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Case Report

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Hypocomplementemic Urticarial Vasculitis Syndrome Masquerading as Systemic Lupus Erythematosus: A Case Report

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Hypocomplementemic urticarial vasculitis syndrome · Glomerulonephritis · Electron microscopy · Rare disease · Urticarial vasculitis

Abstract
Introduction: Hypocomplementemic urticarial vasculitis syndrome (HUVS) is an infrequent immune complex-mediated condition characterized by nonpruritic urticarial lesions, low serum complement levels, and autoantibodies, associated with systemic manifestations like arthralgia/arthritis, angioedema, ocular inflammation with conjunctivitis, episcleritis, uveitis, renal, gastrointestinal, and pulmonary involvement. HUVS and systemic lupus erythematosus (SLE) overlap and the criteria for identifying HUVS as an entity distinct from SLE are lacking. Despite the diagnostic criteria established by Schwartz et al. [*Curr Opin Rheumatol*. 2014; 26(5):502–9], differentiation from SLE is sometimes difficult as patients often also fulfill the classification criteria of the American College of Rheumatology (ACR). The prognosis of HUVS depends on the organ system involved. Lung disease results in significant morbidity and mortality and is made worse by smoking. Kidney involvement with glomerulonephritis may ultimately result in end-stage renal disease with the need for kidney transplant. Death may also occur due to acute laryngeal edema. ***Case Presentation:*** We present a case of a 40-year-old female who had a diagnosis of SLE, presented with severe odynophagia, was found to have an erythematous macular rash, and had acute kidney injury attributed to contrast-related injury and cardiorenal syndrome. After the resolution of the AKI, she continued to have hematuria and low-grade proteinuria that led to a kidney biopsy that aided in the diagnosis of HUVS. ***Discussion/Conclusion:*** Given the rarity of this disease and the difficulty in differentiating HUVS from other rheumatological diseases such as SLE, further accumulation of cases is necessary to understand the best diagnostic modality for this entity.

Introduction

Hypocomplementemic urticarial vasculitis syndrome (HUVS), or McDuffie Syndrome, is a rare small vessel vasculitis characterized by chronic urticaria, hypocomplementemia, and anti-C1q antibodies [1, 2]. It has been

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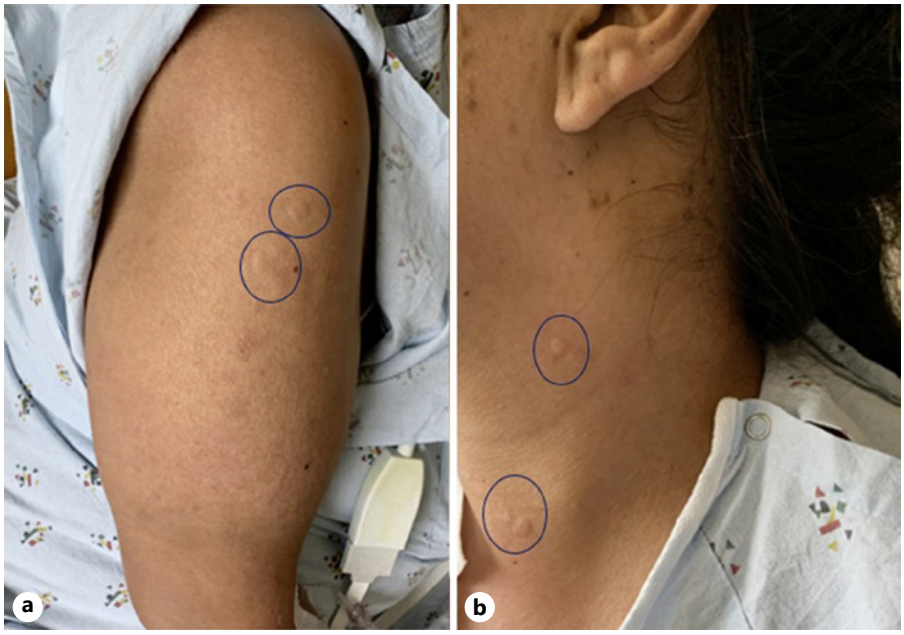

Fig. 1. Skin findings as noted on the patient's right arm (**a**) and neck (**b**). Both sites exhibit multiple erythematous urticaria with evidence of previous excoriation.

associated with multi-organ systemic involvement including angioedema, laryngeal edema, cutaneous lesions, pulmonary manifestations, arthritis, arthralgia, glomerulonephritis, and uveitis [3, 4]. Because of the rarity of this diagnosis, there is scarce data regarding the clinical presentation, pathology, and outcomes of patients with HUVS. Treatment is dependent on disease severity with corticosteroids and other immunosuppressive agents including rituximab, hydroxychloroquine, and mycophenolate mofetil demonstrating some success in case reports [4–6]. We describe a case of HUVS with severe renal involvement, who initially presented with severe odynophagia.

Case Presentation

Forty-year-old female presented with 1 day of right-sided neck pain, swelling, difficulty swallowing, and shortness of breath. Past medical history was notable for nonischemic cardiomyopathy attributed to prior methamphetamine use requiring ICD implantation (9/2020) and daily medications (carvedilol, furosemide, and spironolactone), systemic lupus erythematosus (SLE), hypertension, sleep apnea, tobacco dependence, and opioid use disorder. Per the patient, she was diagnosed with SLE with no prior treatment. The patient reported prior episodes of hand, lip, and throat swelling over the past 3 years with one of these episodes occurring after starting lisinopril. Physical exam was notable for bilateral lower extremity edema, bilateral lung crackles, right cervical lymphadenopathy, and multiple erythematous urticaria on the midline neck and diffusely on the upper chest, back, and arms (Fig. 1). At presentation, her serum creatinine was 1.12 mg/dL, increased from baseline of 0.6 mg/dL and ultimately trended upward to 1.35 mg/dL during admission. Urinalysis was positive for 3+ blood and 1+ protein. Contrast CT imaging of the neck showed soft tissue swelling of the right aryepiglottic fold with associated obliteration of the pre-epiglottic space and right pyriform sinus consistent with supraglottitis. She was noted to have bilateral pleural effusions and a small pericardial effusion. Transthoracic Echo exhibited an ejection fraction of 25–30%. She was treated for supraglottitis thought to be secondary to infection or SLE with IV dexamethasone 10 mg every 8 h, ceftriaxone, and vancomycin. After the patient was able to tolerate oral medications, her home cardiomyopathy medications were restarted: furosemide (40 mg PO daily) and carvedilol (12.5 mg PO twice daily). Within 2 days, her serum creatinine normalized (0.7–0.8 md/dL) and her effusions resolved. However, her hematuria and proteinuria (0.7 g/24 h collection) were persistent.

During her admission, the patient was found to have multiple erythematous urticaria on her upper arms and back (Fig. 1), which also lessened following dexamethasone therapy. A biopsy of the skin lesions demonstrated leukocytoclastic vasculitis. Additionally, a kidney biopsy was performed.

The kidney biopsy (Fig. 2) was composed of cortex and corticomedullary junction containing 39 glomeruli (7 globally sclerotic). Glomeruli displayed a diffuse and global membranoproliferative glomerulonephritis pattern of injury. Three glomeruli exhibited segmental scars. There were no necrotizing lesions or crescents. An active tubulointerstitial nephritis was present, composed of lymphocytes, histiocytes, prominent eosinophils, scattered plasma cells, and occasional neutrophils. There was minimal interstitial fibrosis/tubular atrophy and arterial/arteriolosclerosis. There was no arteritis, venulitis, or vascular thrombi. By immunofluorescence, there was diffuse global granular mesangial and capillary wall staining for IgG (4+), IgA (3+), IgM (3–4+), C1q (4+), C3

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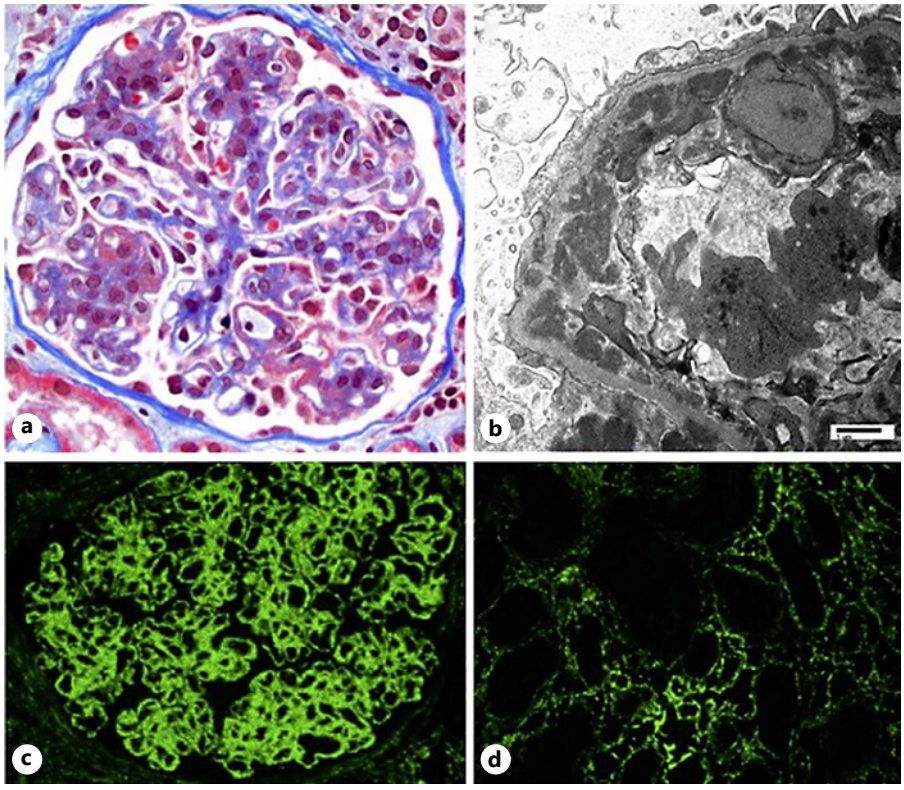

Fig. 2. Kidney biopsy findings. **a** Light micrograph demonstrates a glomerulus involved by a membranoproliferative glomerulonephritis pattern of injury (Trichrome stain, ×400). **b** Electron micrograph of a glomerular capillary loop demonstrating large subendothelial, mesangial, and few subepithelial immune complex deposits. Immunofluorescent micrographs of anti-human C1q antibody staining of (**c**) glomeruli and (**d**) tubulointerstitium demonstrating diffuse and global glomerular capillary wall and mesangial staining as well as extensive tubulointerstitial staining (×400).

(3–4+), kappa light chain (3+), and lambda light chain (3–4+). There was diffuse bright tubular basement membrane and interstitial staining for IgG, IgA, IgM, C1q, C3, and both light chains. Ultrastructural studies demonstrated numerous immune complex deposits in mesangial, subendothelial, and, segmentally, subepithelial locations, as well as in interstitial spaces and on tubular basement membranes. Deposits did not display the substructure. There were many capillary loop double contours. Podocytes exhibited extensive foot process effacement. Glomerular basement membranes were diffusely thin (mean thickness 143 nm, standard deviation 33 nm). Tubuloreticular inclusions were not present.

The biopsy diagnosis was (1) diffuse immune complex glomerulonephritis with full-house immunofluorescence staining, moderate activity, and mild chronicity; membranoproliferative glomerulonephritis pattern of injury with focal segmental glomerular scars; (2) active immune complex-mediated interstitial nephritis; and (3) thin glomerular basement membrane lesion.

Although the patient carried a long-standing diagnosis of SLE, some aspects of her case did not seem to fall within the spectrum of SLE. Even though she was noted to be hypocomplementemic with a C3 concentration of 24 mg/dL (normal range 76–165 mg/dL) and a C4 concentration of 2 mg/dL (normal range 14–46 mg/dL), serological studies demonstrated only a weak positive (1:40) speckled ANA titer and negative DsDNA. Furthermore, the patient also lacked objective clinical findings that are specific to SLE including photosensitivity, mucosal ulcers, and allopecia.

Upon further discussion with the patient, she informed the teams that she had never formally seen a rheumatologist nor did she ever recall undergoing testing for studies that would diagnose with SLE. The patient elaborated on this situation and mentioned that she had been told she "may have something like lupus" from a pain clinic. Previous records prior to transfer were reviewed in-depth and exhibited no evidence of serologies suggestive of SLE. Upon review of the 2019 EULAR/ACR SLE diagnostic criteria, we confirmed what we suspected: the patient did not have SLE and instead had another ongoing medical problem [7].

Additional serological studies were unremarkable (HBV and HCV serologies, antimitchondrial antibody, anti-smooth muscle, anti-ribonucleoprotein, C-1 esterase inhibitor, C-ANCA, P-ANCA, proteinase-3 antibody, myeloperoxidase antibody, SSA/SSB antibody, cryocrit, dilute russel viper venom test, anti-cardiolipin, quantitative immunoglobulins, beta-2 glycoprotein, rheumatoid factor, and anti-cyclic citrullinated peptide IgG). Kappa and lambda free light chains were elevated at 72.79 (normal range 3.30–19.40 mg/L) and 52.54 mg/L (normal range 5.71–26.30 mg/L), respectively, with a normal ratio of 1.39 (normal range 0.26–1.65).

Assessment of C1q antibody level 214 U/mL (normal range 0–19 U/mL) and C1q complement level <50/unmeasurable μg/mL (normal range 109–242 μg/mL) combined with the other clinical pathologic findings confirmed a diagnosis of hypocomplementemic urticarial vasculitis. Given the immune complex GN, patient was initiated on pulse IV steroid 1,000 mg for 3 days and mycophenolate mofetil 500 mg twice a day with plans to increase to 1,000 mg twice a day after 2 weeks. Patient was also started on hydroxychloroquine 200 mg twice a day given her significant recurrent cutaneous vasculitis and arthritis. She had complete resolution of her laryngeal edema and odynophagia with improvement in her dyspnea. Unfortunately, she was lost to follow-up.

Discussion

The diagnostic criteria for HUVS are as follows: two major criteria (recurrent urticaria more than 6 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) [3, 8].

Patients usually present with generalized urticarial eruptions located on the trunk, proximal extremities, and face that are often associated with itching or pain and persist for more than 24 h, with hyperpigmentation after resolution [8–11]. Angioedema occurs in up to 50% of patients, frequently involving the lips, tongue, periorbital tissue, and hands, and can be the first sign of HUVS. Other manifestations include constitutional symptoms (fever, malaise, and fatigue), musculoskeletal symptoms, ocular inflammation (e.g., conjunctivitis, episcleritis, and uveitis), serositis, obstructive lung disease, Raynaud's phenomenon, renal disease, gastrointestinal symptoms, cardiac involvement, and various neurologic problems [6, 12, 13]. Arthralgia and arthritis of various joints are the most frequent systemic manifestations of HUVS, occurring in up to 50 percent of cases. Jaccoud's arthropathy may be present in HUVS and has been associated with aortic and mitral valvulopathy [9, 14]. Myositis may be present in muscle biopsies and resemble idiopathic inflammatory myositis [14]. Anti-C1q antibodies are not specific for HUVS, nonetheless, if associated with multisystem involvement, the characteristic skin findings and low C1q levels, are very helpful to reach the diagnosis [10]. The presence of leukocytoclastic vasculitis on skin biopsy and urticaria are the hallmarks of this disease [8–10]. Up to one-third of patients have pruritis.

Misdiagnosis of HUVS occurs because of similarities to SLE. Arthritis and arthralgia are common to both, urticarial vasculitis occurs in 5–10% of patient with systemic lupus and may be a presenting manifestation, and 28% of 47% of patient with SLE have IgG antibody to C1q [6, 15, 16]. The complement abnormalities are identical in both diseases as well. Antibodies against C1q have been found in several other rheumatic diseases, including SLE [8, 11, 16]. The renal disease of HUVS may not be distinguishable from SLE with renal involvement. These include proliferative glomerulonephritis, focal necrotizing vasculitis, crescentic glomerulonephritis, membranoproliferative glomerulonephritis, and tubulointerstitial nephritis [13].

Given the clinical similarities between HUVS and SLE, diagnosis of HUVS can be quite challenging. In SLE, the spectrum of organ involvement seems more extensive. Urticarial lesions and angioedema are found in SLE; both are the main characteristics of HUVS. On the other hand, the typical butterfly rash occurs only rarely in HUVS [8, 14]. Obstructive lung disease of the incidence and severity found in HUVS rarely, if ever, occurs in SLE [13, 17].

In our case, the ability to discern between SLE and HUVS was complicated from the onset of the patient's transfer. Previous hospital notes and outside provider notes continued to state that the patient was diagnosed with SLE; this was never confirmed nor debunked until the patient was transferred under our care. Although our patient had some clinical findings compatible with SLE, the low ANA titer (1:40) made the diagnosis SLE less likely.

In the past, many case reports and studies have highlighted to the similarities between HUVS and SLE. For many of the previous reports that discussed this debate, criteria to diagnose SLE was not as thorough with relation to clinical and serological criteria. By having more specific and sensitive diagnostic abilities, we were able to quickly discern that our patient did not have SLE. We believe that the ongoing research in the diagnosis of SLE will continue to help clinicians differentiate between SLE and other diagnosis such as HUVS [6, 8, 9, 13, 14].

In conclusion, our case illustrates the fact that the diagnosis of HUVS may be very challenging given the clinical similarities between HUVS and SLE. For our patient, confirming that she did not have SLE was crucial to understanding that she had another disease process leading to her presenting symptoms; this may be a challenge faced by many other practitioners in the past who did not have the same SLE diagnostic criteria of avail to them as we did [7]. Furthermore, our case demonstrates the need for thorough serological evaluation and highlights the value of kidney biopsy in certain situations. Despite the low level of proteinuria in our patient, our case points to the importance of a renal biopsy in the evaluation of hematuria and subnephrotic proteinuria in guiding the diagnosis and treatment of a patient with multisystemic manifestations of diseases such as HUVS [3–5].

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This study was granted an exemption from requiring ethics approval per UCLA IRB and Ethics Policies. This was as per policy approved by the committee overseeing the UCLA Research Administration and Human Research Protection Program.

Conflict of Interest Statement

The authors declare no conflict of interest related to this manuscript.

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No funding sources were used during this case report by any of the authors.

Author Contributions

Jiten Prakash Mehta, DO, Charley Qi Hua Jang, Peter Fahim, MD, Minhtri Khac Nguyen, MD, Jonathan Zuckerman, MD, PhD, Rosha Mamita, and Mohammad Kamgar, MD contributed by assisting in design and drafting of the manuscript submitted. They also agreed and approved the manuscript for submission.

Data Availability Statement

All data generated or analyzed during writing of this manuscript are included in this article. Further inquiries can be directed to the corresponding author.

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