated, correctly diagnosed, and adequately treated to avoid permanent damage.

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