Chapter 6

Urticarial Vasculitis

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/68109

Abstract

Urticarial vasculitis (UV) is a small vessel vasculitis and an immune-complex mediated disease like other leukocytoclastic vasculitis. UV seems similar to common urticaria clinically. Major difference between urticarial vasculitis and urticaria is the duration of lesions. Urticarial lesions regress in 24 hours, but UV lesions persist longer than 24 hours. Residual hyperpigmentation, constitutional symptoms like fever, arthralgia, and abdominal pain are other main clinical differences between these disorders. Upon confirmation of diagnosis, patients are divided into two major categories on the basis of serum complement levels: normocomplementemic UV (NUV) and hypocomplementemic UV (HUV). Consensus meeting in 1996 stated that long lasting (at least 24 hour–5 days) indurated wheals, which may be itchy, painful or tender, be associated with purpura and presence of associated extracutaneous findings, and cutaneous vasculitis confirmed by histopathological examination are defined as UV.

Keywords: hypocomplementemia, normocomplementemic, urticaria, vasculitis

1. Introduction

Urticarial vasculitis (UV) is an entity that is characterized by clinical presence of urticarial lesions and histopathological presence of vasculitis. Major difference between urticarial vasculitis and urticaria is the duration of lesions. Urticarial lesions regress in 24 hours, but UV lesions persist longer than 24 hours. Residual hyperpigmentation, constitutional symptoms like fever, arthralgia, and abdominal pain are other main clinical differences between these disorders [1]. UV lesions can be pruritic but more commonly these lesions are associated with symptom of burning. Skin biopsy shows histopathologic features of leukocytoclastic vasculitis [2]. Lesions usually persist for several months but very rarely they persist for years [3]. UV may be seen as a manifestation of a systemic disease or it may develop into a systemic illness by itself [2].

2. Section

2.1. Epidemiology

UV is a rare condition and the exact incidence is not known as a result of small number of literature reports. UV frequency is reported to be between 2 and 20% in chronic urticaria patients and if histologic definition of vasculitis is used as a criterion for diagnosis then the estimate of the prevalence of UV in chronic urticaria patients becomes approximately 5% [1, 3, 4]. Approximately 80% of UV patients have underlying or associated disease [2]. UV is more common in women and very rare in children [4]. Case report of an infant with UV is the only case report presenting the literature [5]. The peak incidence of the disease is in the fourth decade of life [4].

2.2. Etiopathogenesis

UV is a small vessel vasculitis and an immune-complex mediated disease like other leukocytoclastic vasculitis. Leukocytoclastic vasculitis is an example for type III immune reaction, which is characterized with circulatory immune complexes [6]. Initially antigen-antibody complex is formed in blood and then accumulation of the vessel walls. This complex reaction leads to the activation of complement system by the classical pathway. Anaphylatoxins C3a and C5a induce mast cell degranulation and cytokine synthesis. Mast cells release tumor necrosis factor alpha (TNFα), prostaglandins, histamine, heparin, platelet activating factor, leukotrienes, neutrophil chemotactic factor A, neutral protease, and tryptase [6]. Increase in cytokine and chemokine production results in edema and tissue reaction. Main antibodies in this reaction are IgG or IgM, and rarely IgA. The antigen in the complex may be autologous or it may derive from exogenous origin such as an infection or drugs [4]. But the antigens are mostly not known [1]. Based on the level of complement, UV is divided into two subgroups: normocomplementemic UV (NUV) and hypocomplementemic UV (HUV) [7]. UV is often idiopathic, but in some cases, it can be triggered with drugs, infection (hepatitis B and hepatitis C), connective tissue disease, neoplasia, cold, and exercise. [3, 8–12]. Drugs were found to be responsible for 10% of UV patients. The risk of UV is irrespective of both dose and frequency [8]. Infliximab, procainamide, antidepressants, methotrexate, sulfamethoxazole-trimethoprim, diltiazem, cimetidine, enalaprilin, and nonsteroid anti-inflammatory drugs (NSAIDs) are the main drugs reported in the literature [3, 13]. A patient with UV should also be examined for underlying diseases like viral infections, monoclonal gammopathies, serum sickness, and serum sickness like reactions, SLE, Sjögren's syndrome (SS) or mixed cryoglobulinemia [2, 14, 15]. Polycythaemia rubra vera [16], essential thrombocythemia [17], systemic sclerosis [18], acquired reactive perforating collagenosis [19], lymphoma [20], leukemia [21, 22], and thyroid dysfunction [23] are the other systemic diseases reported in the literature. UV patients with normal serum complement levels have rarely systemic manifestations. By contrast, UV patients with decreased C3 and C4 have systemic diseases including lung, kidney, and eye involvement [14]. At the same time, HUV patients may have extracutaneous symptoms like fever, myalgia, malaise, fatigue, arthralgia, conjunctivitis, episcleritis, nephritis, and cardiac valve involvement [8, 24]. A small group of patients with HUV also

have anti-C1q antibodies (anti-C1q Ab), and this group is considered as a separate entity called HUVS [7]. Ig G autoantibodies to the collagen like region of C1q (anti-C1q Ab) were detected in HUVS patients' serum. Anti-C1q Abs were also detected in patients with systemic lupus erythematosus (SLE) and 85% of these patients had glomerulonephritis. Anti-C1q Ab is associated with glomerulonephritis in SLE patients [2]. However, all HUVS patients have UV lesions and anti-C1q Ab, but only a group of SLE patients have UV lesions [2]. UV occurs in 5–10% of SLE patients and 28–47% of SLE patients have anti-C1q Ab [14]. HUVS patients form a small fraction of idiopathic HUV group (less than 5%), and these patients may have gastrointestinal, neurologic, ophthalmologic, renal, and pulmonary involvement [7]. Pulmonary disease in patients with HUVS was first described in 1982 with an incidence of 50%. However, these patients had history of tobacco exposure. After this report, different incidences (15–50%) were reported in HUVS patients. The exact mechanism of obstructive lung disease is not known but vasculitis of pulmonary capillaries, dysfunction of α 1 antitrypsin and binding of anti-C1q Ab to the surfactant proteins in pulmonary alveoli are the possible hypotheses for pathogenesis [14]. Renal disease was also reported in 20–30% of patients with HUVS [25].

2.3. Clinical features

UV is characterized by widespread urticarial lesions each lasting longer than 24 hours clinically [12, 26]. Classically urticarial plaques of UV are persistent or long lasting (in 64% of patients more than 24 hours) (**Figure 1**) and may resolve with purpura (**Figure 2**) or hyperpigmentation (in up to 35% of patients) in comparison to common urticaria [12]. Lesions may

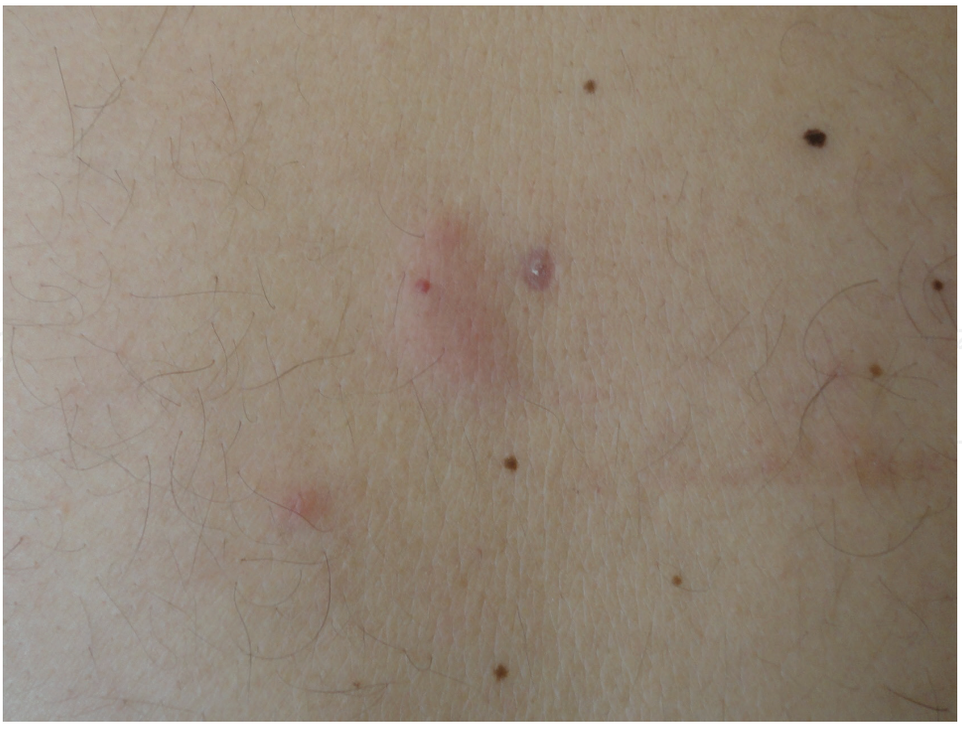

Figure 1. Urticarial lesions on the dorsal trunk of 47 years old male that is present for a month. The histopathological examination revealed lymphocytic vasculitis and laboratory examinations yield a diagnosis of accompanying Sjögren syndrome.

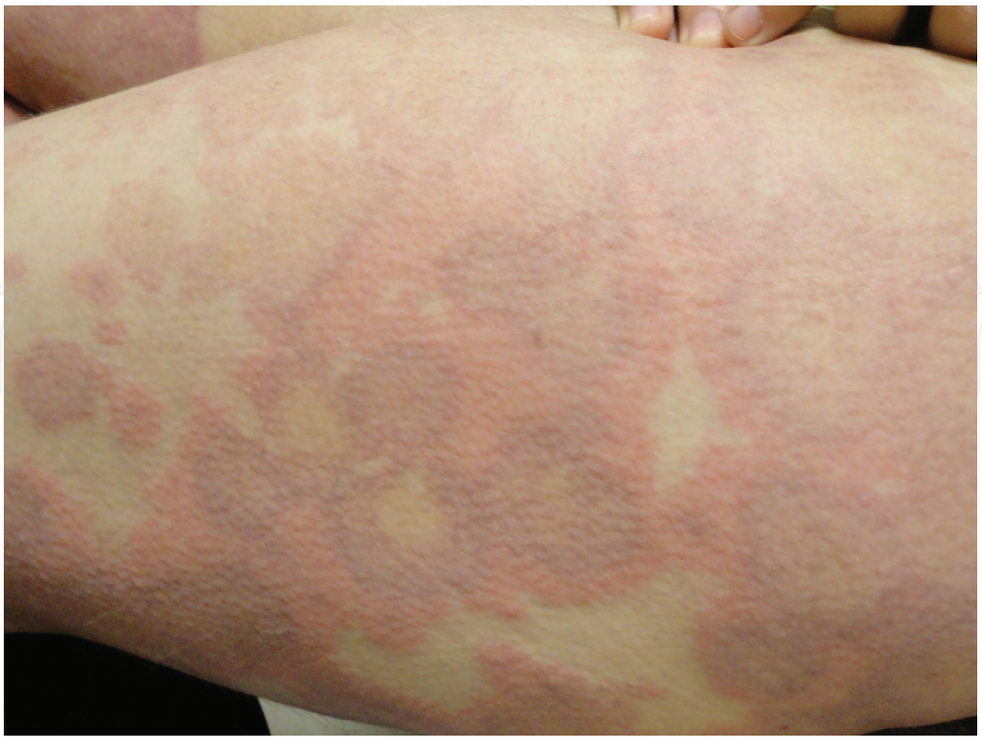

Figure 2. Widespread urticarial lesions with central purpura located on left lateral thigh of 85 years old female patient.

be asymptomatic, are usually pruritic and sometimes painful, tender or burning (in 33% of patients) in comparison to intensely pruritic urticarial lesions (**Table 1**) [12, 27]. UV presents usually with classical wheals but rarely livedo reticularis or even bullae may develop [12]. Angioedema can sometimes accompany urticarial lesions in up to 42% of UV patients [4, 12]. In a study reported it was detected that angioedema was present in 13% of HUV and 23% of NUV cases [28]. Following angioedema, a residual bruising may develop [12]. Typically clinical lesions of UV are recurrent and persist for more than 4–6 weeks even years [27]. As there are different clinical presentations of UV lesions, a biopsy is crucial in establishing a definite diagnosis [12]. All patients show histopathological evidence of leukocytoclastic vasculitis on biopsy [28].

Clinical characteristic	UV	Common urticaria
Lesion predilection	Dependent areas, areas under focal pressure, anywhere	Anywhere
Symptoms	Painful, tender, burning, pruritic	Intensely pruritic
Persistence	More than 24 hours [usually 24–72 hours]	Less than 24 hours [usually 30 minutes–24 hours]
Residual signs	Purpura or hyperpigmentation	None

Table 1. Clinical characteristics of cutaneous lesions of UV in comparison with common urticaria.

http://dx.doi.org/10.5772/68109

Upon confirmation of diagnosis, patients are divided into two major categories on the basis of serum complement levels: normocomplementemic UV (NUV) and hypocomplementemic UV [HUV] cases [28]. Many UV patients have NUV [27]. UV patients also frequently present with systemic manifestations (**Table 2**) [26]. The most commonly observed systemic manifestation of UV is termed as "AHA syndrome": arthralgias and arthritis, hives and angioedema [12]. Like in the situation of cutaneous lesions, common urticariais still in the differential diagnosis of systemic manifestations of UV as common urticariacan rarely has angioedema and systemic symptoms like arthralgia or abdominal pain [12]. Systemic manifestations of UV develop mostly in hypocomplementemic patients [12]. HUV patients frequently have an underlying systemic disease [26, 29]. Systemic manifestations of HUV patients occur regardless of being idiopathic (primary HUV) or associated with an underlying disease (secondary HUV) [12]. Clinical features of UV can exacerbate with some situations like emotional stress, anxiety, exercise, and excessive alcohol consumption [12]. Additionally, heat and spicy foods can increase the pruritus and/or urticarial lesions [30]. UV lesions can develop under pressure of tight and narrow clothing [30]. Smokers can develop more severe respiratory involvement and progression to COPD in HUV patients [31]. UV can sometimes develop in striae distensae and can present a diagnostic challenge in pregnancy [13]. UV can sometimes be a presenting sign of SLE or present with a clinical picture similar to SLE [12, 28]. Some patients have autoimmune idiopathic HUV with a lupus-like clinical picture, hence termed HUVS [2, 27]. HUVS patients usually have accompanying systemic involvement involving more than one organ system [26]. These patients presenting clinically as HUVS are mostly young women and many aspects of the clinical picture are similar to SLE [12, 28]. Schnitzler syndrome is another clinical condition related to UV [32]. It is defined as the presence of UV in association with mostly IgM monoclonal gammopathy and increased markers of systemic inflammation [32].

Occurrence	Systemic features
Common	Musculoskeletal: arthralgia, arthritis
Less common	Respiratory: cough, dyspnea, hemoptysis, COPD, asthma, pleural effusion Renal disease: hematuria, proteinuria, glomerulonephritis Gastrointestinal: substernal pain, abdominal pain, nausea, vomiting, diarrhea
Rare	Cardiac: pericarditis, pericardial effusion, cardiac tamponade Ophthalmologic: conjunctivitis, episcleritis, uveitis, geographic serpiginous choroidopathy, visual loss Other: fever, splenomegaly, lymphadenopathy, cold sensitivity, reversible tracheal stenosis
Very rare	CNS: pseudotumor cerebri, cranial nerve palsies, aseptic meningitis Miscellaneous: transvers myelitis, cardiac valve disease, optic atrophy, Jaccaud's syndrome [chronic postrheumatic fever arthropathy], peripheral neuropathy, pleuritis

Table 2. Clinical features of systemic involvement in UV.

Patients can present with general constitutional symptoms, like fever, arthralgias, malaise, and fatigue [12]. Most UV patients have musculoskeletal involvement presenting as arthralgia or arthritis [12, 26, 28]. Jaccoud's syndrome or arthropathy was defined as joint deformities similar to that of rheumatoid arthritis [12]. It consists of ulnar deviation of the fingers, swan neck deformities and subluxations in the hands [12]. This hand deformity is most commonly associated with SLE and rarely with HUV [12]. Ophthalmologic involvement is rare (10% of UV patients) and can present as conjunctivitis, episcleritis, uveitis, or geographic serpiginous choroidopathy leading to visual loss [12]. Eye involvement in the form of episcleritis and uveitis can develop mostly in HUV patients (21%) [28]. Pulmonary involvement may present clinically as cough, dyspnea, hemoptysis, COPD, asthma, pleuritic, emphysema, or pleural effusion [12]. HUVS patients presenting with COPD are usually young smokers, and the observed COPD is more severe than that seen in heavy smoker patients without HUVS [12]. Emphysema can develop in UV patients as a result of leukocytoclastic vasculitis of pulmonary vessels. Lung involvement may present clinically late in the disease process but is a leading cause of morbidity and mortality [12]. Renal disease can occur in 5–10% of patients with HUVS and is discovered by finding proteinuria and microscopic hematuria [12]. Renal involvement can present as glomerulonephritis in 20–30% of HUV cases [12]. Gastrointestinal involvement can present clinically as nausea, vomiting, substernal pain, abdominal pain, diarrhea, or general feeling of gastrointestinal distress [12]. Cardiac involvement can develop rarely [12]. Recurrent pericarditis, pericardial effusion, cardiac tamponade, and cardiac valvular disease have been reported [12]. Several HUVS patients with Jaccoud's arthropathy were reported to develop valvular heart disease requiring valvular replacement [12, 24, 33, 34]. Central and peripheral nervous systems can rarely be affected [12].

2.4. Diagnosis

Consensus meeting in 1996 stated that long lasting (at least 24 hour–5 days) indurated wheals, which may be itchy, painful, or tender, be associated with purpura and presence of associated extracutaneous findings, and cutaneous vasculitis confirmed by histopathological examination are defined as UV [35]. UV should be suspected in any patient with urticarial lesions lasting more than 24 hours. The prevalence of UV among all patients that present with urticarial lesions is 11% and among patients with chronic urticaria it is 15–20% [23, 36, 37]. To ascertain the exact duration of urticarial lesions, a particular lesion could be encircled with a marking pen and the patient is re-examined 24 hour later to confirm the persistence of urticarial lesions [23]. Diascopy and dermatoscopy can help to suspect UV [23, 38]. The lesions of UV may be non- or partially-blanchable on diascopic examination [23, 38]. It was termed as "disappearing halo test" in which upon diascopy clinically invisible purpura becomes evident as dark red or slightly brown macule in the center of a blanched UV lesion [38]. UV can disclose purpuric dots or globules in a patchy orange-brown background dermatoscopically corresponding to extravasation and degradation of red blood cells due to leukocytoclastic vasculitis [39–41]. These purpuric dots are reddish initially and later they become more purplish [40]. Conversely, urticarial lesions disclose prominent and sometimes reticular red lines corresponding to ectatic and horizontal subpapillary vessels [39–41]. Definitive diagnosis of UV

requires a lesion biopsy demonstrating typical histopathological features in addition to the previously described clinical characteristics in a patient presenting with urticarial lesions [4]. Two lesion biopsies, one for routine histopathology and one for direct immunofluorescence, should be obtained [2]. Biopsies should be taken from the early lesions, which are maximum 24–48 hours old [42]. Multiple biopsies may be required to establish a biopsy [42]. In the case, an UV diagnosis is made, the physician should additionally search for the presence of any underlying infectious etiology [43, 44]. The major finding to be searched for is the presence or absence of hypocomplementemia [2]. It was previously reported that 53–82% of UV patients have normal complement levels and hence NUV, 18–47% of UV patients have decreased complement levels and hence HUV [28, 45]. Approximately, 65% of HUV and 45% of NUV patients have systemic involvement [23]. Hypocomplementemic patients are rare (10–20% of all UV patients) and more likely to have systemic involvement and hence they should be appropriately investigated [23, 28, 42, 46]. Optimal classification of UV patients should be done by multiple (two to three) measurements of C1q, C3, C4, and CH50 during clinical observation of several months duration [2]. Measurements should be done during active and quiescent periods [2]. Rare patients with HUVS may have cardiac valvular incompetence with/without Jaccoud's arthropathy [24, 33, 35, 47]. In 1973, criteria to diagnose HUVS have been proposed [48]. A patient is diagnosed to have HUVS if he/she has two major and at least two minor criteria (**Table 3**) [48].

2.5. Laboratory examinations

A patient diagnosed to have UV should be appropriately tested [2]. Complete blood count, ESR, renal and liver functions, urinalysis, ANA, complements, should be examined in all cases with appropriate clinical findings of UV [2]. A scheme would be helpful for planning the laboratory examinations in all patients with clinical UV presentation and specialized tests should be performed in some patients who have clinical clues of systemic involvement [30]. Once

• Two major criteria
• Chronic urticarial eruption
• Low levels of complements
• At least two minor criteria
• Leukocytoclastic vasculitis
• Arthralgia/arthritis
• Ocular involvement [episcleritis or uveitis]
• Renal involvement [glomerulonephritis]
• Recurrent abdominal pain
• Presence of anti-C1q antibody

Table 3. Proposed criteria for diagnosing HUVS.

basic diagnostic evaluation has been performed, additional laboratory examinations should not be so extensive and should be directed with regard to clues in the history and physical examination [30]. Hematologic examinations can reveal anemia and leukocytosis in nearly half of the patients [49]. Patients with positive anti-C1q antibodies have been detected to have more frequent HUVS, angioedema, livedo reticularis, musculoskeletal, ocular and kidney involvement, and less frequent gastrointestinal and pulmonary involvement than patients without anti-C1q antibodies [46]. These anti-C1q autoantibodies may sometimes be detected in patients having SLE, Good-pasture syndrome or idiopathic membranoproliferative glomerulonephritis without showing signs of urticarial vasculitis [4, 50, 51]. A case having circulating immune complexes and a positive autologous serum skin test was also reported [52]. There are numerous reported cases who were associated with gammopaties and so patients should be appropriately evaluated [53–56]. Soluble serum vascular endothelial-cadherin is detected in systemic vasculitis cases in the acute period, and this can be used as a marker for endothelial cell damage and inflammatory response, but this is nonspecific for UV [57].

2.6. Histopathology

A lesional biopsy demonstrating the features of UV is the gold standard for diagnosis [4]. The key histopathologic feature is leukocytoclastic vasculitis affecting dermal capillaries and postcapillary venules (**Figure 3**) [2, 4]. Inflammation is located within the vessel walls and perivascularly [4]. Cellular infiltrate is primarily composed of neutrophils, rarely eosinophils, and lymphocytes may take place (**Figure 4**) [4]. Lymphocytes predominate in lesions older

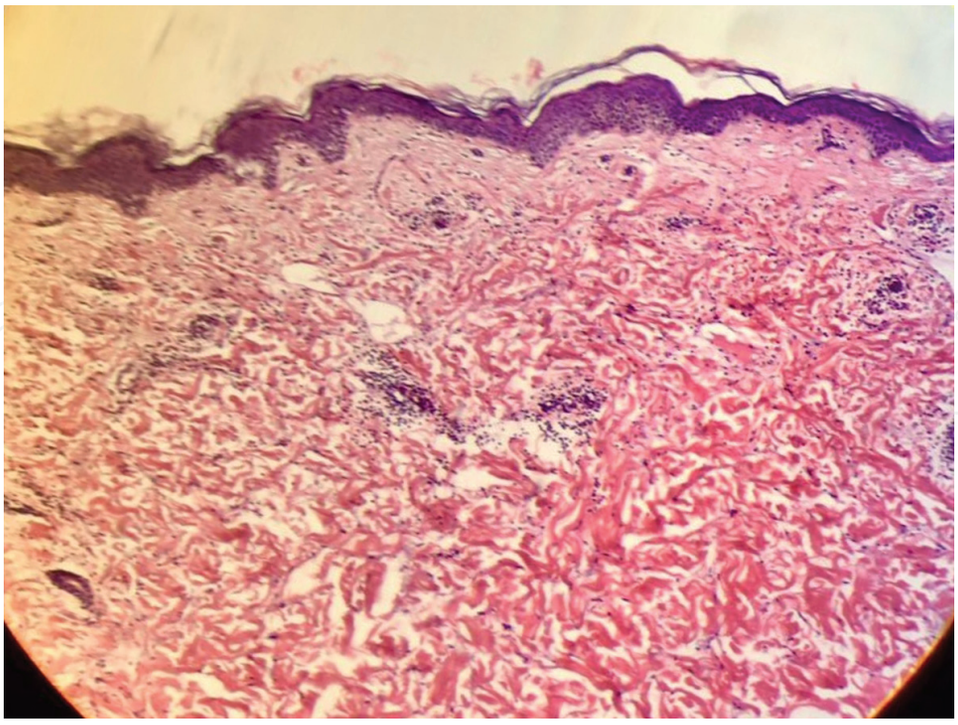

Figure 3. Superficial perivascular infiltration and leukocytoclastic vasculitis [Hemotoxylin & Eosin, original magnification ×100] [Courtesy, Onat Akin, MD].

than 48 hours [23]. In a study, 86% of specimens showed lymphocytic vasculitis, probably due to the age of the lesion biopsied [58]. If these histopathological changes described for UV involve the capillaries and postcapillary venules of the deep dermal layers, subcutaneous tissue, and submucosal connective tissue layers then it is termed as angioedema [2]. Direct immunofluorescence examination shows deposition of immunoglobulins, complement, and/or fibrinogen within and around vessel walls in 58–79% of cases [1, 4, 30, 46]. Basement membrane positive immunofluorescence examination is more frequent in HUV (70–96%) patients than in NUV (1–18%) patients [1]. However, the presence of basement membrane staining in a hypocomplementemic patient may suggest the diagnosis of SLE [30].

2.7. Differential diagnosis

The main differential diagnosis of UV is common urticaria [42]. The lesions in urticaria typically resolves in minutes to hours, migrates continually, and leaves no residual pigmentation after resolving in contrast to UV [42]. The main symptom in urticaria is the presence of intense pruritus, UV lesions may present with a more burning sensation [2]. Indurated urticarial lesions of UV are indistinguishable especially from that of chronic spontaneous urticaria [4]. Urticaria lesions may be huge and are usually larger than those of UV [2]. Chronic urticarial lesions are clinically more indurated than that of acute urticaria [4]. Eleven percent of all patients presenting with urticarial lesions are found to have UV [23]. In cases of chronic and antihistamine unresponsive chronic urticaria, when biopsies of lesions were performed, 15–20% of patients were found to have histopathological features of UV and hence diagnosed as UV [36, 37]. So performing a biopsy is necessary to differentiate exactly these two conditions. When patients

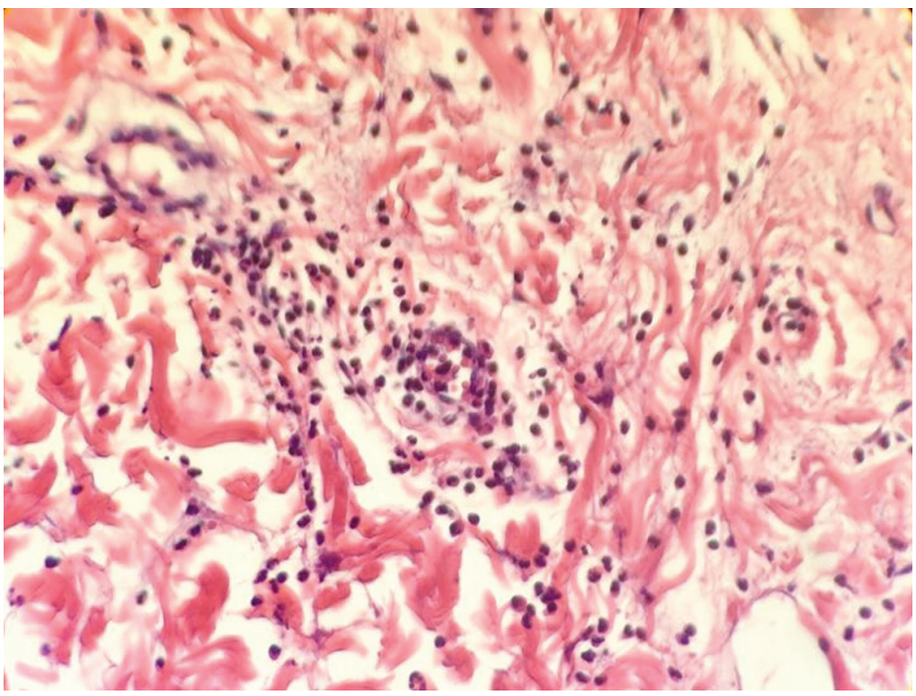

Figure 4. Small vessel vasculitis with neutrophilic infiltration and leukocytoclasia [Hemotoxylin & Eosin, original magnification ×400] [Courtesy, Onat Akin, MD].

with acute urticaria are biopsied, histopathology shows sparse cellular infiltrate and moderate to intense dermal edema [4]. Lesions of UV are usually smaller than ordinary urticaria and never present with annular lesions [38]. Additionally ordinary urticarial lesions are more pinkish than darker reddish lesions of UV [38]. In addition, UV lesions tend to be located more on dependent areas of the body [38]. Serum-sickness is a type-III hypersensitivity reaction that develops for example against horse-serum diphtheria antitoxin and can present with urticarial lesions [59]. Serum-sickness like reaction is a similar clinical entity triggered by drugs or infections [59]. Urticaria multiforme presents with annular lesions and acral edema or angioedema, mostly triggered by viral infections [59]. Both are self-limited and have favorable long-term prognoses [59]. Acute infantile hemorrhagic edema is another self-limited disorder that should be remembered in differential diagnosis of hemorrhagic urticarial lesions in pediatric cases [59]. Henoch-Schönlein purpura can present with urticarial lesions and should be searched for especially in pediatric cases with renal and/or gastrointestinal and/or arthritic involvement [59]. Urticarial arthritis is a condition observed in HLA-B51 positive patients, presenting with arthritis, urticaria (lasting less than 24 hours), and facial angioedema [49]. Some of the patients may show a biopsy with leukocytoclastic vasculitis some only leukocytic infiltration without vasculitis [49]. Acquired angioedema should be differentiated from HUV associated with angioedema and both disorders have decreased complement levels. Pruritic urticarial papules and plaques of pregnancy is the main differential diagnosis when UV develops in the pregnancy, especially in the striae distensae [60]. Likewise erythema multiforme, bullous pemphigoid, sweet's syndrome, and urticarial pigmentosa can be added to the differential diagnoses of UV [27].

Auto-inflammatory diseases are a group of rare hereditary monogenic disorders of innate immunity with presenting symptoms of fever and inflammatory, sometimes urticarial, skin lesions [3, 61, 62]. Auto-inflammatory diseases usually cause a familial life-long disease that starts in childhood in hereditary fever syndromes [62]. Auto-inflammatory syndromes cause flatter wheals and erythematous patches without surrounding flare and they last hours and even up to 24 hours and are accompanied by burning sensation rather than itching and they may be painful [62]. Lesions do not give any response to antihistamines and are associated with systemic symptoms of fever, fatigue, and arthralgia [62]. Very recently, vasculitis has been described histopathologically in three cases of auto-inflammatory diseases [61]. Hence, the clinician should take into account the rare possibility of auto-inflammatory associated vasculitis presenting with urticarial lesions and fever in the differential diagnosis of UV [61]. Some autoimmune disorders like SLE, Sjögren syndrome, dermatomyositis, or rheumatoid arthritis may present clinically with urticarial lesions [3]. Histopathological findings of UV are not specific in general and similar histopathological findings can be seen in SLE [42]. It is still unclear that HUVS is a similar disease to or a subtype of SLE [12, 28, 48, 63]. Both diseases share similar clinical findings and can present together [12, 28, 48, 63]. So when a patient is diagnosed as HUVS, he/she should also be evaluated for SLE [48]. Other systemic vasculitides may present clinically with urticarial lesions [3]. Rarely polyarteritis nodosa and Churg-Strauss syndrome may present clinically with urticarial lesions [3]. Some hematologic malignancies (lymphoma or gammopathies) and hematologic disorders (polycythemia vera and thrombocythemia) can also present clinically with urticarial lesions [3, 16, 17]. Other rare syndromes like PAPA, Blau, or Majeed syndromes can also present clinically with urticarial lesions [3].

2.8. Treatment

In any given patient with UV, if an underlying condition is present, it must be treated initially [2, 42]. Different degrees of clinical severity of the disease preclude proposal of any standard form of therapy [30]. Therefore, there is no universal therapy and variation in individual response to any form of therapy that exist [30]. In general, the more severe the systemic involvement (as in HUVS) is, the more challenging it becomes to treat the disease [42]. The most difficult patient to treat is the one who develops COPD or has established COPD in the setting of HUVS [2]. COPD in HUVS develops more frequently and most severely in patients who smoke, so patients should give up smoking and also avoid inhaling second-hand smoke [31]. One case has been reported to go into remission with an elimination diet [64]. This case may show the possibility of pseudoallergens' role in the etiopathogenesis of UV and similar to chronic urticaria treatment a pseudoallergen-free diet can be tried in selected cases. Antihistamines are helpful for the symptomatic control of pruritus in all patients and may be sufficient for the therapy of mild cutaneous UV without systemic involvement [4, 30]. However, antihistamines do not affect immune-complex-mediated inflammation and hence do not alter the course of the disease [4]. Cinnarizine, an antihistaminic used for Meniere's disease and car sickness, was found to be effective in UV patients [36]. A brief course of systemic corticosteroids may be useful to control intermittent exacerbations of UV, with both cutaneous and systemic involvement [4]. However, a dose of systemic corticosteroids up to 40 mg/day of prednisolone may be needed [30]. Long-term use is limited by the well-known side effects of corticosteroids and they should only be used in cases who are intolerant to or unresponsive to other alternative drugs [30]. A variety of alternatives to corticosteroids are used in the treatment of milder forms of UV [4]. These alternatives include indomethacin, colchicine, and dapsone that are commonly used in the clinical practice [4]. NSAIDs like indomethacin may help approximately half of patients with minimal disease [42]. Indomethacin use is usually discontinued or restricted by its gastrointestinal adverse effect potential, like upset stomach [4, 42]. In some unfortunate patients, NSAIDs can even cause UV or exacerbation of the existing UV [30]. Dapsone is a sulfone and shows more effectiveness than other alternatives in the treatment of UV [4]. Dapsone may work synergistically with pentoxifylline [4]. The mechanism of action of dapsone is poorly understood in the treatment of UV [4]. Before commencing on dapsone treatment, serum levels of glucose-6-phosphate dehydrogenase enzyme should be measured as deficiency of it results in severe hemolysis with dapsone usage [4]. Headache, nonhemolytic mild anemia and most importantly agranulocytosis may develop less frequently [4]. Hence, monitorization of complete blood count should be performed periodically in patients who use dapsone [4]. Patients having UV in the clinical setting of SLE or lupus-like disorder may have a more favorable response to treatment with dapsone [4]. Antimalarials like hydroxychloroquine have been reported to be effective in approximately 50% of patients with only cutaneous involvement [4, 30, 52]. Colchicine is an alkaloid that inhibits neutrophil chemotaxis, generation of lysosomes and stabilizes lysosomal membranes [4, 65]. It has clinical efficacy in selected cases of UV [65]. Reserpine is an alkaloid extracted from the roots of the plant Rauwolfia serpentine [66]. Reserpine was once used for the treatment of psychosis and hypertension [66]. It can be added to the antihistamines /corticosteroids in a dose of 0.3–0.4 mg thrice daily and reported to be helpful in majority of patients with UV [25, 66, 67]. If these alternative drugs do not get enough benefit or intermittent

systemic corticosteroids do not control symptoms adequately then chronic systemic corticosteroid usage can be considered in milder forms of disease [4]. Higher dosage systemic corticosteroid treatment is necessary in the presence of hypocomplementemia or systemic involvement [4]. Systemic prednisone or equivalent is usually given at 1 mg/kg dose till clinical remission, later the dose could be slowly tapered [4]. Systemic corticosteroids could be tapered and discontinued without relapse in some patients [4]. However, many patients do experience disease relapse and need chronic corticosteroid treatment [4]. In the case of inadequate systemic corticosteroid response or when unacceptable corticosteroid adverse effects do occur than second line treatment choices should be considered, like azathioprine or cyclophosphamide [4]. In the resistant patients, systemic corticosteroids can even be effectively combined with dapsone, azathioprine, and cyclophosphamide [30]. In the chronic and resistant subset of patients, corticosteroid-sparing immunosuppressive agents such as azathioprine, cyclophosphamide, cyclosporine A, or mycophenolate mofetil have been shown to be effective [4]. Azathioprine has been shown to be a useful adjunct to corticosteroids for stabilization of renal and pulmonary function [4, 68]. Methotrexate has usually inconsistent and disappointing results in the treatment of UV [4, 24, 33, 69]. Methotrexate is typically effective in inflammatory myositis associated with HUVS [70]. Favorable clinical responses have been achieved with cyclophosphamide in corticosteroid-resistant UV cases [4, 71]. Cyclosporine A has provided favorable clinical efficacy in the treatment of HUVS, including cases that are resistant to cyclophosphamide [4]. Cyclosporine A has been shown to improve respiratory involvement in HUVS patients with improvements in the forced expiratory volume in one second (FEV1), the diffusing capacity of the lung for carbon monoxide (DLCO) and regression of leukocytosis in bronchoalveolar lavage (BAL) [2]. Cyclosporine A has also been shown to be effective in renal involvement associated with HUVS [72]. Mycophenolate mofetil has also been shown to be efficacious in the treatment and maintenance of patients with HUV/HUVS [24, 73, 74]. Gold injections were tried and found to be effective in UV as in rheumatoid arthritis, but it is now a historical approach [75]. Plasmapheresis can provide rapid but temporary benefit in recalcitrant cases of UV [4, 76]. Plasma exchange has been shown to control symptoms rapidly during treatment but lesions recurred later in some patients [30, 76, 77]. High dose intravenous immunoglobulin (IVIG) also has been tried and shown to be effective in some recalcitrant HUVS cases [20, 78]. However, there are cases with inefficient response to IVIG [67, 79]. Rituximab can be used in refractory and/or relapsing or severe cases with prolonged duration of efficacy [46, 56, 80]. Anti-IL-1 blockage (anakinra, canakinumab) has shown promising results in the treatment of UV [81, 82]. However, these patients may have UV associated with auto-inflammatory diseases. A therapy-resistant SLE patient with UV lesions showed good response to IL-6 antagonist tocilizumab [83]. Omalizumab was used in a small number of NUV patients with success but some displayed a quick relapse following discontinuance [84, 85]. First line treatments used were determined to be mostly corticosteroids, hydroxychloroquine, and colchicine in decreasing order in a large retrospective study that involved only HUV patients [46]. Second and third line treatments given in this study were corticosteroids, hydroxychloroquine, and immunosuppressive agents in decreasing order [46]. In patients having hepatitis C infection, cryoglobulinemia and resultant UV, effective antiviral therapy (interferon-alpha and ribavirin) should be instituted [2]. Effective antiviral therapy has been shown to control HCV infection and cure UV in nearly half of these

patients [2, 86, 87]. However, if the antiviral treatment is stopped the UV lesions do recur [87]. Angioedema may develop at any time in the course of UV [31]. If angioedema develops and involves larynx, the initial treatment may be epinephrine [31].

2.9. Course and prognosis

UV is a complicated disease and it has an unpredictable course [12]. An individual can have lesions for weeks to many years continuously or intermittently [12, 30]. The average duration of the disease was found to be 3 years and disease could last up to 23 years [30, 42]. Response of patients with UV to any given treatment is variable [4]. The course of the idiopathic NUV is favorable overall and patients usually do not develop any other diseases or mortality in the follow up [12, 30]. The course of HUV and HUVS may be less favorable [12, 30]. Patients with HUV may need an additional add-on therapeutic after about a median of 8 months duration [46]. Musculoskeletal, ocular, and renal disease usually responds to systemic treatment without any long-term severe consequences [14]. After adequate therapy serum complements increase to or near to normal values and anti-C1q antibody titers decrease [14]. However, serum C1q levels remained below normal values even in the presence of complete remission [14]. UV presents clinically in a spectrum of disease severity from NUV to HUV to HUVS [42, 46]. However, there is no finding to support the presence of any transition from one to another in follow up of these patients [42]. The main causes of morbidity and mortality are pulmonary manifestations like COPD, cardiac manifestations and laryngeal edema in patients with HUVS [14, 30, 31]. Precocious emphysema and COPD develop in patients with HUVS and especially in those patients who are moderate to heavy smokers [14, 88]. Onset of dyspnea heralds a poor outcome in HUVS patients with pulmonary involvement [14]. Treatment usually did not appear to alter the progression of COPD [14]. Of these HUVS patients with chronic or recurrent dyspnea, 55% die of respiratory failure [14]. In this subset of patients bronchogenic carcinoma can also be seen and adds to the overall morbidity and mortality risk [46, 88]. Cardiac involvement with pericarditis or valvulitis and significant valvular damage may develop in rare cases with HUVS and may be progressive and fatal [24, 33, 34, 46]. As cardiac involvement may cause significant morbidity and mortality and as its frequency is unknown, all patients should be evaluated [89]. Angioedema develops in 51% of cases with HUVS and may be life-threatening if it involves larynx [31, 46]. Pediatric and young adult patients (onset of disease before age of 30) may experience more renal involvement and show severe pulmonary complications and may have graver prognosis [89]. There may be significant morbidity resulting from involvement of other organ systems. Rarely vasculitis can affect optic nerve and retina and hence can threaten vision [90]. All UV patients need to be evaluated ophthalmologically as 15–20% of all UV cases may have ocular involvement in the disease course [90]. A patient with Muckle-Wells disease with associated UV developed sudden bilateral sensorineural hearing loss and had modest outcome following cochlear implantation [91]. Gastrointestinal involvement can lead to ischemic ulceration in the bowel [30]. Renal involvement can lead to renal insufficiency, this is especially common in pediatric cases and should be promptly treated [30, 89].

There are other rare associated cutaneous findings in UV patients reported in the literature. A case with rapidly progressing acquired cutis laxa following involvement of the skin areas with lesions of NUV was reported [92]. A reported pregnant woman developed acquired

reactive perforating collagenosis at the sites of resolved UV lesions 3 weeks following the onset and treatment of UV [19]. A reported UV case developed acquired hemophilia following 4.5 years of follow up [93]. Another reported NUV case first presented with acquired hemophilia and developed NUV and angioedema in the following 5 months [94]. Rarely inflammatory myositis can develop in HUVS cases despite ongoing immunosuppressive therapy [70]. Complement deficiency may lead to increased susceptibility to the infections with encapsulated bacteria, especially meningococcus [95]. As a result, a case of meningococcal meningitis that developed in a patient with HUVS was reported [95]. The course of the UV may accompany the course of underlying disease. A paraneoplastic NUV case was reported to clear with chemotherapy for underlying chronic lymphocytic leukemia and disease recurred with the recurrence of underlying hematologic malignancy [21]. Three women with UV were evaluated in a study including 29 systemic vasculitis patients with 51 pregnancies to search for the outcome of pregnancy in systemic vasculitis [96]. The authors have found that the patients with a diagnosis of systemic vasculitis may have exacerbation of the vasculitic disease during pregnancy or following delivery, may have more pregnancy related morbidity like preeclampsia and may have a lower median gestational age [96].

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