

SYSTEMATIC REVIEWS AND META-ANALYSIS

Comorbidity and pathogenic links of chronic spontaneous urticaria and systemic lupus erythematosus – a systematic review

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Clinical & Experimental Allergy

Summary

Chronic spontaneous urticaria (CSU) is a common mast cell-driven disease characterized by the development of wheals (hives), angioedema (AE), or both for > 6 weeks. It is thought that autoimmunity is a common cause of CSU, which is often associated with autoimmune thyroiditis, whereas the link to other autoimmune disorders such as systemic lupus erythematosus (SLE) has not been carefully explored. Here, we systematically reviewed the existing literature for information on the prevalence of CSU in SLE (and vice versa) and we examined the possible clinical and pathogenetic relationship between CSU and SLE. The prevalence of CSU and CSU-like rash in SLE was investigated by 42 independent studies and comorbidity in adult patients reportedly ranged from 0% to 21.9% and 0.4% to 27.5%, respectively (urticarial vasculitis: 0–20%). In children with SLE, CSU was reported in 0–1.2% and CSU-like rash in 4.5–12% (urticarial vasculitis: 0–2.2%). In contrast, little information is available on the prevalence of SLE in patients with CSU, and more studies are needed to determine the rate of comorbidity. Recent insights on IgG- and IgE-mediated autoreactivity suggest similarities in the pathogenesis of CSU and SLE linking inflammation and autoimmunity with the activation of the complement and coagulation system. Future studies of patients with either or both conditions could help to better define common pathomechanisms in CSU and SLE and to develop novel targeted treatment options for patients with CSU and SLE.

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Cite this as: P. Kolkhir, D. Pogorelov, O. Olisova and M. Maurer. *Clinical & Experimental Allergy*, 2016 (46) 275–287.

Introduction

Chronic spontaneous urticaria (CSU), formerly also called chronic idiopathic urticaria, is a mast cell (MC)-driven disease characterized by the recurrence of wheals (hives), angioedema (AE), or both for > 6 weeks in the absence of specific triggers [1]. At any given time, 0.5–1% of the population suffers from CSU and its prevalence is thought to be increasing [2].

It is widely held that several distinct causes and conditions including autoimmunity can be responsible for CSU. Over the last 10 years, numerous groups have investigated and reported on the relevance and the signals involved in autoimmune mechanisms in CSU [3–5]. Although CSU does not meet all of Witebsky's criteria for autoimmune diseases [3, 6], significant circumstantial evidence supports the notion that CSU can be an autoimmune disorder, at least in a subpopulation of patients. For example, patients with CSU exhibit T lymphocytic infiltration of wheals [7], cytokine profiles

typical for autoimmunity [8–10], MC activating autoantibodies and positive responses to cutaneous injections of their own serum, autologous serum skin test (ASST), in up to 50% [3, 6]. Patients with CSU also respond to immunosuppression, for example by cyclosporine [11] or glucocorticosteroids, and they show high rates of comorbidity for other autoimmune disorders [12]. The latter can be explained by a very strong association with major histocompatibility complex (MHC) class I alleles HLA-Bw4 and HLA-DQ1 and MHC-II alleles HLA-DRB1*04 and DQB1*0302, noted in patients with CSU, especially in ASST-positive cases [12, 13]. CSU is most frequently found to be associated with autoimmune thyroiditis [14], whereas the link to other autoimmune diseases including systemic lupus erythematosus (SLE) has not been systematically explored except for the study by Confino-Cohen et al. [15] which will be discussed below.

Systemic lupus erythematosus is an autoimmune multisystem disease with an unpredictable course

affecting different organs including skin and mucous membranes and is characterized by the loss of immune tolerance to self-antigens and deregulated autoantibody production [16, 17]. Patients with SLE have been reported to show considerable comorbidity for CSU, and SLE is held to be one of the underlying conditions that can cause CSU. But a number of questions still remain unresolved. What is the prevalence of CSU in patients with SLE and vice versa? Are CSU and SLE pathogenically related or merely concomitant? Can CSU be a predictor of SLE severity and duration? Can the presence of other autoimmune diseases such as SLE in patients with CSU point to an autoimmune pathogenesis in these patients?

The aim of our review is to address these questions by describing the prevalence of CSU in SLE and of SLE in CSU, by examining the clinical and pathogenic relationship between CSU and SLE and by revealing common underlying mechanisms in these conditions.

Comorbidity of CSU and SLE

Prevalence of CSU in patients with SLE

Patients with SLE have been investigated for the presence of skin problems and the prevalence of skin diseases including CSU in a large number of studies (Table 1). The prevalence of cutaneous manifestations in SLE varies from 30% to 100% (Tables 1 and 2) [18–31]. The types of skin involvement are diverse ranging from classical butterfly erythema and atrophic hyperkeratotic lesions to vasculitis, alopecia, livedo reticularis and Raynaud's phenomenon [20].

According to Gilliam and Sontheimer, the skin manifestations of SLE are classified as LE-specific and LE-non-specific based on histopathological findings [32]. LE-specific mucocutaneous lesions are important for making the diagnosis of SLE and comprise 3 of 11 revised American Rheumatism Association (ARA) criteria for disease classification. Typical histological features of LE-specific skin disease include hydropic changes along the epidermal basal cell layer and mononuclear cell infiltrates in dermis [20]. LE-non-specific lesions are related to the underlying SLE process, imply active disease course [18, 33–35] and systemic involvement, but are also frequently encountered in other autoimmune diseases [36, 37].

Chronic urticarial rash (CUR) is a common feature in SLE. The two most common underlying causes of CUR in SLE are CSU and urticarial vasculitis (UV). Urticaria and UV are considered to be histologically non-specific lesions of SLE [32, 38], the latter belonging to the group of vascular cutaneous disease, the former being a separate category in the Gilliam and Sontheimer classification. Of note, CUR due to CSU may be pathogenically

unrelated to SLE in some cases, for example when CUR is due to the administration of anti-rheumatic treatment such as immunosuppressive (e.g. methotrexate) [39], non-steroidal anti-inflammatory drugs (NSAIDs) [40] or biologicals (e.g. tumour necrosis factor α (TNF- α) inhibitors [41]. Urticaria-like lesions can also appear in lupus tumidus (urticarial plaque of LE) [32, 38] that is an LE-specific, uncommon, but distinct subtype of chronic cutaneous LE with specific erythematous, non-scarring plaques and an urticaria-like morphology. These lesions appear in sun-exposed areas and, unlike in other variants of chronic cutaneous LE, there is no epidermal involvement [42, 43].

Urticarial vasculitis has a similar appearance as CSU, but the lesions persist longer (> 24 h). They are often accompanied by residual pigmentation, burning of the skin rather than itching, and systemic symptoms such as fever, arthralgia and abdominal pain. Hypocomplementaemia can be found in 18–32% of UV patients and indicates a more severe disease [44]. Rare hypocomplementemic urticarial vasculitis syndrome (HUVS) is considered to be an unusual type of SLE, SLE-associated syndrome or an entirely separate entity [45–47]. Histologically, UV is characterized by signs of leukocytoclastic vasculitis involving small veins in superficial layers of the skin [1, 5, 26, 44, 48]. Despite these differences between CSU and UV, it can be challenging to distinguish between the two disorders when assessing patients with SLE, also because there may be partial overlap [44, 49].

For our review of the literature (search criteria: systemic lupus erythematosus and rash, urticaria and/or vasculitis), we assessed all relevant publications identified ($n = 42$, 1950–2015) for information on the numbers and percentages of SLE patients with skin manifestations, with 'urticarial rash', with chronic spontaneous urticaria (designated in some publications as chronic idiopathic urticaria or chronic urticaria) or with UV in both adult and paediatric patients with SLE (see Tables 1 and 2).

We identified 36 studies that report information on CUR, CSU, and/or UV in adult patients with SLE. We grouped these studies in five groups, depending on whether they reported data on 1) CUR and UV, but not CSU (group 1; $n = 14$), 2) CUR, but not CSU or UV (group 2; $n = 12$), 3) CSU and UV, but not CUR (group 3; $n = 8$), 4) CRU, CSU and UV (group 4; $n = 1$), or 5) CSU, but not CUR or UV (group 5; $n = 1$). We consider CUR in group 1 study patients to be due to CSU, that is to be CSU-like rash. CUR in group 2 study patients may have been due to CSU, UV or other causes. Group 2 studies were, therefore, not included in our analyses. Group 3 studies were included in our analysis of prevalences of CSU and UV, as was the group 1 study. For UV, only studies in which UV was distinguished

Table 1. Prevalence of chronic urticarial rash (CUR), chronic spontaneous urticaria (CSU) and urticarial vasculitis (UV) in adult patients with SLE according to published studies

Study	<i>n</i>	<i>n</i> (%) of patients with skin manifestations	<i>n</i> (%) of patients with chronic urticarial rash	<i>n</i> (%) of patients with CSU	<i>n</i> (%) of patients with UV	Country	Year	Ref
Hawro et al.	68	52 (76.5) [†]	—	0	5 (7.4)	Poland	2013	35
Biazar et al.	408	—	—	0	< 2%	Germany	2013	138
Bhattarai et al.	41	26 (63.4)*/30 (73.2) [†]	—	9 (21.9)	5 (12.2)	Nepal	2012	124
Das et al.	30	—	8 (26.7)	—	3 (10) [‡]	India	2011	125
Grönhagen et al.	260	164 (63.1)	18 (7)	—	21 (8) [‡]	Sweden	2010	20
Parks et al.	228	—	29 (13)/37 (16) [§]	—	—	USA	2010	132
Fathi et al.	185	148 (80.5)*/70 (37.84) [†]	7 (3.87)	—	70 (37.84) [‡]	Egypt	2010	126
Mowla et al.	40	38 (95)	11 (27.5)	—	25 (62.5) [‡]	Bangladesh	2010	127
Kole et al.	150	45 (30)	10 (6.67)	—	50 (33.3) [‡]	India	2009	19
Koskenmies et al.	77	5–59 (6.5–85.5)	7 (9.1)	—	6 (7.8) [‡]	Sweden	2008	128
Nazarinia et al.	410	367 (89.5)	45 (11)	—	90 (22) [‡]	Iran	2008	133
Bouaziz et al.	50	> 88%	1 (2)	—	1 (2)	France	2007	134
Ramos-Casals et al.	670	68 (89)	3 (0.4)	—	5 (0.7)	Spain	2006	135
Hau	115	—	11 (9.6)	—	3 (2.6) [‡]	China	2006	129
Wozniacka et al.	72	—	—	0 [¶]	—	Poland	2003	91
Rabbani et al.	198	140 (70)	20 (10)	—	—	Pakistan	2003	21
Cardinali et al.	58	50 (86.2)*/18 (31) [†]	—	0	8 (13.7) [‡]	Italy	2000	37
Morton et al.	49	—	8 (16.3)	—	—	England	1998	130
Al-Attia and Al Ahmed	42	—	—	0	11 (27) [‡]	UAE	1998	141
Drenkard et al.	540	160 (30)	6 (1.1)	—	—	Mexico	1997	22
Yell et al.	73	73 (100)	32 (44)	—	—	England	1996	18
Kapadia and Haroon	40	35 (87.5)	3 (7.5)	—	20 (50) [‡]	Pakistan	1996	23
Vitali et al.	> 10 000	> 3000 (> 30%)	6.3%	—	18.6% [‡]	Worldwide	1996	140
Beutner et al.	50	—	—	0	10 (20)	USA	1992	142
Wallace et al.	464	255 (55)	17 (3.7)	—	—	USA	1992	131
Weinstein et al.	84	69 (82)	—	9 (11)	0	Australia	1987	25
Callen	17	17 (100)	—	0	1 (5.9)	USA	1985	31
Provost et al.	143	—	3 (2.1)	—	7 (4.9)	USA	1980	26
O'Loughlin et al.	54	—	1 (1.8)	2 (3.7)	9 (16.7)	USA	1978	53
Lee et al.	110	95 (86.3)	5 (4.5)	—	—	Canada	1977	27
Hendrix	28	—	4 (14.3)	—	—	Denmark	1973	143
Becker	50	—	14 (28)	—	—	USA	1973	144
Estes et al.	150	122 (81)	19 (13)	—	31.5 (21) [‡]	USA	1971	28
Dubois and Tuffanelli	520	372 (72)	36 (6.9)	—	—	USA	1964	29
Scott and Rees	30	—	15 (50)	—	—	England	1959	73
Harvey et al.	105	85 (80.9)	7 (7)	—	—	USA	1954	30

The prevalence of CSU and CSU-like rash in adult patients with SLE was found to range from 0% to 21.9% and 0.4% to 27.5%, respectively. The range of prevalence of UV in patients with SLE was 0–20%.

*Specific for SLE skin lesions.

[†]Non-specific for SLE skin lesions.

[‡]These data represent the total numbers (percentages) of patients with any type of vasculitis or cutaneous vasculitis, which includes but is not limited to UV cases. This report was, therefore, not considered when we evaluated the minimum and maximum prevalence values for UV in SLE.

[§]Childhood onset/adult onset of urticaria (data on self-reported history based on interview and questionnaire).

[¶]Only acute urticaria cases were described.

—: the number of patients was not reported (no data).

from other forms of vasculitis were included in our analysis.

The prevalence of CSU and CSU-like rash in adult patients with SLE was found to range from 0% to 21.9% and 0.4% to 27.5%, respectively. The range of prevalence of UV in patients with SLE was similar to

that of CSU or CSU-like rash: 0–20%. We identified only six studies with results on CUR, CSU, and/or UV in children with SLE. We analysed these studies by applying the strategy used for adult studies outlined above and found CSU and CSU-like rash to range from 0% to 1.2% and from 4.5% to 12%, respectively. The

Table 2. Prevalence of chronic urticarial rash (CUR), chronic spontaneous urticaria (CSU) and urticarial vasculitis (UV) in children patients with SLE according to published studies

Study	<i>n</i>	<i>n</i> (%) of patients with skin manifestations	<i>n</i> (%) of patients with chronic urticarial rash	<i>n</i> (%) of patients with CSU	<i>n</i> (%) of patients with UV	Country	Year	Ref
Ferriani et al.	852	245 (28.8)	—	10 (1.17)	—	Brazil	2015	58
Dickey et al.	25	—	3 (12)	—	3 (12)*	USA	2013	56
Spadoni et al.	271	—	—	2 (0.7)	0	Brazil	2011	55
Bader-Meunier et al.	155	108 (70)	7 (4.5)	—	47 (27)*	France	2005	54
Iqbal et al.	39	28 (72)	3 (8)	—	1 (2.5)*	USA	1999	139
Wananukul et al.	57	44 (77)	—	0	1 (2.2)	Thailand	1998	57

CSU and CSU-like rash was found to range from 0% to 1.2% and from 4.5% to 12%, respectively. The prevalence of urticarial vasculitis in children with SLE ranged from 0% to 2.2%.

*These data represent the total numbers (percentages) of patients with any type of vasculitis or cutaneous vasculitis, which includes but is not limited to UV cases. This report was, therefore, not considered when we evaluated the minimum and maximum prevalence values for UV in SLE.

—: the number of patients was not reported (no data).

prevalence of urticarial vasculitis in children with SLE ranged from 0% to 2.2%.

Our findings show that CSU and CSU-like rash may be more common in patients with SLE than previously thought. They also call for a move from 'urticarial rash' to a clear distinction between CSU and UV in future studies of the features and comorbidities of SLE. Based on our analyses of the literature, the most recent studies have adopted this strategy. In addition to the differences in the nomenclature used in the studies reviewed, we found that methodologies in some studies were different and this could have also influenced the observed differences.

Recent publications suggest that neutrophilic urticaria or urticaria with predominantly neutrophilic inflammatory infiltrate may be a marker for SLE [44, 49, 50]. For example, Saeb-Lima et al. [44] performed biopsy in six patients with CSU and active SLE. Microscopy demonstrated interstitial and perivascular neutrophilic infiltrates with leukocytoclasia, vacuolar alteration along the dermal-epidermal junction, and no signs of vasculitis in all patients. The authors [44] suggested the term 'autoimmunity-related neutrophilic dermatosis' to be used for CSU in the context of autoimmune connective tissue diseases instead of 'neutrophilic urticarial dermatosis' [50] or 'neutrophilic urticaria' as proposed earlier by Peters and Winkelmann [51].

Urticaria in adult patients with SLE – what does it mean?

Up to 22% and 28% of adult patients with SLE present with CSU or CSU-like rash, in the studies we reviewed. The authors of some studies concluded that CSU, CSU-like rash and other LE-non-specific skin lesions are detected mainly in patients with SLE (but not in CLE) and usually in the active phases of the disease [26, 35, 37, 52]. O'Loughlin et al. observed CSU-like rash as a major cutaneous symptom in 12 (23%) of 54 patients with SLE.

Skin biopsy performed in 11 of these patients revealed necrotizing vasculitis with leukocytoclasia in nine patients suggesting UV. CSU was found only in 2 (3.7) of 54 patients with SLE [53]. Provost et al. followed 143 patients with SLE, 10 of them with CSU-like skin rash. In two of six patients, direct immunofluorescence showed IgM and C3 deposits in the walls of and surrounding blood vessels. Nine of 10 patients had active SLE with systemic symptoms (arthritis, renal diseases etc.), high levels of antibodies (to DNA and Sm), immune complexes and hypocomplementaemia. Similar urticarial lesions were not detected in 35 patients with discoid lupus erythematosus. Therefore, the authors concluded that CSU-like rash is a skin manifestation of SLE, occurs more often in patients with active SLE, is not IgE-mediated and may be due to immune complex deposition [26]. Horváth et al. [52] went further suggesting that urticaria in patients with SLE predicts unfavourable prognosis and is mediated not only by immune complexes, but also by anaphylatoxin formation resulting from complement activation.

Urticaria in children with SLE – what does it mean?

The prevalence of CSU and CSU-like rash in children with SLE seems to be lower than in adult patients with SLE (range: 0–12% and 4.5–12%, respectively, Table 2) [54–57]. For example, in a retrospective Brazilian multicenter study, CSU was observed in 10 (1.17%) of 852 paediatric patients with SLE [58]. In this study, Ferriani et al. demonstrated that CSU occurs predominantly at SLE onset and is associated with moderate/severe SLE without major organ involvement. In a retrospective French multicenter study urticaria was found in 7 (4.5%) of 155 children (female : male ratio was 4.5 : 1) in whom SLE developed before the age of 16 years [54]. Dickey et al. [56] described urticaria in 3 (12%) of 25 patients with SLE. Spadoni et al. [55] observed acute

urticaria in 4 (1.5%) of 269 and CSU in only 2 (0.7%) of 271 juvenile SLE cases, where it appeared to be the first manifestation of the disease: in a 5-year-old girl with a 3-month history of CSU, elevated complement levels, and ANA, the diagnosis of SLE was made 1 year later, and in a 13-year-old girl with a 1.5-month history of CSU, ANA 1 : 160 and normal complement levels SLE was diagnosed 3 years later. Several other studies [59–61] have described that autoimmune CSU is found in children, as assessed by ASST (positive result in 76 [28%] of 267 patients [62]). In contrast to adult studies they do not point to the fact that ASST-positive or ASST-negative patients may be more likely to develop other autoimmune diseases and they indicate that investigations for autoimmune thyroid disease or SLE and other connective vascular diseases in children with CSU are not of benefit [55, 61–67]. The likelihood of having an autoimmune disease increases with age [64].

Wananukul et al. [57] assessed mucocutaneous involvement in 57 children with classical SLE during a 6-year period (4–15 years old, female : male ratio was 4.2 : 1). Cutaneous manifestations were found very often (77%), but only one child had urticaria-like lesions and the histopathology showed leukocytoclastic vasculitis.

Prevalence of SLE in patients with CSU

Little is known about the prevalence of SLE in CSU, although SLE has been described to occur in patients with chronic urticaria as early as 1978 [68]. Based on a few case reports, CSU is sometimes considered as an initial harbinger of future SLE development [44, 55, 69]. In the only published study that investigated this, 12 778 adult patients in Israel were assessed retrospectively [15]. Patients with CSU were found to have a significantly higher risk of developing SLE (odds ratio, 14.6; $P < 0.001$) as compared to the control group [15]. The incidence of SLE in patients with CSU, based on the data from this study, is $2\text{--}4.7/10^5$ [15] as compared to $1\text{--}8.7/10^5$ in the general population [70]. Interestingly, the incidence of SLE was found to be significantly higher in women than in men with CSU or women of the control group. 49 of 52 (94.2%) patients with CSU and SLE were women and only three of 52 (5.8%) were men. The risk of having SLE was increased 26.7 times when comparing women with CSU with women in the control group ($P < 0.0005$). Women are affected by CSU twice as often as men [71, 72]. In SLE, the female : male ratio is 4 : 1–15.7 : 1 [18, 19, 21, 23, 24, 28, 73, 74]. In only eight of 52 (15.4%) cases, SLE was diagnosed before the onset of CSU, whereas CSU was diagnosed before SLE in 44 of 52 (84.6%) patients [15].

Common pathomechanisms in CSU and SLE

The role of autoantibodies

SLE is characterized by B and T cell abnormalities (e.g. changes in receptor structure and cell signalling) and production of a variety of autoantibodies, mainly against nuclear antigens, complement fragments, for example C1q [75, 76], and DNA followed by immune complex formation and deposition in different organs, causing tissue damage and clinical manifestations [77, 78]. Most of these autoantibodies are dsDNA-specific IgG [79]. Their levels often increase prior to exacerbation of the disease [77], and they deposit in the kidneys and produce glomerular nephritis [80]. In many patients with SLE clinical manifestations follow the appearance of antibodies by many years, sometimes by more than a decade [15].

CSU is also characterized by the production of IgG autoantibodies in approximately 40% of cases [81]. IgG autoantibodies against the high-affinity IgE receptor FcεRI, IgE, or both can cause MC degranulation (Fig. 1), and these autoantibodies appear to be involved, in some patients, in the development of wheal-and-flare reactions after intradermal autologous serum injections (ASST) [82]. This IgG autoreactivity in patients with CSU is reportedly associated with a longer duration of the disease and a poor response to treatment with antihistamines [81].

Interestingly, patients with CSU can also exhibit increased levels of autoantibodies typically found in SLE, although this is an inconsistent finding and not common. For example, in a recent study with 12 778 patients with CSU and 10 714 control subjects, autoantibodies to double-stranded DNA were detected in 16 patients with CSU and only 1 control subject, antinuclear antibodies were found in 248 patients with CSU and in 17 of the control group, and rheumatoid factor was found in 233 patients with CSU and in two control subjects [15]. On the other hand, CSU-specific autoantibodies have been described to occur in patients with SLE. Fiebiger et al. [83] detected anti-FcεRIα IgG autoantibodies not only in 38% of patients with CSU, but also in patients with SLE (20%) as well as other autoimmune diseases: pemphigus vulgaris (39%), dermatomyositis (36%) and bullous pemphigoid (13%), but not in sera of atopic dermatitis patients or healthy volunteers. Antibodies found in CSU reportedly belong mainly to the complement-fixing subtypes IgG1 and IgG3 and have pronounced histamine-releasing activity. In contrast, the autoantibodies found by the authors in other autoimmune disorders were IgG2 and IgG4, non-functional and non-pathogenic, that is without histamine-releasing and complement-activating properties. Other groups have obtained and published similar

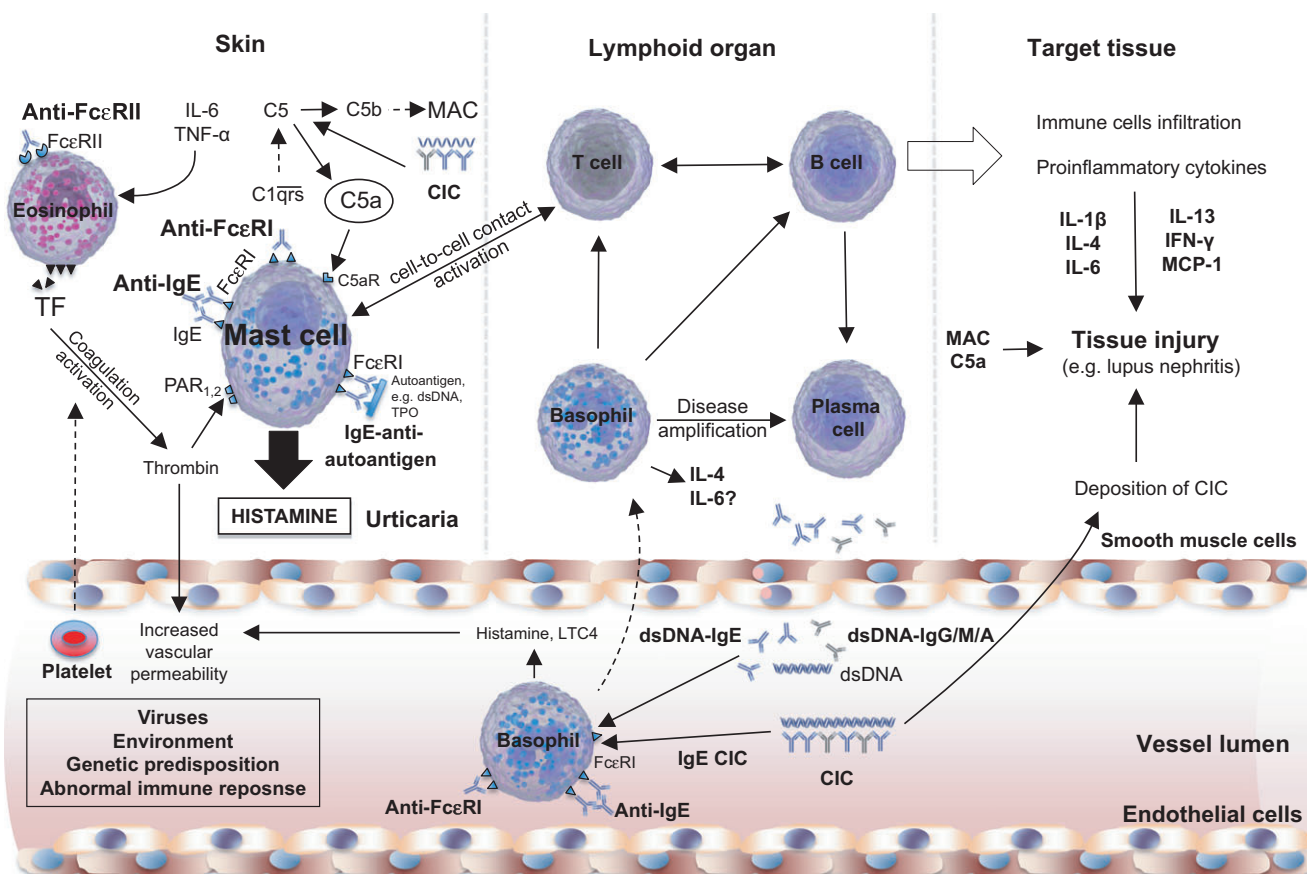


Fig. 1. Possible pathogenetic relationship between chronic urticaria and systemic lupus erythematosus. Eosinophils, mast cells (MC) and basophils may play a substantial role in the development and progression of both chronic urticaria (CU) and systemic lupus erythematosus (SLE). Autoantibodies to the low-affinity receptors (FcεRII) and proinflammatory cytokines (e.g. IL-6, TNF-α) can activate eosinophils leading to the expression of tissue factor (TF). TF causes the activation of extrinsic coagulation pathway activation via the generation of thrombin, a serine protease. Its action on the protease-activated receptors (PAR) 1 and 2 on MC results in the degranulation of MC, the increase of vascular permeability and ultimately in CU symptom development. Large activated platelets might enhance activation of the coagulation cascade and histamine release from MC. Moreover, functional autoantibodies to IgE or to the high-affinity IgE receptor (FcεRI) cause histamine release extravascularly (from mast cells) or intravascularly (from basophils). In addition, these autoantibodies of IgG1 and IgG3 subclasses are able to fix the complement and lead to MC activation and degranulation indirectly by generation of the anaphylatoxin C5a and its action on complement receptor (C5aR). On the other hand, the activation of the complement system results in the activation of C5 with formation of membrane attack complex (MAC) that contributes to inflammation and tissue injury in SLE. At the same time, autoreactive B and T cells, having escaped negative selection, are responsible for production of autoreactive IgE, G, M, A antibodies against autoantigens such as dsDNA and complement factors. Basophils activated by autoreactive IgE migrate to lymph nodes where they interact directly with autoreactive lymphocytes, promote TH2 cell differentiation and enhance the production of self-reactive antibodies due to secretion of IL-4 and IL-6. Aggregation of autoantibodies with autoantigens enables subsequent formation of IgE- and IgG/M/A-containing immune complexes, their deposition in different organs, causing tissue damage and determining clinical manifestations of SLE such as nephritis. This process is maintained by immune cell infiltration and production of proinflammatory cytokines. Furthermore, autoreactive IgE (e.g. anti-dsDNA), in its turn, can cause degranulation of MC and basophils with histamine release and development of CU symptoms in patients with SLE via cross-linking high-affinity IgE receptors (FcεRI). IL-1β: interleukin-1β; IL-4: interleukin-4; IL-6: interleukin-6; IL-13: interleukin-13; LTC4: leukotriene C4; TF: tissue factor; TNF-α: tumour necrosis factor-α; MCP-1: monocyte chemotactic protein-1; IFN-γ: interferon-γ; MAC: membrane attack complex; CIC: circulating immune complexes.

results [84, 85], indicating that CSU and SLE share a higher prevalence of autoantibodies to FcεRI and IgE and that some autoantibodies may be specific only for CSU or SLE, whereas other autoantibodies may be present in both conditions.

Recently, we and others have described autoantibodies of the IgE class in CSU [10, 86–88]. These IgE antibodies were found to be directed against double-

stranded DNA [10, 87], thyroglobulin or thyroperoxidase [10, 86, 88]. Patients who have these autoantibodies frequently have high total IgE levels and/or autoimmune conditions, especially autoimmune thyroiditis or SLE [10]. Increased IgE levels have also been described in patients with SLE, where they are not associated with atopy [89, 90], but with active disease [91] and lupus nephritis [92].

Atta et al. described that antinuclear IgE autoantibodies are detectable in 17 of 21 (81%) sera from patients with SLE. These IgE autoantibodies showed a fine speckled pattern of fluorescence, which was also observed in IgG-ANA [89]. Six years later, the same authors confirmed these findings in a larger group of patients with SLE. They found antinuclear IgE antibodies in 29 of 92 patients with SLE (31.5%), but not in healthy controls [93]. Importantly, high total IgE levels were reportedly associated with ANA-IgE ($P < 0.0001$), but not with IgE antibodies to environmental allergens.

Significantly elevated levels of autoreactive basophil-activating IgE anti-dsDNA have been found in some patients with CSU [87] and SLE [77, 92–95]. Charles et al. [92] found IgE against dsDNA in the plasma samples of all 43 patients with SLE screened. Recently, Dema et al. [77] demonstrated a high prevalence (65%) of autoreactive IgEs against dsDNA, Sm/RNP, SSA/Ro and SSB/La in patients with SLE, and these antibodies were more frequent in those with active disease (85%). Both studies suggest that high levels of IgE and IgG anti-dsDNA are strongly associated with increased disease activity. For example, a four-fold increase in IgE anti-dsDNA levels was seen in SLE patients with active nephritis in comparison with those without it [92]. Moreover, a significant correlation was found between increased levels of autoreactive IgG and increased levels of autoreactive IgE and vice versa, suggesting intimate co-regulation and a joint role of these autoantibody subclasses in disease progression.

In a mouse model (*Lyn*^{-/-} mice), basophils activated via stimulation of FcεRI by autoreactive IgE express CD62L on their cell surface, which causes their migration to and accumulation in peripheral lymph nodes (Fig. 1). There, they can promote TH2 cell differentiation, secrete cytokines (IL-4 and IL-6) and express MHC-II, and they may enhance plasma cell survival and the production of self-reactive antibodies with subsequent formation of IgE-containing immune complexes that causes lupus-like nephritis [77, 92, 96]. Crossing of *Lyn*-deficient mice to IL-4-deficient or IgE-deficient mice lead to a pronounced decrease in autoantibody production and a failure of these double-deficient mice to develop the lupus-like phenotype [77, 92]. In line with these findings, several studies have proposed that IgE can get deposited in the kidneys of patients with SLE [97], but this appears to be rare [77].

Taken together, these findings suggest that, in CSU and SLE, autoreactive IgE may 1) contribute to the signs and symptoms and 2) amplify the loss of self-tolerance through promoting plasma cell autoantibody production [77, 92]. These data do not preclude a role for Th1, Th17 and the loss of regulatory T cell function in the development of CSU and SLE, but they do point

to a strong humoral component in the pathogenesis of these diseases [92].

The role of complement activation

The complement system is a key player in autoimmunity and contributes to the pathogenesis of both CSU and SLE [98]. Activation of the complement system leads to the activation of C5, formation of the membrane attack complex (MAC) and subsequent inflammation and tissue damage in autoimmune diseases (Fig. 1) [99].

In a subpopulation of patients with CSU, IgG1 and IgG3 autoantibodies to the high-affinity IgE receptor on MC can fix complement and induce MC degranulation by a direct mechanism and by the generation of anaphylatoxin C5a and its action via the complement receptor C5aR [100, 101]. In patients with SLE, complement contributes to the pathogenesis by forming complexes of C1q and C3 with IgG, IgA and IgM along the dermal-epidermal border. Low levels of C1, C2, C3, or C4 are common especially at times of exacerbation, because of their extensive consumption [102], which can lead to hypocomplementaemia [48]. The presence of dsDNA-specific IgE, as was described above, can also be associated with hypocomplementaemia in severe SLE [77].

Garmendia et al. [103] observed significantly higher levels of anti-C1q antibodies in 34 patients with CSU as compared to 30 healthy controls, without clinical evidence of HUVS or SLE. In SLE, anti-C1q autoantibodies are associated with severe disease [45]. These autoantibodies fix to the classical complement pathway protein C1q, which leads to immune complex formation and complement activation resulting in the generation of C3a, C5a and MAC. This can cause the development of systemic manifestations of SLE such as glomerulonephritis [45] and may be responsible for the onset of CSU, due to the degranulation of skin MC by C5a.

The role of coagulation cascade

The role of the coagulation cascade in the pathophysiology of CSU and a tight interplay between coagulation and inflammation has been discussed for many years [104–106]. In CSU, autoantibodies to low-affinity receptors (FcεRII) and proinflammatory cytokines such as IL-6 and tumour necrosis factor alpha (TNF-α) [107] may activate eosinophils leading to the expression of tissue factor (TF) [104] (Fig. 1). TF is thought to be the main initiator of the extrinsic coagulation pathway which leads to thrombin formation and its interaction with protease-activated receptors (PAR) 1 and 2 on MC [104]. The action of thrombin results in the subsequent degranulation of MC and in increased vascular perme-

ability. Asero et al. [105] observed significantly higher levels of prothrombin fragment 1 + 2, a marker of thrombin generation, in patients with CSU in comparison with control subjects.

In addition, thrombin can also induce the generation of C5a in the absence of C3, bypassing the first stage of the complement cascade [108]. Recently, Zhu et al. [106] confirmed the concept of interaction of the complement and coagulation systems in CSU. They found increased levels of thrombin-antithrombin complex (TAT), prothrombin fragment 1 + 2 (F1 + 2), D-dimer and C5a in patients with active CSU. Katayama et al. [109] observed high plasma levels of the platelet-derived factors platelet factor IV and β -thromboglobulin in more than half of 23 patients with active CSU, and these levels dropped to normal values after treatment with antihistamines. Some patients with refractory CSU may respond well to anticoagulant therapy [110].

A close relationship between immune complex formation and alterations in coagulation were also observed in patients with SLE [111]. For example, thrombin generation and activation of the coagulation system are common in SLE and antiphospholipid syndrome [112]. In contrast to CSU [113], this is reportedly associated with a risk of thrombosis in these conditions [114]. Pereira et al. [114] found that circulating platelet-derived microparticles and thrombin generation were significantly higher among 30 patients with SLE as compared to controls ($P = 0.0007$ and $P = 0.025$, respectively). The number of microparticles correlated significantly with thrombin generation and thrombin-anti-thrombin levels. In some studies, IgA autoantibodies to phospholipids (anti-cardiolipin) have been found to be a risk factor for thrombosis in patients with SLE [115, 116], whereas others did not confirm this [114]. The lack of an increased thrombotic risk in patients with CSU, in spite of hypercoagulation, may be explained by an efficient activation of fibrinolysis and the anticoagulation system as well as the predominant extravascular activation of the coagulation cascade and location of fibrin deposition [104, 117].

Confino-Cohen et al. [15] observed high mean platelet volume (MPV) as the most common abnormal laboratory finding in 3662 (28.5%) of 12 778 patients with CSU, some of which had accompanying systemic autoimmune diseases. Magen et al. [118] found a similar increase in MPV as well as high serum levels of CRP in ASST-positive CSU patients with a severe course of disease. The alteration in platelet size may indicate an increase in platelet reactivity and altered release of substances that are crucial mediators of coagulation, thrombosis and chronic systemic inflammation [15, 119, 120]. Interestingly, the results of recent studies show that MPV levels are also increased and correlated with disease activity and levels of inflammation mark-

ers in patients with SLE [121], RA [120, 122] and ankylosing spondylitis [123]. Yavuz and Ece found that MPV might be used as an early indicator of reactivation in children with SLE, and MPV appeared to be a more accurate marker for monitoring SLE activity than ESR, CRP and C3 [121]. Taken together, large activated platelets and activation of the coagulation cascade appear to be possible indicators of disease activity in CSU [15] and SLE [121]. Activation of the coagulation cascade may be associated with autoimmunity (via autoantibodies), inflammation (via proinflammatory cytokines) and activation of the complement system (via C5a). Further investigation is required to better characterize the mechanisms and relevance of coagulation system activation in the pathogenesis of CSU and SLE.

Unmet needs

Our systematic review of the literature on the association of CSU and SLE has uncovered significant gaps in our understanding of how these two diseases are related. The clear differentiation between CSU and UV as well as between acute and chronic urticaria in patients with SLE should be made in further research for better prevalence interpretation. From our point of view, the following questions need to be addressed by future studies: What is the prevalence and incidence of SLE in patients with CSU? What are the activators of mast cells in autoimmune CSU and what are the rates of comorbidity of autoimmune CSU and SLE? What are the links between autoimmunity, the coagulation and complement systems, and inflammation in the pathogenesis of CSU and SLE? Can some features of CSU, for example ASST results, autoantibodies or histological markers (type of infiltrate) or clinical characteristics (e.g. duration, severity, response to treatment) be predictors of SLE development and its activity, duration and prognosis? What is the prevalence and significance of autoantibodies (e.g. ANA, RF, IgE anti-dsDNA, IgG anti-Fc ϵ RI α) in patients with SLE, CSU and both conditions? In patients with SLE and CSU, can the treatment of SLE improve CSU and vice versa, for example can both diseases in these patients be controlled by omalizumab, a very effective treatment option for CSU? However, we have managed to find only one ongoing study aiming to evaluate the efficacy of omalizumab in SLE (NCT01716312).

Summary

Systemic lupus erythematosus and CSU often coexist, especially in female patients [15]. CSU and CSU-like rash is relatively common in SLE (range: 0–21.9% and 0.4–27.5%, respectively, in adults and range: 0–1.2% and 4.5–12%, respectively, in children), and patients

with CSU have an increased risk of developing SLE [15]. CSU can be the first manifestation of SLE, and in most cases, CSU precedes SLE onset by 10 years [15]. CSU may indicate a severe course of SLE with unfavourable prognosis [26, 37, 52, 53].

The results of published studies of the mechanisms that drive disease activity in CSU and SLE suggest that CSU may be closely pathogenically related to SLE. In both diseases, inflammation, autoimmunity, complement and coagulation are closely linked (Fig. 1), and they can activate each other, thus amplifying disease activity [104]. IgG and IgE autoantibodies appear to be the key initial driver in the pathogenesis of both CSU and SLE. Future studies should further characterize their role in both diseases and explore the benefit of therapies that target them and their effects.

Legend for Tables 1 and 2

A systematic literature search was conducted using PubMed and Google Scholar databases and 'urticaria' and 'systemic lupus erythematosus' as keywords, covering a period from 1950 to 2015. In most of the studies CSU or chronic urticarial rash in patients with SLE was termed 'chronic urticaria' [18,124], 'urticaria' [19–23,27,54,56,125–131], 'urticarial eruptions of varying duration' [73], 'hives' [28,30,132,133], 'non-vasculitic urticaria' [25], 'urticarial lesions' [134,135] and 'chronic urticaria-like lesions' [26, 53]. We did not include in the table reports where information on urticaria as a cutaneous manifestation of SLE was not reported in the paper [34,74,136,137]. The distinction between CSU and

UV was made only in some studies [25,35,53,55,57, 58,124,138]. Many other studies had no clear differentiation between CSU and UV but the latter may have been termed 'vasculitis' [20,23,54,125,128,129], 'vasculitic rash' [139], 'dermal vasculitis' [28,133] or 'cutaneous vasculitis' [28,37,126,127,140] that allowed us to assume that most of the patients with urticarial rash in these studies are patients with CSU. Almost all authors in these studies used Gilliam and Sontheimer classification of SLE skin manifestations [32] that support this suggestion. The authors of some studies did not point out clearly whether patients had acute or chronic urticaria. But based on circumstantial evidence (e.g. such as duration of the disease and the prolonged period of follow-up) we regarded such cases as CSU.

Acknowledgements

We thank Tomasz Hawro, Martin Church, Marina Abajian and Karsten Weller for valuable recommendations in preparation of the manuscript.

Funding

Pavel Kolkhir is a recipient of European Academy of Allergy and Clinical Immunology (EAACI) Clinical Fellowship Award 2014.

Conflict of interest

The authors declare no conflict of interest.

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