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Case Report

Systemic Lupus Erythematosus Versus Hypocomplementemic Urticarial Vasculitis: A Diagnostic Dilemma in Clinical Practice☆

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ABSTRACT

Hypocomplementemic urticarial vasculitis syndrome is part of the hypocomplementemic urticarial vasculitis, occurring in patients with urticarial lesions and systemic and immune compromise, which can appear simultaneously with a connective tissue disease such as systemic lupus erythe matosus or an independent disorder. The case is presented of a patient with systemic lupus erythematosus qualifying features, however, with a clinical presentation of an hypocomplementemic urticarial vasculitis syndrome. A literature review was performed in order to present the potential differences and similarities.

Lupus eritematoso sistémico versus urticaria vasculítica hipocomplementémica: un dilema diagnóstico en la práctica clínica

Palabras clave:
Vasculitis
Urticaria
Lupus eritematoso sistémico
Anti C1q

RESUMEN

El síndrome urticarial vasculítico hipocomplementémico forma parte de la vasculitis urticarial hipocomplementémica, presentándose en paciente con lesiones urticariales y compromiso sistémico e inmunológico, puede manifestarse de manera simultánea con una enfermedad del tejido conectivo como el lupus eritematoso sistémico o como una entidad independiente. Presentamos un caso de un paciente con características clasificatorias de lupus eritematoso sistémico, sin embargo, con presentación clínica de un síndrome

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urticarial vasculítico hipocomplementémico, realizando una revisión de la literatura, de sus posibles diferencias y similitudes.

Introduction

Hypocomplementemic urticarial vasculitis syndrome (HUVS) is part of the hypocomplementemic urticarial vasculitis, being an entity with a more severe presentation, which was described for the first time by McDuffie et al., at the Mayo Clinic in 1973.[1,2] It is characterized by urticarial lesions with a presentation of more than 24 hours, associated with systemic renal, pulmonary, ocular, and cardiac involvement, and with immunological alterations such as the presence of anti-C1q antibodies and decreased levels of C1q due to activation of the complement classical pathway.[3]

The proposal that HUVS is part of the connective tissue diseases is being debated; instead, it is suggested that it can be an independent entity with a long-term risk for developing one of these diseases or being associated simultaneously with them, especially with systemic lupus erythematosus (SLE),[4] since they share multiple characteristics and some authors even consider it an unusual type of SLE. It has been described that HUVS is present in 7% to 8% of patients with SLE and that 54% of patients with HUVS meet criteria for SLE when they are followed-up over time.[5] There are several case reports in the literature of patients who meet classification criteria both for SLE and for HUVS.[6,7]

Taking into account this discussion, we conducted a review on the topic and brought up a case of a patient with clinical and immunologic characteristics both of HUVS and SLE, considering a pathophysiology that may be similar and suggesting that both entities could be part of the same spectrum of autoimmune diseases.

Clinical Case

A 55-year old male patient, with a history of coronary heart disease, chronic pneumopathy in treatment with inhaled therapy and prednisone in doses of 25 mg/day, due to multiple exacerbations, who relates symptoms of arthralgia of small joints of 3 years of evolution, associated with non-pruritic wheal type lesions in the trunk and extremities of more than 24 hours of duration (Figs. 1 and 2).

He relates that during the first year he underwent a skin biopsy, which according to him showed an initial diagnosis of neutrophilic dermatosis, being requested paraclinical tests (Table 1), in which calls the attention the presence of bicytopenia, complement consumption, positive ANA with homogeneous pattern, positive anti-DNAds, positive anti-chromatin and anti-C1q antibodies; under suspicion of hematologic malignancies, it was performed a bone marrow aspirate and biopsy (BMB) which did not show neoplastic alterations.

Given the lack of clarity of previous diagnosis, the presence of new skin lesions, the association with hypocomplementemia and the presence of markers of autoimmunity, it was decided to perform a biopsy of the skin lesions (Figs. 3 and 4) which describes findings compatible with urticarial vasculitis, shaping a clinical picture of hypocomplementemic urticarial vasculitis associated to the presence of ANA and

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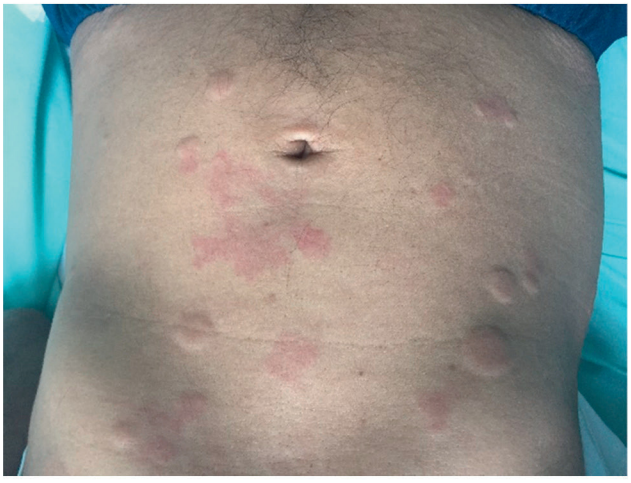

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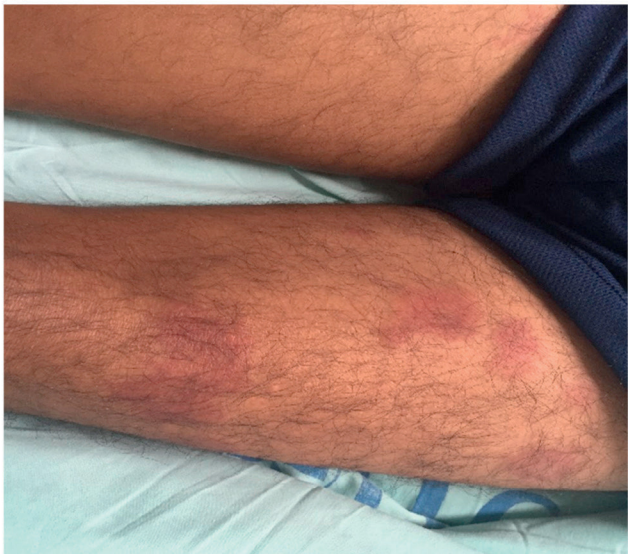
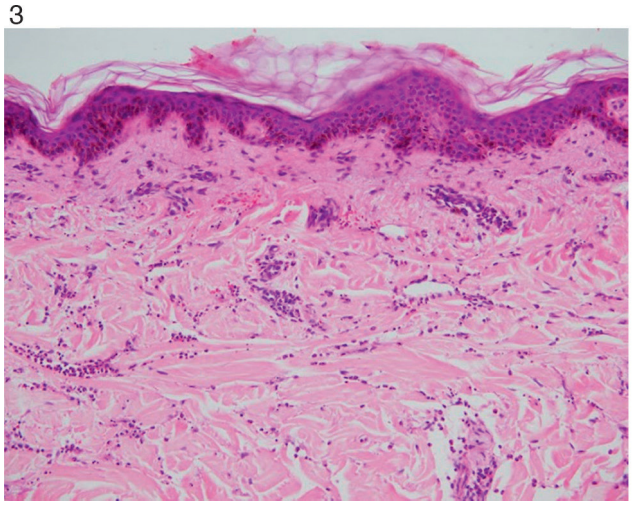


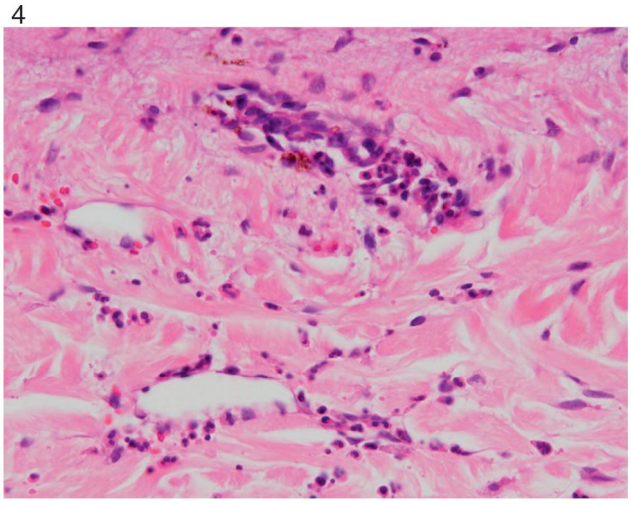
Figures 1 and 2 – Lesions of the skin of the abdomen and the legs, of wheal type, with violaceous coloration, non-pruritic, some of them forming coalescent plaques.

Table 1 – Laboratories.

Paraclinical tests	Result	Paraclinical tests	Result
Leukocytes	1,270 ul	RCP	20.7 mg/L
Neutrophils	950 ul	C3	31.4 mg/dl
Lymphocytes	250 ul	C4	14.1 mg/dl
Hemoglobin	12.3 g/dl	Anti -DNAds	Positive-dilution 1:40
Platelets	102,000 ul	ANA	Positive - dilution 1:160 Pattern: homogeneous
MCV	81 fl	ENAS	Negative
Creatinine	0.8 mg/dl	Anti-cardiolipin IgM- IgG Ab	Negative
BUN	24.1 mg/dl	Anti-nucleosome (chromatin) Ab	71.87
GOT	31.8 U/L	Direct COOMBS	Positive
GPT	25.7 U/L	Haptoglobin	186
LDH	187	Anti-C1q Ab	61.01
Ferritin	541 ng/ml	RPR	Non-reactive
TSH	8.78	Urinalysis	Without proteinuria

ANA: antinuclear antibodies; Anti-DNAds: anti-double stranded DNA antibodies; BUN: blood urea nitrogen; C3 and C4: C3 and C4 fractions of complement; ENAS: extractable nuclear antigens; LDH: lactate dehydrogenase; RCP: reactive C protein; RPR: rapid plasma reagin test; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; TSH: thyroid stimulating hormone; MCV: mean corpuscular volume.





Figures 3 and 4 – It can be seen dermis with severe edema between the collagen fibers, extravasation of erythrocytes and perivascular and interstitial infiltrate of lymphocytes where polymorphonuclear neutrophils and eosinophils predominate. Findings compatible with urticarial vasculitis.

positive anti-DNAds, without major organ affected, no oral ulcers, no alopecia, no photosensitivity, no Raynaud's phenomenon, no hematuria, normal serial urinary sediment, without skin lesions typical of lupus erythematosus, leaving in doubt whether the skin lesions are an independent entity, setting up a HUVS, or if they are part of the complex of atypical or non-specific manifestations of lupus.

Discussion

HUVS is a rare entity within the type of urticarial vasculitis (UV), characterized by non-pruritic urticarial lesions of more than 24 hours of evolution,[8] decrease of the C3, C4, CH50 and C1q fractions of complement and presence of antibodies against the portion of C1q[3,5,9] and systemic manifestations given by arthralgia/arthritis,[1,3,10] angioedema,[7,10] ocular inflammation with conjunctivitis, episcleritis, uveitis,[7,8] glomerulonephritis,[3,10,11] COPD[3,12] and more rarely, pericarditis.[3]

In 1982 Schwartz established the major and minor preliminary criteria for the diagnosis of HUVS[12] (Table 2).[6,13] The histological examination shows lesions of leukocytoclastic vasculitis type, most often with a predominantly neutrophilic infiltrate but without interruption of the walls of the vessels.[9]

The incidence of UV ranges from 2% to 20%,[14] however, the incidence of HUVS is unknown; in a retrospective study, 18% of patients with UV exhibited hypocomplementemic biopsies.[5] HUVS affects more women than men, with a 2:1 ratio and the peak incidence is around the fifth decade of life, although there also have been reports in children.[9] It is present in 7% to 8% of patients with SLE, taking into account that approximately 250,000 Americans have SLE, this would indicate that between 17,500 and 20,000 Americans might suffer from HUVS.[15]

Table 2 – Diagnostic criteria for HUVS.

Major criteria
Skin lesions of urticarial vasculitis
Serum hypocomplementemia
Minor criteria
Dermal vasculitis on biopsy
Arthralgia or arthritis
Uveitis or episcleritis
Glomerulonephritis
Recurrent abdominal pain
Anti-C1q antibodies associated with low levels of C1q
Exclusion criteria
Positive Cryoglobulins
Increased ANA titers
Increased anti-DNA titers
Positive hepatitis B antigenemia
Decreased levels of C1-esterase inhibitor
Inherited deficiency of complement

The pathophysiology of HUVS is not clear, multiple mechanisms have been proposed including the participation of deposits of immune complexes, activation of the T lymphocytes and the presence of anti-C1q antibodies.[16] The presence of immune complexes represents an activation of the humoral immune response, which may be responsible for the urticaria, the angioedema and the COPD in HUVS; the antibodies of IgG type bind against the Fc portion of regions that are similar to the collagen of the C1 molecule, forming immune complexes and activating the classical complement pathway, generating large amounts of C3a and C5a[17] and other anaphylatoxins and chemokines that contribute to increase vascular permeability, chemotaxis of inflammatory cells and deposition of immune complexes around the vessels.[18,19]

IgG2 anti-C1q antibodies have been found in 100% of HUVS and in 35% of SLE, suggesting that these antibodies bind to the same epitope in these two entities,[20,21] although some reports reveal that these IgGs may have different specificities.

The exact mechanism of the lung involvement in HUVS is not entirely clear,[9] however, anti-C1q antibodies are detected in COPD, outlining that the molecules of C1q bind to lung surfactant proteins causing pulmonary capillaritis, which contributes to the obstructive pulmonary disease,[22] additionally, it has also been found overexpression of neutrophil elastases which can hydrolyze complement proteins and components of the connective tissue in HUVS.[3,23]

Concerning the activation of T lymphocytes, the C1q has been associated with the activation of T-cell inhibitors, in addition, the anti-C1q interfere with the clearance of apoptotic cells, influencing the expression of autoimmunity like in SLE. Regarding the pathogenesis of the anti-C1q, it is related with the activation of the classical complement pathway and, additionally, other biological functions have been found, including a modulating role on cellular functions within the adaptive response,[24] this molecule has been found in a lower percentage in healthy people and in a higher percentage in patients with SLE (61%), rheumatoid arthritis (20%), scleroderma (15%), Sjôgren's syndrome (15%) and mixed connective tissue disease (15%).[25] It is not clear if these antibodies have binding specificity for the C1q, but the evidence suggests that in SLE the anti-C1q bind to the intact tertiary structure of the C1q, while in HUVS they bind to reduced and denatured C1q epitopes.[26,27]

Among the systemic manifestations, HUVS and SLE may share some characteristics (Table 3).[3,4,6] The skin is the dominant organ in HUVS, with recurrent,[1,16] painful, non-pruritic urticaria, of more than 24 hours of evolution, with a centrip-

Table 3 – Clinical and laboratory alterations in HUVS and in SLE.

HUVS		SLE	
Symptom	Frequency (%)	Symptom	Frequency (%)
Urticarial lesions (biopsy with leukocytoclastic vasculitis)	100	Urticaria	< 10
		Cutaneous symptoms (malar rash, oral ulcers or photosensitivity)	80
Arthralgia or arthritis	100	Arthralgia or arthritis	95
Angioedema	72	Angioedema	< 5
COPD		Restrictive lung disease	24-30
Ocular involvement	61	Ocular involvement	15
Renal involvement	50	Renal involvement	35-50
Pericardial effusion	17	Pericardial effusion	30
Laboratory	Frequency (%)	Laboratory	Frequency (%)
Anti-C1q antibodies	100	Anti-C1q antibodies	35
Low C1q levels	100	Hypocomplementemia	22-47
ANA	61-71	ANA	95
Elevated ESR	60-70	Elevated ESR	50
Anti-DNA	17-transient	Anti-DNA	> 70
AntiSS-A/AntiSS-B	16-17	AntiSS-A/AntiSS-B	30-45
Hematologic abnormalities	11	Hematologic abnormalities	85
Rheumatoid factor	8	Rheumatoid factor	25-33

etal tendency in the trunk and extremities that resolves with post-inflammatory hyperpigmentation.[28] Angioedema, which is very rare to occur in the context of SLE,[3,16] can be present in up to 50% of patients with HUVS involving the lips, the tongue, periorbital tissue and the hands. This may be the first sign of HUVS and it suggests involvement of deep vessels.

In the immunohistochemistry, deposits of Ig and complement are evidenced in the walls of the vessels or in the endothelium; these findings can appear with vasculitis in SLE, however, in SLE there are deposits in the basement membrane with a positive lupus band test.[9,14] Within the articular involvement, arthritis and arthralgia may occur in 50% of cases, the pain is vague and transient and typically affects the elbows, wrists, knees and ankles. Joint deformity may occur with Jaccoud's arthropathy which is associated to cardiac involvement with aortic and mitral valve disease.[29,30]

Renal involvement in HUVS is usually mild, proteinuria and hematuria may be found,[14] histology may show membranous, membranoproliferative, or intra-or extra capillary glomerulonephritis, which cannot be differentiated from the renal involvement in SLE,[16] the involvement is usually more severe in children, and when it occurs with end-stage kidney failure, another differential diagnosis should always be sought. A study of 18 patients with HUVS showed 50% of renal involvement, with manifestations ranging from minimal proteinuria to nephrotic syndrome with different degrees of hematuria and glomerular commitment.[3]

The lung involvement can be very varied, ranging from dyspnea, cough, hemoptysis, pleural effusion and COPD, the latter has been associated in up to 50% of patients with HUVS,[3,28] presenting 80%-90% of anti-C1q antibodies,[3,20,31] the lung involvement usually occurs in patients under 30 years old and is related with increased morbidity and mortality; the history of smoking can worsen the prognosis, however, COPD may occur without history of cigarette smoking.[12,32]

The gastrointestinal tract involvement is around 30%, given by pain, nausea, vomiting, diarrhea, and ascites associated with serositis, hepatomegaly and splenomegaly.[14,33] 30% of patients may have ocular inflammatory involvement, primarily uveal, there are also reports of conjunctivitis and episcleritis.[1,3,9] Cardiac involvement, as already mentioned above, has been found in the presence of joint deformity with valvular compromise.[14,30]

Among the immunological serological characteristics, all patients with HUVS have anti-C1q antibodies associated with UV lesions, but rarely the patients with SLE who are seropositive for anti-C1q develop UV lesions and conversely, in the context of SLE these antibodies correlate more with glomerulonephritis. Unlike SLE in which almost 100% of patients have positive ANA, only between 50% and 60% of patients with HUVS have positive ANA in moderate titers and in the latter group of patients the anti-DNAds antibodies are transient and infrequent.[13]

There is no specific treatment for patients with HUVS; the therapy is directed according to the organ involved and the severity of the clinical picture. Antihistaminic agents are typically used in urticaria, but they are insufficient for the management of HUVS; non-steroidal anti-inflammatory drugs can be used when there is joint involvement,[6] however, similarly to the treatment of SLE, different types of immunosuppressants, such as corticosteroids, hydroxychloroquine, dapsone, and even cyclophosphamide, rituximab or immunoglobulin, can be used when there is a severe compromise of renal function or in refractory cases.[3,7,9,12,20,34,35]

Conclusion

With the exposition of this case, the difficulty in differentiating HUVS from some types of presentation of SLE is evidenced, however, the diagnostic challenge should not be to classify the patient within one syndrome or the other, but to understand the pathophysiological and clinical similarities of these two entities and thus to formulate an early and adequate therapeutic approach, that allows a clinical follow-up in order to determine whether we are facing an independent entity or a polyautoimmunity syndrome.

Ethical Disclosures

Protection of people and animals. The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Right to privacy and informed consent. The authors state that patient data do not appear in this article.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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