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ORIGINAL ARTICLE

Clinical profile of pathological urticarial vasculitis: A retrospective study

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Abstract

Background: As there are no definite classification criteria for urticarial vasculitis (UV), its diagnosis is often challenging and usually proposed when urticarial lesions and pathological vasculitis coexist. By analysing the final diagnosis of patients whose skin biopsies showed both urticaria and vasculitis, we sought to decipher the clinical heterogeneity of this condition.

Objectives: To describe the characteristics of patients with pathological signs of urticaria and vasculitis.

Methods: We conducted a retrospective, descriptive, single-centre study within Lille University Hospital and included adult patients with a skin biopsy performed between 2000 and 2021, and whose pathological report mentioned the codes for "leukocytoclastic angiitis" and "urticaria". Clinical data were then collected from medical records.

Results: We identified 61 patients with pathological diagnosis of UV and classified them into four groups according to the final diagnosis made by the managing clinicians: 14 patients were diagnosed with UV (normo-[NUV] or hypocomplementemic UV [HUV]), 10 with urticaria (including 8 chronic urticaria [CU]), 24 with an "undetermined diagnosis" (when elements did not allow firm diagnosis between CU and UV, due to an atypical clinical presentation of urticarial lesions), and 13 with an "other but well-defined diagnosis". Fibrinoid necrosis, classically associated with UV, was observed in 4/9 patients (44%) in the urticaria group. Antihistamines were effective not only in all patients with urticaria, but also in NUV and "undetermined diagnosis" group.

Sarah Benarab and Aurélien Chepy contributed equally to this work (these authors have contributed equally and are designated to have co-first authorship).

Conclusions: These data suggest that pathological signs of UV may be shared by various clinical situations, raising the hypothesis of a continuous spectrum between CU and UV.

KEYWORDS
chronic urticaria, leukocytoclastic angiitis, urticarial vasculitis

INTRODUCTION

Urticarial vasculitis (UV) is a rare systemic vasculitis affecting primarily cutaneous small vessels.[1] It is characterised by recurrent episodes of wheals-like lesions, that may be pruritic, burning, or painful, frequently lasting more than 24 h, in fixed locations. It resolves with residual post-inflammatory hyperpigmentation or ecchymosis.[2–5] Angioedema occurs in approximately 50% of UV patients.[6–8]

The Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides and Dermatologic Addendum divided UV into two groups according to complement levels and the presence of anti-C1q antibodies: normocomplementemic UV (NUV) and hypocomplementemic UV (HUV).[1,4,9,10] NUV represents 80% and HUV 9%–21% of UV cases.[2,11,12] Usually, HUV are more likely to present with systemic involvement and to be more severe than NUV.[1,3,6,12–14] HUV may be associated to an underlying cause in 21%–54% of cases,[2,6,12–14] such as systemic autoimmune diseases (systemic lupus erythematosus [SLE] and Sjogren's syndrome [SjS]), viral infections, solid-organ or blood malignancies, and drugs.[11,15–20]

As there are no definite classification criteria for UV, its diagnosis is often challenging and usually yielded by assembling evidence of the coexistence of urticarial lesions and vasculitis. However, this approach is hindered by several hurdles. Indeed, it is often difficult to discriminate between UV and differential diagnoses, especially chronic urticaria (CU), based on clinical history and appearance.[2,21,22] CU refers to daily recurrent urticaria that occurs for more than 6 weeks[23] and usually presents with recurrent itching migratory wheals, lasting less than 24 h and leaving no trace after resolution.[5,17,24] However, these stereotypical characteristics may be missing in some patients.[25,26] The diagnosis of UV usually relies on skin pathological data. The admitted pattern corresponds to the association of urticarial features and usually mild leukocytoclastic angiitis of small vessels.[10,27] However, whether this pattern can be observed in other diseases, especially chronic spontaneous urticaria (CSU), is currently controversial.[25,28,29]

We hypothesised that UV classical pathological aspects may be observed in different patient profiles, especially in CU and UV patients. Our objective was to describe the clinical and biological characteristics of patients with classical pathological features of UV on skin biopsy.

MATERIALS AND METHODS

Study design and population

We conducted a single-centre retrospective cross-sectional study within Lille University Hospital. Patients were screened from the Pathology Department ADICAP (Association pour le Développement de l'Informatique en Cytologie et en Anatomie Pathologiques) database and included in the study if they were older than 18 years old and had a skin biopsy with both the codes "leukocytoclastic angiitis" and "urticaria" performed between 1 January 2000 and 31 December 2021. These are diagnosis codes that dermatopathologists have to fill in for each report.

Leukocytoclastic vasculitis (LV) is a histological description corresponding to a vasculitis of small vessels, based on several features: infiltration of the dermal blood vessel walls by neutrophils with leukocytoclasia (neutrophils with pycnotic and fragmented nuclei), fibrinoid necrosis, damaged endothelial cells, extravasation of red blood cells (Figure 1). Histologic analysis of urticaria is characterised by the presence of dermal oedema, and often a sparse dermal perivascular and interstitial mixed inflammatory infiltrate composed of variable numbers of lymphocytes, neutrophils and eosinophils (Figure 2).

The data were deidentified and complied with requirements of the "Commission Nationale de l'Informatique et des Libertés" (CNIL), the organisation responsible for ensuring the ethical use of data collected for scientific purposes in France. The CNIL approved the methods used to collect and analyse data from our patient database (approval #DEC22-008).

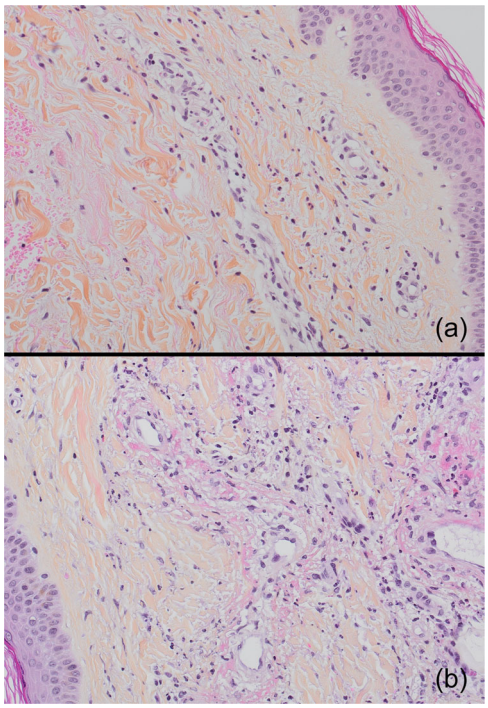

FIGURE 1 Pathological examination of LV (x20 magnification). Discrete infiltration of the dermal blood vessel walls by neutrophils with leukocytoclasia (neutrophils with pycnotic and fragmented nuclei) (a); fibrinoid necrosis (b).

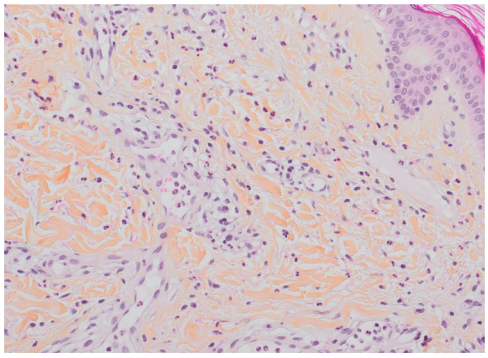

FIGURE 2 Pathological examination of urticaria (x20 magnification). The presence of dermal oedema with a sparse dermal perivascular of eosinophils.

Data collection

Relevant data were retrospectively retrieved from medical records at baseline (defined as the date of skin biopsy) and up until the last follow-up visit. We collected patient characteristics (gender, age, smoking history, personal history of malignancy, personal history of autoimmune disease), dermatological presentation (angioedema, characteristics of urticarial lesions), systemic symptoms and other clinical features (musculoskeletal, pulmonary, ocular, digestive, cardiac, endocrinological, neurological, ear-nose-throat and renal symptoms), nature of biopsied lesions, pathological characteristics (fibrinoid necrosis and direct immunofluorescence [DIF]), biological results (haemoglobin, leucocytes, platelets, C-reactive protein [CRP], creatinine, proteinuria, haematuria, monoclonal gammopathy, complement fraction 3 [C3] level, complement fraction 4 [C4] level, total haemolytic complement [CH50] level, anti-C1q antibodies, cryoglobulin, antinuclear antibodies [ANA] and rheumatoid factor) and treatment data (including use and efficacy of antihistamines [AH]). If data concerning the follow-up were available, we assessed infections, cutaneous and systemic evolution, biological data (haemoglobin, leucocytes, platelets, CRP and creatinine) and changes in treatments.

Group classification

Patients were classified into four groups based on medical record data. The clinical diagnosis used for classification was based on the expert opinion of the managing physicians. Four groups were identified based on the final diagnosis of the patients: "UV" (divided into HUV and NUV based on complement levels), "urticaria" (acute and chronic [CU]), "undetermined diagnosis", and "other diagnosis" (Figure 3). Patients were classified into the "other diagnosis" group if they had a definite diagnosis other than UV and CU. Patients were classified into the "undetermined diagnosis" group when the clinical, biological, and therapeutic data (at diagnosis and follow-up) did not allow to firmly establish a diagnosis in particular between CU and UV.

Statistical analyses

Characteristics of the four groups were described using number (percentage) for qualitative variables and median (±interquartile range) for quantitative variables. There was no imputation for missing data. Descriptive statistics were calculated using GraphPad Prism V9.3.1 software.

RESULTS

Classification of patients

Our database search identified 71 skin biopsies with both the codes "leukocytoclastic angiitis" and "urticaria" performed in 65 patients followed in the Dermatology and/or Clinical Immunology Departments. Four patients were excluded: three patients were under 18-year-old,

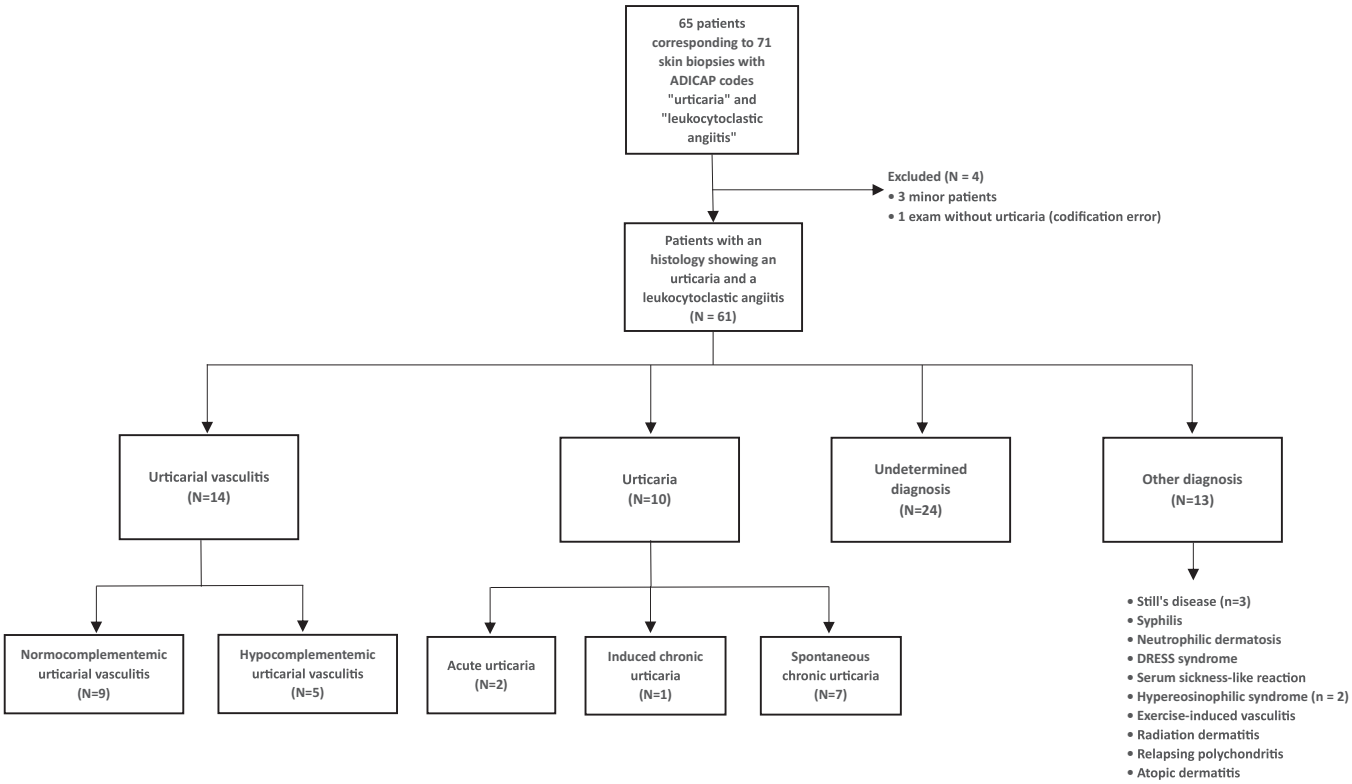

FIGURE 3 Flow chart of study. ADICAP, Association pour le Développement de l'Informatique en Cytologie et en Anatomie Pathologiques; DRESS' syndrome: drug reaction with eosinophilia and systemic symptoms syndrome.

and one had a biopsy that showed no urticarial sign. The remaining 61 patients were classified into four groups: UV ($n = 14$) with NUV ($n = 9$) and HUV ($n = 5$), urticaria ($n = 10$) with acute urticaria ($n = 2$) and CU ($n = 8$), undetermined diagnosis ($n = 24$) and other diagnosis ($n = 13$) (Figure 3).

Patients' characteristics

Patients' characteristics in the different groups at the time of skin biopsy are described below (Table 1).

Demographics

We observed a female predominance in the "urticaria" (60%) and the "undetermined diagnosis" (79%) groups, contrasting with mostly males in the HUV and the NUV groups (60% and 56% respectively). A balanced sex ratio was observed in the "other diagnosis" group.

The median age (±IQR) ranged between 36 and 52 years old for all groups: 36 (22) years old for urticaria, 46 (24) years old for NUV, 36 (26) years old for HUV, 52 (25) years old for the "undetermined diagnosis" and 52 (26) years old for the "other diagnosis" groups.

The median follow-up duration was 3 (2) years for HUV, 2 (5) years for NUV, 5 (12) years for urticaria, 4 (7) years for the "undetermined diagnosis", 1 (7) year for the "other diagnosis" groups.

Personal history of autoimmune disease was found in 3/4 (75%) of HUV (2 SLE and 1 autoimmune thyroiditis), 3/8 (38%) of NUV (1 SLE, 1 autoimmune thyroiditis and 1 ulcerative colitis), 3/9 (33%) of urticaria (1 autoimmune thyroiditis, 1 SjS, and 1 patient with both inclusion myopathy and SjS) and 9/20 (45%) of the "undetermined diagnosis" group (1 SLE, 1 systemic sclerosis, 1 psoriatic arthritis, 1 pleuroparenchymal fibroelastosis, 1 with SjS associated with IgG4-related disease and primary biliary cholangitis, and 4 autoimmune thyroiditis). Personal history of malignancy, associated infection and suspected drug origin are described in Table 1.

In the "other diagnosis group", various conditions were represented: Still's disease (three patients), syphilis, neutrophilic dermatosis, drug reaction with eosinophilia and systemic symptoms syndrome, serum sickness-like reaction, hypereosinophilic syndrome (two patients), exercise-induced vasculitis, radiation dermatitis, relapsing polychondritis and atopic dermatitis.

Overall, four patients died: one patient with SLE and HUV died as a result of digestive vasculitis, two patients

TABLE 1 Characteristics of the Urticaria, HUV and NUV, "undetermined diagnosis", and "other diagnosis" groups.

	Urticaria		UV				Undetermined		Other	
			HUV		NUV					
	N	Value	*N*	Value	*N*	Value	*N*	Value	*N*	Value
Demographics										
Male, *n* (%)	10	4 (40%)	5	3 (60%)	9	5 (56%)	24	5 (21%)	13	6 (46%)
Personal history of autoimmune diseases, *n* (%)	9	3 (33%)	4	3 (75%)	8	3 (38%)	20	9 (45%)	10	4 (40%)
Personal history of cancer or hematopathy, *n* (%)	10	3 (30%)	5	1 (20%)	8	2 (25%)	20	6 (30%)	12	4 (33%)
Associated drugs, *n* (%)	8	2 (25%)	5	0 (0%)	7	2 (29%)	18	3 (17%)	9	1 (11%)
Associated infections, *n* (%)	9	3 (33%)	5	1 (20%)	8	2 (25%)	19	5 (26%)	12	4 (33%)
Dermatologic presentation										
Angioedema *n* (%)	10	5 (50%)	5	0 (0%)	9	1 (11%)	24	6 (25%)	13	2 (15%)
Angioedema and superficial urticaria, *n* (%)	10	5 (50%)	5	0 (0%)	9	1 (11%)	24	6 (25%)	13	2 (15%)
Urticarial lesions	10	10 (100%)	5	5 (100%)	9	9 (100%)	24	21 (88%)	13	12 (92%)
– Fixed character, *n* (%)	10	0 (0%)	5	4 (80%)	9	8 (89%)	24	12 (50%)	13	7 (54%)
– Vasoconstriction halo, *n* (%)	10	1 (10%)	5	1 (20%)	9	2 (22%)	24	5 (36%)	13	3 (23%)
– Livedo, *n* (%)	10	0 (0%)	5	0 (0%)	9	0 (0%)	24	2 (8%)	13	1 (8%)
– Purpura, *n* (%)	10	0 (0%)	5	0 (0%)	9	2 (22%)	24	4 (17%)	13	2 (15%)
– Ecchymosis, *n* (%)	10	1 (10%)	5	0 (0%)	9	2 (22%)	24	3 (13%)	13	0 (0%)
– Residual pigmentation, *n* (%)	10	0 (0%)	5	0 (0%)	9	3 (33%)	24	3 (13%)	13	3 (23%)
– Pruritus, *n* (%)	10	10 (100%)	5	5 (100%)	9	6 (67%)	24	15 (63%)	13	8 (62%)
– Burning feeling, *n* (%)	10	1 (10%)	5	0 (0%)	9	0 (0%)	24	2 (8%)	13	2 (15%)
– Photosensitivity, *n* (%)	10	1 (10%)	5	0 (0%)	9	0 (0%)	24	1 (4%)	13	0 (0%)
Biopsy of an urticarial lesion, *n* (%)	10	10 (100%)	5	5 (100%)	9	9 (100%)	24	21 (88%)	13	8 (62%)
Histopathological characteristics										
Fibrinoid necrosis, *n* (%)	9	4 (44%)	4	3 (75%)	6	2 (33%)	19	6 (32%)	11	4 (36%)
Positive direct immunofluorescence at the vessel walls, *n* (%)	7	0 (0%)	5	1 (20%)	6	1 (17%)	22	2 (9%)	10	1 (10%)
Biological characteristics										
Low CH50, *n* (%)	6	0 (0%)	5	3 (60%)	8	0 (0%)	16	0 (0%)	8	0 (0%)
Low C4, *n* (%)	5	0 (0%)	5	4 (80%)	8	0 (0%)	16	1 (6%)	8	0 (0%)
Low C3, *n* (%)	5	0 (0%)	5	5 (100%)	8	0 (0%)	16	0 (0%)	8	0 (0%)
Positive C1q antibodies, *n* (%)	2	0 (0%)	3	2 (66%)	4	0 (0%)	7	1 (14%)	1	0 (0%)
Positive cryoglobulin, *n* (%)	4	1 (25%)	4	3 (75%)	4	1 (25%)	12	5 (42%)	7	0 (0%)
Positive anti-nuclear antibodies, *n* (%)	6	2 (33%)	5	4 (80%)	7	3 (43%)	16	6 (38%)	8	3 (38%)
Therapeutic management										
Antihistamines use	10	10 (100%)	5	2 (40%)	9	6 (66%)	24	18 (75%)	13	8 (62%)
– Alone, *n* (%)	10	10 (100%)	2	1 (50%)	6	5 (83%)	18	12 (67%)	8	3 (38%)
– Combined therapy, *n* (%)	10	0 (0%)	2	1 (50%)	6	1 (17%)	18	6 (33%)	8	5 (63%)

(Continues)

TABLE 1 (Continued)

	Urticaria		UV				Undetermined		Other	
			HUV		NUV					
	N	Value	*N*	Value	*N*	Value	*N*	Value	*N*	Value
– Total efficiency, *n* (%)	10	10 (100%)	1	0 (0%)	5	1 (20%)	12	10 (83%)	3	0 (0%)
– Partial efficiency, *n* (%)	10	0 (0%)	1	0 (0%)	5	4 (80%)	12	2 (17%)	3	1 (33%)
– No efficiency, *n* (%)	10	0 (0%)	1	1 (100%)	5	0 (0%)	12	0 (0%)	3	2 (66%)
– Primary resistance, *n* (%)	10	0 (0%)	1	1 (100%)	5	0 (0%)	12	0 (0%)	3	2 (66%)
– Secondary resistance, *n* (%)	10	3 (30%)	1	0 (0%)	5	2 (40%)	12	4 (33%)	3	0 (0%)

Abbreviations: C3, complement fraction 3; C4, complement fraction 4; CH50, total haemolytic complement; HUV, hypocomplementemic urticarial vasculitis; NUV, normocomplementemic urticarial vasculitis; UV, urticarial vasculitis.

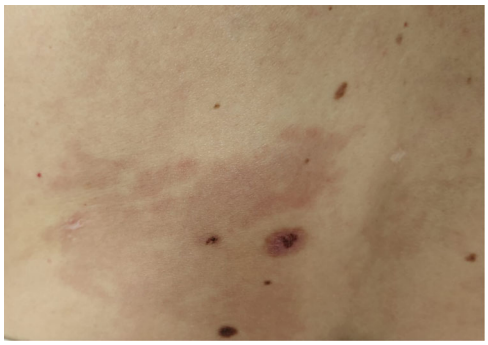

FIGURE 4 Clinical picture of a NUV patient. Post-inflammatory pigmentation of an urticarial lesion. NUV, normocomplementemic urticarial vasculitis.

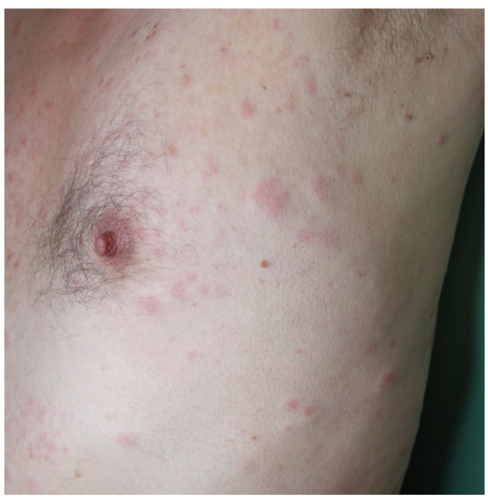

FIGURE 5 Clinical picture of an HUV patient. Fixed urticarial lesion. HUV, hypocomplementemic urticarial vasculitis.

in the "undetermined diagnosis" group (one due to myeloma and the other to mullerian carcinosarcoma), and one patient in the "other diagnosis" group (breast cancer).

Dermatological characteristics

Urticarial skin lesions were reported by the clinicians at the examination of all patients in the HUV, NUV and urticaria groups. More than 88% of patients in the "undetermined diagnosis" (21/24) and the "other diagnosis" (12/13) groups also exhibited skin lesions described as urticarial. Four patients did not have any clinical form of urticaria (three in the "undetermined diagnosis" group and one in the "other diagnosis" group). We presented examples of urticarial lesions for the NUV group (Figure 4), HUV group (Figure 5), urticaria group (Figure 6), and "undetermined diagnosis" group (Figure 7).

Fixed character of skin lesions was reported in 4/5 (80%) cases in the HUV group, in 8/9 (89%) in the NUV group, in 12/24 (50%) in the "undetermined diagnosis" group and in 7/13 (54%) in the "other diagnosis" group. Pruritus was noted in all patients in the HUV group, in 6/9 (67%) in the NUV group, in all patients in the "urticaria" group, 15/24 (63%) in the "undetermined diagnosis" group and in 8/13 (62%) in the "other diagnosis" group. Patients exhibited purpura in 2/9 (22%) cases in the NUV group, 4/24 (17%) in the "undetermined diagnosis" group and 2/13 (15%) in the "other diagnosis" group. History of angioedema occurred in 1/9 (11%) patient in the NUV group, in 5/10 (50%) in the urticaria group, in 6/24 (25%) in the "undetermined diagnosis" group, and 2/13 (15%) in the "other diagnosis" group.

Other symptoms

Thirty-nine patients presented signs of systemic involvement such as fever, arthralgias, myalgias, dyspnoea and digestive symptoms: 5 patients in the HUV group, 6 in the NUV, 4 in the "urticaria" group, 15 in the

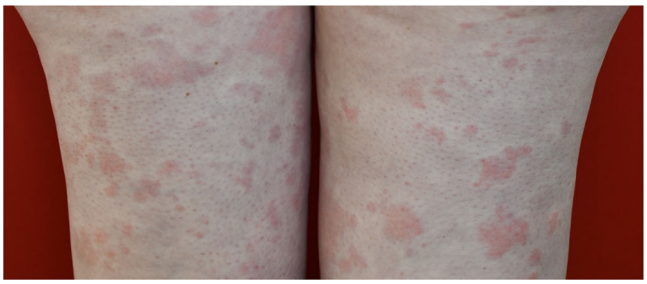

FIGURE 6 Clinical picture of an urticaria group patient. Pruritic and migratory urticarial lesions.

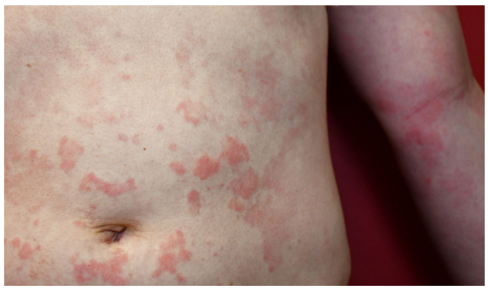

FIGURE 7 Clinical picture of an "undetermined diagnosis" group patient. Fixed and pruritic urticarial lesions.

"undetermined diagnosis" and 9 in the "other diagnosis" group (Table 2).

Pathological characteristics

Skin biopsy was performed on urticarial lesions for all HUV, NUV, and urticaria patients, and in 21/24 (88%) of patients in the "undetermined diagnosis" group and 8/13 (62%) patients in the "other diagnosis" group. Fibrinoid necrosis was observed in 3/4 (75%) of HUV patients, 2/6 (33%) of NUV patients, in 4/9 (44%) of "urticaria" patients, in 6/19 (32%) of the "undetermined diagnosis" group, and in 4/11 (36%) of the "other diagnosis" group.

Direct immunofluorescence was positive in 3/5 (60%) patients of HUV, in 1/6 (17%) of NUV, in 1/7 (14%) of "urticaria", in 3/22 (14%) in the "undetermined diagnosis" group and in 1/10 (10%) in the "other diagnosis" group (Table 3).

Biological characteristics

In the HUV group, complement levels were low in all patients with low C3 levels in all cases, low C4 levels in 4/5 (80%) cases and low CH50 levels in 3/5 (60%) patients. One patient in the "undetermined diagnosis" group presented low C4 levels with positive anti-C1q antibodies. Complement levels were normal in the NUV, "urticaria" and "other diagnosis" group. Positive anti-C1q antibodies were found in 2/3 (66%) patients in the HUV group. Anti-C1q antibodies were always negative when tested in the NUV, "urticaria" and "other diagnosis" group.

Antinuclear antibodies were significatively positive (titre >1/80) in 4/5 (80%) patients in the HUV group, 3/7 (43%) in the NUV group, 2/6 (33%) in the "urticaria" group, 6/16 (38%) in the "undetermined diagnosis" group and 3/8 (38%) in the "other diagnosis" group (Table 4).

Positive cryoglobulin was detected in one patient (25%) in NUV group, three patients (75%) in the HUV group (type IIa, IIb and III, respectively), one patient (25%) in the urticaria group (type IIa), and five patients in the "undetermined diagnosis" group (including three patients with type III cryoglobulin).

Response to antihistamine therapy

A complete or partial response to AH monotherapy was reported in all patients of the "urticaria" group, NUV group and "undetermined diagnosis" group. In the "other diagnosis" group, AH therapy was used in 8/13 (62%) patients; and when used alone, it was effective in 1/3 patients (33%). Omalizumab (recombinant monoclonal antibody targeting immunoglobulin E) was used as a second-line therapy in 1 patient (11%) in the NUV group, two patients (20%) in the "urticaria" group and three patients (13%) of the "undetermined diagnosis" group, and was effective in all cases. Only one patient in the HUV group was treated by omalizumab, with no efficacy.

Other therapies

Regarding first-line therapy data, colchicine was mainly used in the NUV group (56% of patients). In the HUV group, patients were treated with hydroxychloroquine (60% of HUV patients) or glucocorticoids (40%). In the "undetermined diagnosis" group, colchicine, hydroxychloroquine, non-steroidal anti-inflammatory drugs, or glucocorticoids were used; and 6 patients had AH in combination (Table 5).

DISCUSSION

Our results can be summarised as follows: (1) pathological signs of UV can be shared by different clinical profiles, including UV (23%), CU (16%) and even other

TABLE 2 Systemic involvement in the urticaria, HUV and NUV, "undetermined diagnosis", and "other diagnosis" groups.

	Urticaria		UV				Undetermined		Other	
			HUV		NUV					
	N	Value	*N*	Value	*N*	Value	*N*	Value	*N*	Value
General presentation										
Fever, *n* (%)	8	0 (0%)	5	3 (60%)	7	3 (43%)	21	5 (24%)	12	6 (50%)
Asthenia, *n* (%)	7	2 (29%)	4	4 (100%)	7	2 (29%)	22	8 (36%)	12	7 (58%)
Weight loss, *n* (%)	7	0 (0%)	4	3 (75%)	7	2 (29%)	19	2 (11%)	11	4 (36%)
Lymph nodes enlargement, *n* (%)	7	1 (14%)	4	2 (50%)	6	1 (17%)	19	4 (21%)	13	6 (46%)
Splenomegaly, *n* (%)	5	0 (0%)	4	1 (25%)	7	1 (14%)	19	0 (0%)	11	2 (18%)
Musculoskeletal involvement										
Arthralgias, *n* (%)	6	3 (50%)	4	4 (100%)	7	4 (57%)	16	10 (63%)	9	7 (78%)
Arthritis, *n* (%)	4	1 (25%)*	4	3 (75%)	7	1 (14%)	15	5 (33%)	8	4 (50%)
Myalgias, *n* (%)	4	1 (25%)	4	1 (25%)	6	2 (33%)	12	4 (33%)	8	3 (38%)
Ocular involvement										
Red eye, *n* (%)	6	0 (0%)	4	1 (25%)	5	1 (20%)	13	1 (8%)	5	1 (20%)
Painful eye, *n* (%)	6	1 (17%)	4	1 (25%)	5	0 (0%)	12	4 (33%)	5	1 (20%)
Reduced visual acuity, *n* (%)	6	0 (0%)	4	0 (0%)	5	1 (20%)	11	0 (0%)	6	1 (17%)
Digestive involvement										
Abdominal pain, *n* (%)	5	2 (40%)	4	1 (25%)	6	1 (17%)	15	5 (33%)	11	1 (9%)
Nausea or vomiting, *n* (%)	6	2 (33%)	5	1 (20%)	5	0 (0%)	14	1 (7%)	10	1 (10%)
Diarrhoea, *n* (%)	6	1 (17%)	4	0 (0%)	6	1 (17%)	15	4 (27%)	10	0 (0%)
Rectal bleeding, *n* (%)	6	0 (0%)	3	0 (0%)	4	0 (0%)	11	0 (0%)	11	1 (9%)
Renal involvement										
High blood pressure, *n* (%)	4	0 (0%)	4	1 (25%)	5	4 (80%)	9	3 (33%)	5	1 (20%)
Oedemas, *n* (%)	3	0 (0%)	3	1 (33%)	3	1 (33%)	6	1 (17%)	5	2 (40%)
Proteinuria, *n* (%)	4	1 (25%)**	5	2 (40%)	6	1 (17%)	16	0 (0%)	5	1 (20%)
Haematuria, *n* (%)	4	0 (0%)	5	1 (20%)	6	1 (17%)	14	1 (7%)	9	1 (11%)
Acute renal failure, *n* (%)	4	0 (0%)	5	1 (20%)	8	1 (13%)	16	1 (6%)	9	1 (11%)
Pulmonary involvement										
Dyspnoea, *n* (%)	6	1 (17%)	5	2 (40%)	6	3 (50%)	18	6 (33%)	9	3 (33%)
Cough, *n* (%)	6	1 (17%)	5	1 (20%)	6	2 (33%)	18	5 (28%)	8	2 (25%)
Active smoking, *n* (%)	5	3 (60%)	5	3 (60%)	6	2 (33%)	13	3 (23%)	5	1 (20%)
Presence of sibilants, *n* (%)	5	0 (0%)	4	1 (25%)	4	2 (50%)	12	0 (0%)	7	0 (0%)
Other involvement										
Ear, nose and throat involvement, *n* (%)	5	3 (60%)	3	1 (33%)	3	1 (33%)	7	4 (57%)	6	5 (83%)
Neurologic involvement, *n* (%)	4	0 (0%)	3	0 (0%)	5	2 (40%)	12	1 (8%)	7	2 (29%)
Cardiologic involvement, *n* (%)	6	0 (0%)	4	1 (25%)	5	1 (20%)	12	1 (8%)	8	4 (50%)
Endocrinologic involvement, *n* (%)	3	1 (33%)	4	1 (25%)	5	1 (20%)	7	4 (57%)	0	0 (0%)

Abbreviations: HUV, hypocomplementemic urticarial vasculitis; NUV, normocomplementemic urticarial vasculitis; UV, urticarial vasculitis.

*Chondrocalcinosis relapse.

**Proteinuria related to diabetic nephropathy.

TABLE 3 Pathological characteristics of the urticaria, HUV and NUV, "undetermined diagnosis", and "other diagnosis" groups.

	Urticaria		UV				Undetermined		Other	
			HUV		NUV					
	N	Value	*N*	Value	*N*	Value	*N*	Value	*N*	Value
Pathological characteristics										
Fibrinoid necrosis, *n* (%)	9	4 (44%)	4	3 (75%)	6	2 (33%)	19	6 (32%)	11	4 (36%)
Positive direct immunofluorescence	7	1 (14%)	5	3 (60%)	6	1 (17%)	22	3 (14%)	10	1 (10%)
– C3 deposit, *n* (%)	1	0 (0%)	3	3 (100%)	1	0 (0%)	3	1 (33%)	1	1 (100%)
– C1q deposit, *n* (%)	1	1 (100%)	3	0 (0%)	1	0 (0%)	3	0 (0%)	1	0 (0%)
– IgM deposit, *n* (%)	1	0 (0%)	3	2 (67%)	1	1 (100%)	3	3 (100%)	1	0 (0%)
– IgG deposit, *n* (%)	1	0 (0%)	3	2 (67%)	1	0 (0%)	3	0 (0%)	1	0 (0%)
– IgA deposit, *n* (%)	1	0 (0%)	3	2 (67%)	1	0 (0%)	3	0 (0%)	1	0 (0%)
– Located at the dermal-epidermal junction, *n* (%)	1	1 (100%)	3	2 (67%)	1	0 (0%)	3	2 (67%)	1	1 (100%)
– Located at the vessel walls, *n* (%)	1	0 (0%)	3	1 (33%)	1	1 (100%)	3	2 (67%)	1	1 (100%)

Abbreviations: HUV, hypocomplementemic urticarial vasculitis; NUV, normocomplementemic urticarial vasculitis; UV, urticarial vasculitis

TABLE 4 Positive antinuclear antibodies of the urticaria, HUV and NUV, "undetermined diagnosis", and "other diagnosis" groups.

	Urticaria		UV				Undetermined		Other	
			HUV		NUV					
	N	Value	*N*	Value	*N*	Value	*N*	Value	*N*	Value
Anti-nuclear antibodies										
Positive anti-nuclear antibodies, *n* (%)	6	2 (33%)	5	4 (80%)	7	3 (43%)	16	6 (38%)	8	3 (38%)
– Homogenous fluorescence, *n* (%)	6	0 (0%)	5	2 (40%)	7	0 (0%)	16	0 (0%)	8	0 (0%)
– Speckled fluorescence, *n* (%)	6	2 (33%)	5	3 (60%)	7	1 (14%)	16	2 (13%)	8	1 (13%)
– Nucleolar fluorescence, *n* (%)	6	0 (0%)	5	0 (0%)	7	2 (29%)	16	1 (6%)	8	1 (13%)
– Peripheral fluorescence, *n* (%)	6	0 (0%)	5	0 (0%)	7	0 (0%)	16	1 (6%)	8	0 (0%)
– Centromere fluorescence, *n* (%)	6	0 (0%)	5	0 (0%)	7	0 (0%)	16	1 (6%)	8	0 (0%)
– Anti-SS-A antibodies, *n* (%)	2	1 (50%)	4	1 (25%)	3	1 (33%)	6	2 (33%)	3	0 (0%)
– Anti-SS-B antibodies, *n* (%)	2	1 (50%)	4	0 (0%)	3	0 (0%)	6	1 (17%)	3	0 (0%)
– Anti-Sm antibodies, *n* (%)	2	0 (0%)	4	1 (25%)	3	0 (0%)	6	0 (0%)	3	0 (0%)
– Anti-RNP antibodies, *n* (%)	2	0 (0%)	4	1 (25%)	3	0 (0%)	6	0 (0%)	3	0 (0%)
– Anti-DNA antibodies, *n* (%)	2	0 (0%)	4	1 (25%)	3	1 (33%)	6	0 (0%)	3	0 (0%)
– Anti-centromere antibodies, *n* (%)	2	0 (0%)	4	0 (0%)	3	0 (0%)	6	1 (17%)	3	0 (0%)

Abbreviations: HUV, hypocomplementemic urticarial vasculitis; NUV, normocomplementemic urticarial vasculitis; UV, urticarial vasculitis.

systemic diseases (21%); (2) fibrinoid necrosis, classically present in vasculitis, was reported in 44% in the urticaria group; and (3) 40% of patients had an atypical clinical presentation for both UV and CU suggesting a relatively frequent situation of overlap between UV and CU.

Our study has some limitations that mainly stem from its small sample size (although relatively large for a rare disease such as UV), its retrospective design, the absence of independent review of pathological analyses, and missing data. However, it also draws strength from its originality—as we included patients according to their "objective" pathological features and not their final clinical diagnosis, unlike most of the previous studies - and its clinical relevance.

TABLE 5 First line therapy in of the urticaria, HUV and NUV, "undetermined diagnosis", and "other diagnosis" group.

	Urticaria		UV				Undetermined		Other	
			HUV		NUV					
	N	Value	*N*	Value	*N*	Value	*N*	Value	*N*	Value
First line treatment										
Antihistamines, *n* (%)	10	8 (80%)	5	2 (40%)	9	4 (44%)	21	16 (76%)	12	7 (58%)
Colchicine, *n* (%)	10	2 (20%)	5	0 (0%)	9	5 (56%)	20	2 (10%)	12	3 (25%)
Hydroxychloroquine, *n* (%)	10	0 (0%)	5	3 (60%)	9	2 (22%)	22	3 (14%)	12	0 (0%)
Dapsone, *n* (%)	10	0 (0%)	5	0 (0%)	9	1 (11%)	22	0 (0%)	12	0 (0%)
Nonsteroidal anti-inflammatory drugs, *n* (%)	10	0 (0%)	5	0 (0%)	9	0 (0%)	22	2 (9%)	12	2 (17%)
Glucocorticoids, *n* (%)	10	2 (20%)	5	2 (40%)	9	1 (11%)	22	2 (14%)	12	6 (50%)
Methotrexate, *n* (%)	10	0 (0%)	5	0 (0%)	9	0 (0%)	22	1 (5%)	12	0 (0%)

Abbreviations: HUV, hypocomplementemic urticarial vasculitis; NUV, normocomplementemic urticarial vasculitis; UV, urticarial vasculitis.

One of our most interesting findings is the presence of pathological and clinical characteristics classically found in UV in various diseases, including CU. General symptoms, such as arthralgias and abdominal pain, were experienced in more than 40% of patients from the urticaria group. Additionally, 17% of them had episodes of dyspnoea, as described classically in UV but also in some patients with CU.[24,30] Pruritus, classically found in CU and known to be less present or absent in UV, was also found in all patients from the HUV group and in two-third of patients from the NUV group, consistent with some studies that have described pruritus in UV with a range of 31%–100%.[3,14,25,27,28,31,32]

Skin biopsy is not recommended in the case of classical urticarial lesion. However, an atypical dermatological presentation of urticaria may lead the clinician to the realisation of a skin biopsy, such as: fixed urticarial lesions, vasoconstriction halo, livedo, purpura or residual pigmentation.[18,33] Moreover, our results show that the presence of fibrinoid necrosis and a positive DIF can be found in patients with different clinical profiles including CU. In UV, fibrinoid necrosis is present in 8.8%–88% of cases from the literature, whereas it is not expected in patients with CU. Some previous studies also showed that pathological and immunologic signs of vasculitis may be found in patients with CU, such as LV (observed in 10%–52% of CU patients,[29,34–36] but fibrinoid necrosis was reported as very infrequent (1.9%–9.7%) in CU patients.[25,37] We assume that these pathological characteristics may be influenced by the age of the biopsied lesion. Indeed, a rather young lesion would tend to show early signs of LV with no fibrinoid necrosis, as opposed to lesions older than 48 h where fibrinoid necrosis would tend to be more frequent.[29,31,38]

Furthermore, we also observed that 40% of patients with pathological signs of UV had an atypical clinical presentation for both UV and CU, more than half of these patients having pruritus and fixed skin lesions. Indeed, we noted a frequent occurrence in the "undetermined diagnosis" group of dermatological characteristics classically found in UV[6,9,11]: fixed lesions (50%), vasoconstriction halo, livedo, purpura and residual pigmentation. Pruritus, traditionally present in CU, was found in more than half of these patients. They were classified into the "undetermined diagnosis" group and may be situated on a disease continuum that ranges from CU to UV, suggesting that this "undetermined group" corresponds to a relatively frequent situation of overlap between CU and UV. The existence of this intermediate group of patients with uncertain diagnosis between UV and CU had been previously discussed in the literature.[12,24,34,39] Jones et al.[34] described an intermediate group of patients with CU, histologically characterised by a dense perivascular infiltrate with leukocytoclastic signs but no vascular lesions, associated with a positive DIF in more than half of patients.[29,34,35]

Thus, it can be very difficult to distinguish CU from NUV, which remains a less well-characterised entity than HUV.[22,26,34] Indeed, diagnosis was more easily done in our patients from the HUV group, as it was facilitated by the presence of a systemic involvement and/or immunologic abnormalities (anti-C1q antibodies or low complement levels).[3,14,18] These elements were more critical than the skin biopsy for the diagnosis of HUV in our patients. Puhl et al. found that pathological signs of UV appeared more obvious in HUV with more affected vessels, matching our observation with the presence of fibrinoid necrosis in 75% of HUV patients and DIF positive in more than half of the patients.[25]

Taken together, our data suggest that there is a continuum spectrum between CU and UV with a frequent overlap of clinical and pathological signs between UV and CU. Moreover, the pathological aspect of UV on skin biopsy may also be found in other diagnoses, as represented by our group of 13 patients with "other diagnoses" including various inflammatory conditions and infectious diseases.

This continuous spectrum is also suggested by our data regarding AH therapy. Indeed, we observed a complete or partial response to AH in all patients from the "urticaria", NUV and "undetermined diagnosis" groups. Omalizumab, used classically in AH-resistant CU,[33] was prescribed for one NUV patient and one patient with "undetermined diagnosis" with a complete remission. As in our observations, omalizumab has been reported as effective in NUV.[32,40–45]

CONCLUSION

In conclusion, our study indicates that skin biopsy alone cannot discriminate between UV (especially NUV) and CU, and even other systemic conditions. Based on pathological data, our results also suggest that there is a continuous spectrum between UV and CU. This underlines the importance of a clinicopathological confrontation with a multidisciplinary approach (Dermatology, Dermatopathology and Clinical Immunology Departments), to place pathological results in perspective of the clinical presentation.

AUTHOR CONTRIBUTIONS

All individuals listed as authors met the ICMJE guidelines for determining authorship. Delphine Staumont-Sallé and Sébastien Sanges conceived of the original idea. Sarah Benarab, Aurélien Chepy, Fréderic Dezoteux, Sébastien Sanges, and Delphine Staumont-Sallé contributed to the conception and design of the study. Marie Verhasselt-Crinquette provided patient's database. Sarah Benarab and Aurélien Chepy collected patient's clinical, biological and pathological data, performed statistical analyses and wrote the first draft of the manuscript. Delphine Staumont-Sallé and Sébastien Sanges made major revisions to the manuscript. Delphine Staumont-Sallé, Sébastien Sanges, Fréderic Dezoteux, Selma Azib, Eric Hachulla, and David Launay provided their expertise on chronic urticaria and urticarial vasculitis. Marie Verhasselt-Crinquette provided her expertise on dermatopathology. All authors read and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The authors confirm that the data supporting the findings of this study are available within the article. Raw data that support the findings of this study are available from the corresponding author, upon reasonable request.

ETHICS STATEMENT

The study complied with the recommendations of the Helsinki declaration. French legislation on noninterventional studies does not require ethics committee approval for the use of deidentified data collected during patient care. The data were deidentified and complied with the requirements of the "Commission Nationale de l'Informatique et des Libertés" (CNIL), the organisation responsible for ensuring the ethical use of data collected for scientific purposes in France. The CNIL approved the methods used to collect and analyse data from our patient database (approval #DEC22-008). All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details (including photographs) for publication.

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