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Original study article

Clinical and morphological characteristics of patients with urticarian rasches

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ABSTRACT

BACKGROUND: The most common diagnosis given to patients with chronic urticarial rashes is chronic spontaneous urticaria (prevalence in the population is 0.1–1.4%). However, similar symptoms can also be observed in other rarer diseases: urticarial vasculitis, hypocomplementemic urticarial vasculitis syndrome, cryopyrine-associated syndromes and Schnitzler's syndrome.

AIM: to analyze the clinical features and histological characteristics of skin biopsies in patients with chronic urticarial rashes to optimize the management and improve differential diagnosis.

MATERIALS AND METHODS: At a retrospective stage, 9 patients with chronic urticarial rashes and a histological examination were selected from the archival data of the Clinic of Skin and venereal fiseases named after V.A. Rakhmanov Sechenov University from January 2019 to April 2022. Prospective patient recruitment was from January 2022 to September 2023 and included 11 patients who underwent skin biopsy. Data obtained from the analysis of demographic characteristics are presented as median and interquartile range. Histological parameters were assessed by qualitative and quantitative methods.

RESULTS: The study included 20 patients (16 women and 4 men) aged 23 to 63 years, 36.5. Depending on the clinical and histological characteristics, the patients were divided into three groups: 9 patients with chronic spontaneous urticaria, disease duration from 2 to 132 months, 24 months [18; 33]; 9 patients were diagnosed with urticarial vasculitis, the duration ranged from 7 to 180 months, 30 [24; 84]. There were 2 patients diagnosed with hypocomplementemic urticarial vasculitis syndrome; the duration of the disease was 24 months. Clinically, chronic spontaneous urticaria was distinguished by a shorter duration of the disease and a shorter duration of existence of individual elements. Standard or increased doses of antihistamines were effective in five patients with chronic spontaneous urticaria. In addition, patients with chronic spontaneous urticaria also had atypical signs of rashes, which indicates a transition group between chronic spontaneous urticaria and urticarial vasculitis. In patients with urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome, clinical features such as longer duration of blistering, burning and soreness, residual hyperpigmentation, and resistance to antihistamine therapy were more often observed. When conducting a histological examination, the main histological features for urticarial vasculitis were leukocytoclasia, fibrin deposits and damage to the vascular walls with fibrin deposition; fibrinoid necrosis was rarely visualized, which, in combination with the above features, was present in only two patients with hypocomplementemic urticarial vasculitis syndrome.

CONCLUSION: This study presents the results of our own observations, analysis of the clinical and histological characteristics of patients with various diseases (chronic spontaneous urticaria, urticarial vasculitis, hypocomplementemic urticarial vasculitis syndrome). The results obtained may be useful for optimizing the differential diagnosis of diseases accompanied by urticarial rashes.

Keywords: chronic spontaneous urticaria; urticarial vasculitis; hypocomplementemic urticarial vasculitis syndrome; histology.

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Оригинальное исследование

Клинико-морфологическая характеристика пациентов с уртикарными высыпаниями

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АННОТАЦИЯ

Обоснование. Наиболее частым диагнозом, устанавливаемым пациентам с хроническими уртикарными высыпаниями, является хроническая спонтанная крапивница (распространённость в популяции до 0,1–1,4%). Однако подобные симптомы могут также наблюдаться при других, более редких заболеваниях (уртикарный васкулит, синдром гипокомплементемического уртикарного васкулита, криопиринассоциированные синдромы и синдром Шнитцлера).

Цель исследования — анализ клинических особенностей и гистологических характеристик биоптатов кожи у пациентов с хроническими уртикарными высыпаниям для оптимизации протокола ведения и усовершенствования дифференциальной диагностики.

Материалы и методы. На ретроспективном этапе отобраны 9 пациентов с хроническими уртикарными высыпаниями и проведённым гистологическим исследованием. Проспективный набор включил 11 пациентов, которым была проведена биопсия кожи.

Результаты. Пациенты, включённые в исследование (*n*=20; мужчин — 4, женщин — 16; возраст от 23 до 63 лет) разделены на три группы: с хронической спонтанной крапивницей (*n*=9; продолжительность заболевания от 2 до 132 мес, в среднем 24 мес), уртикарным васкулитом (*n*=9; продолжительность заболевания от 7 до 180 мес, в среднем 30 мес) и синдромом гипокомплементемического уртикарного васкулита (*n*=2; длительность заболевания 24 мес). Клинически хроническая спонтанная крапивница отличалась меньшей длительностью заболевания, меньшим временем существования отдельных элементов; кроме того, у пациентов присутствовали атипичные признаки высыпаний, что свидетельствовало о переходной группе между хронической спонтанной крапивницей и уртикарным васкулитом; стандартные или повышенные дозы антигистаминных препаратов были эффективны у 5 пациентов. При уртикарном васкулите и синдроме гипокомплементемического уртикарного васкулита клинические особенности проявлялись большей длительностью существования волдырей, ощущением жжения и болезненности, остаточной гиперпигментацией, а также резистентностью к терапии антигистаминными препаратами. Гистологическими особенностями уртикарного васкулита были лейкоцитоклазия, отложение фибрина и повреждение сосудистых стенок с отложением фибрина; редко визуализировался фибриноидный некроз, который в сочетании с вышеперечисленными признаками присутствовал только у 2 пациентов с синдромом гипокомплементемического уртикарного васкулита.

Заключение. В исследовании представлены результаты собственных наблюдений, анализ клинических и гистологических особенностей пациентов с различными заболеваниями (хроническая спонтанная крапивница, уртикарный васкулит, синдром гипокомплементемического уртикарного васкулита). Полученные результаты могут быть полезны для оптимизации дифференциальной диагностики заболеваний, сопровождающихся уртикарными высыпаниями.

Ключевые слова: хроническая спонтанная крапивница; уртикарный васкулит; синдром гипокомплементемического уртикарного васкулита; гистология.

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BACKGROUND

Chronic urticarial rashes are observed in 0.1% to 1.4% of the general population [1]. The most common diagnosis in patients with urticarial rashes persisting for more than six weeks is chronic spontaneous urticaria (CSU), a disease associated with mast cell degranulation, characterized by recurrent pruritic blisters and/or angioedema [2]. CSU is associated with a significant burden on both the patient and society [3]. However, chronic urticarial rashes may be seen in other, rarer disorders, including urticarial vasculitis (UV), Schnitzler syndrome, and cryopyrin-associated periodic syndromes (CAPS). Urticarial vasculitis is characterized by recurring urticarial rashes with a morphological pattern of leukocytoclastic vasculitis [4–7]. A rare nosologic form of UV is hypocomplementemic urticarial vasculitis syndrome (HUVS), which is diagnosed on the basis of a combination of urticarial rashes, systemic clinical symptoms, and hypocomplementemia in laboratory tests [8].

The differential diagnosis of chronic urticarial rashes is frequently challenging in clinical practice. In accordance with Russian and foreign guidelines, CSU is diagnosed when episodes of urticarial rashes accompanied by pruritus persist for more than six weeks in the absence of a triggering factor and resolve without residual symptoms for up to 24 hours [2, 9] (Figure 1). The diagnosis of UV, which is characterized by urticarial rashes lasting more than 24 hours, accompanied by burning and soreness, residual hyperpigmentation and/or palpable purpura, combined with systemic manifestations of fever, arthralgia and malaise, necessitates a skin biopsy [10] (Figure 2). The combination of chronic urticaria and hypocomplementemia with at least two secondary criteria, including leukocytoclastic vasculitis on histologic examination, arthralgia or arthritis, glomerulonephritis, uveitis or episcleritis, abdominal pain, and the presence of anti-Clq antibodies, results in the diagnosis of HUVS [8]. CAPS is diagnosed based on the detection of a *CIAS1* gene mutation [11]. The Strasbourg criteria are currently used for the diagnosis of Schnitzler syndrome. They comprise two mandatory criteria — chronic urticarial rashes and monoclonal IgM- or IgG-gammapathy — and four additional criteria, including recurrent fever, bone remodeling disorder, neutrophil infiltration of the skin on biopsy and leukocytosis (neutrophilia) at a level of 10,000/mm^3, and/or C-reactive protein levels above 30 mg/L in the blood [12] (Table 1).

The difficulties in differential diagnosis are also due to the heterogeneity of clinical and histologic manifestations, the presence of a transitional group of patients, and an incomplete understanding of the pathogenesis of these diseases. Furthermore, the presence of all histologic criteria in one patient is extremely rare, which results in the diagnosis being often established on the basis of partial criteria. This can explain the discrepancies observed in studies on the incidence of UV. Furthermore, there is a lack of consensus regarding the classification of CSU, UV, and HUVS within the broader clinical and histologic spectrum of diseases accompanied by urticarial rashes. Thus, the study of clinical

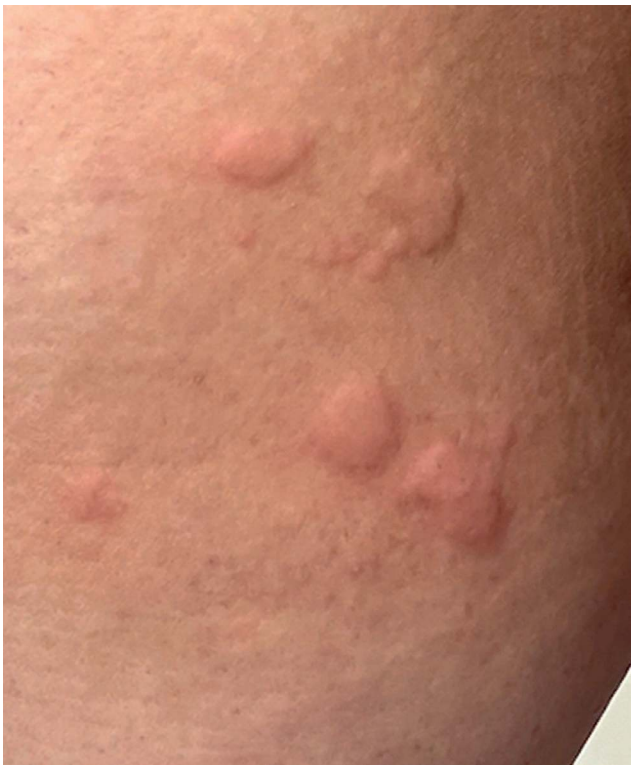

Fig. 1. Typical urticarial rash in a patient with chronic spontaneous urticaria.

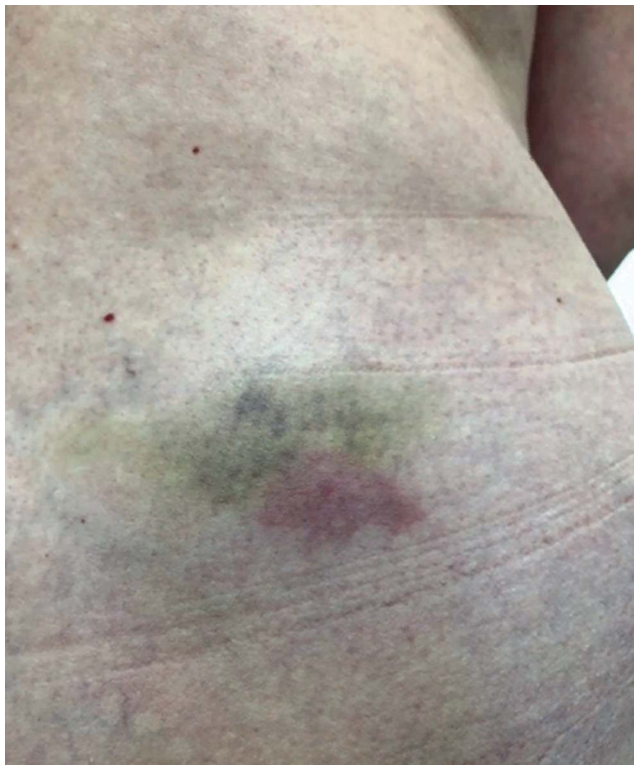

Fig. 2. Resolving urticarial rashes with the formation of hemosiderin staining in a patient with urticarial vasculitis.

Table 1. Differential diagnosis of diseases accompanied by urticarial rashes in adults

Diagnosis	Chronic spontaneous urticaria	Urticarial vasculitis	Hypocomplementemic urticarial vasculitis syndrome
Incidence	80%–90%	2.3%–10%	Rare disease (0.5/100,000 population)
Diagnostic criteria	Urticarial rashes without an established trigger for more than 6 weeks	Recurrent urticarial rashes. Histological features of leukocytoclastic vasculitis	Mandatory criteria (chronic urticaria and hypocomplementemia) + at least 2 secondary (leukocytoclastic vasculitis on histological examination, arthralgia or arthritis, glomerulonephritis, uveitis or episcleritis, abdominal pain; anti-Clq antibodies)
Clinical criteria	Blister persists for < 24 h	Blister persists for > 24 h	
	Accompanied by pruritus	Accompanied by burning and soreness	
	Disappears without residual effects	Resolved with hemosiderin hyperpigmentation	
	Increased body temperature during the period of active rashes (rare)	General malaise, fever	Arthralgia, fever, polyneuropathy, uveitis, episcleritis, glomerulonephritis, and abdominal pain
Histological criteria	-		Leukoclasia
	Increased number of mast cells in the dermis	Fibrinoid necrosis with vascular integrity disruption (rare)	Fibrinoid necrosis with vascular integrity disruption
	-	Extravasation of red blood cells (rare)	
	-	Damaged and swollen venule cells	
	Perivascular cellular infiltrate with admixture of lymphocytes, neutrophils, and eosinophils	Perivascular cellular infiltrate consisting predominantly of neutrophils and eosinophils	Perivascular cellular infiltrate consisting predominantly of neutrophils

and morphological correlations in patients with urticarial rashes is of interest for understanding the pathogenetic features of individual diseases and, accordingly, optimizing differential diagnosis.

The study aimed to analyze the clinical features and histological characteristics of skin biopsy specimens in patients with chronic urticarial rashes to optimize the management protocol and improve the differential diagnosis of diseases with urticarial rashes in the clinical practice of dermatologists, allergists-immunologists, and rheumatologists.

MATERIAL AND METHODS

Study design

The study included 2 stages: an observational single-center retrospective study and an observational multicenter prospective study.

Eligibility criteria

Inclusion criteria. The study included patients with chronic urticarial rashes who were indicated for histological

examination. According to contemporary foreign and Russian guidelines, biopsy of urticarial elements is performed according to strict indications, which include the long-term existence of individual rashes (more than 24 hours), a burning sensation and pain, and residual phenomena in the form of hyperpigmentation and/or palpable purpura.

Non-inclusion criteria. The study did not include patients with acute urticaria and patients with chronic urticarial rashes who did not undergo histological examination.

Study setting

The retrospective stage of the study was carried out at the Clinic for Skin and Venereal Diseases named after V.A. Rakhmanov of Sechenov University. The prospective recruitment of patients was conducted at the Clinic for Skin and Venereal Diseases named after V.A. Rakhmanov of Sechenov University, the Moscow City Research and Practice Center of Allergology and Immunology of the State Budgetary Institution of Healthcare City Clinical Hospital No. 52 of the Moscow Department of Healthcare, and the Federal State Budgetary Scientific Institution V.A. Nasonova Research Institute of Rheumatology.

Study duration

Retrospective clinical data was obtained from the archive of the Clinic for Skin and Venereal Diseases named after V.A. Rakhmanov of Sechenov University from January 2019 to April 2022. The morphological material was obtained from the archive of the Institute of Clinical Morphology and Digital Pathology of Sechenov University.

The prospective phase of the study was conducted from January 2022 to September 2023. Skin biopsies of patients with urticarial rashes were performed at the Clinic for Skin and Venereal Diseases named after V.A. Rakhmanov of Sechenov University, the Moscow City Research and Practice Center of Allergology and Immunology of the State Budgetary Institution of Healthcare City Clinical Hospital No. 52 of the Moscow Department of Healthcare, and the Federal State Budgetary Scientific Institution V.A. Nasonova Research Institute of Rheumatology.

Intervention description

Histological examination was performed before the administration of biological and hormonal therapy. Histological material for the study was obtained from the blister, existing for less than 24 hours, under local anesthesia with a 2% lidocaine hydrochloride solution. The material was then fixed in 10% neutral buffered formalin solution. The fixation and histological embedding of the material were performed according to a standard protocol. Subsequently, serial paraffin sections with a thickness of 4–5 μm were prepared. The obtained skin biopsy specimens were stained with hematoxylin-eosin and toluidine blue. Neutrophils, eosinophils, and mast cells were counted at 400x magnification in five fields of view using a Zeiss Axio Lab. A1 microscope (Carl Zeiss TM, Germany).

Ethical review

The study was approved by the local ethics committee of Sechenov University (protocol No. 22–21, dated December 9, 2021) and by the local ethics committee of the State Budgetary Institution of Healthcare City Clinical Hospital No. 52 of the Moscow Department of Healthcare (protocol No. 02/0223, dated February 22, 2023).

Statistical analysis

The data obtained through the analysis of demographic characteristics is presented as a median and interquartile range.

Histological parameters were assessed qualitatively and quantitatively.

The degree of expression of leukocytoclasia, fibrin deposition, fibrinoid necrosis, damaged vessel walls, edema of the dermis and endothelial cells was assessed in points from 0 to 3. A score of 0 indicates the absence of a sign, while a score of 1 indicates a weakly expressed sing, a score of 2 indicates a moderately expressed sing, and a score of 3 indicates a strongly expressed sign. The number of eosinophils, neutrophils, and mast cells in skin biopsy specimens was evaluated according to the following criteria: a small number was defined as less than five cells per field of view, a moderate number was defined as five to ten cells per field of view, and a significant number was defined as more than ten cells per field of view.

RESULTS

Participant characteristics

At the first stage, archival data from the Clinic for Skin and Venereal Diseases named after V.A. Rakhmanov of Sechenov University from January 2019 to April 2022 was analyzed. A total of 70 patients with urticarial rashes were observed at the clinic, of whom 50 exhibited a chronic form. Nine of these patients underwent histologic examination. A total of 11 patients participated in the prospective phase of the study. Thus, 20 patients (16 women and 4 men) who underwent histologic examination of skin biopsy specimens were included in the clinical and histologic analysis. The age of patients ranged from 23 to 63 [26; 36.5] years (Table 2).

Primary findings

The study included 20 patients with chronic urticarial rashes. Blisters were accompanied by pruritus in 16 patients and burning and soreness in 10 patients. Residual phenomena in the form of hyperpigmentation or purpura upon resolution of rashes were observed in 10 patients. In 10 patients, individual elements existed for more than 24 hours, while in the other 10 patients, they resolved within a day.

A skin biopsy was conducted in all patients to differentiate between CSU and UV. Upon histological examination, the

Table 2. Demographic characteristics of patients with urticarial rashes

Characteristics	Chronic spontaneous urticaria	Urticarial vasculitis	Hypocomplementemic urticarial vasculitis syndrome
Gender, female/male	9/0	6/3	1/1
Age, years, Me	25–61 36 [25; 37]	23–60 30.5 [26; 48]	41.63
Disease duration, months, Me	2–132 24 [18; 33]	7–180 30 [24; 84]	24

signs of UV, including leukocytoclasia, fibrinoid necrosis, and erythrocyte extravasation, were identified in 11 patients, leading to a diagnosis of UV (Figure 3, 4).

Accordingly, patients were classified into three groups based on their clinical and histologic characteristics: CSU (n = 9), with a disease duration ranging from 2 to 132 months, with a median of 24 months (18–33); UV (n = 9), with a disease duration ranging from 7 to 180 months, with a median of 30 months (24–84); and HUVS (n = 2), with a disease duration of 24 months.

Clinical and histological characteristics. In the cohort of patients with CSU, urticarial rashes were accompanied by pruritus in nine patients and angioedema in the facial area in four patients. The duration of urticarial elements was less than 24 hours in four cases. However, the patients exhibited atypical characteristics for CSU, including the presence of elements for more than 24 hours (in four cases), burning sensation/pain (in three cases), hemosiderin staining at rash resolution (in four cases), and fever up to 39 °C (in one case) (Table 3). Consequently, the patients underwent skin biopsy. A histological examination of patients with CSU revealed fibrin deposition in the vascular wall (in two cases) and erythrocyte extravasation (in two cases). Leukocytoclasia and fibrinoid necrosis were not detected, and therefore the patients were diagnosed with CSU.

The urticarial rashes observed in patients with UV were characterized by burning and pain in four cases, with a duration exceeding 24 hours in four cases. Additionally, six patients exhibited concomitant angioedema in the neck, auricles, eyelids, and lips. Residual phenomena were noted in four cases following the resolution of the rashes. Resistance to standard and high doses of non-sedating antihistamines was observed in eight patients. Additionally, systemic manifestations were observed, including soreness (in one patient), swelling (in one patient), limitation of hand joint mobility (in one patient), neuropathy (in one patient), and fever (in two patients). In nine patients, hematoxylin-eosin staining of skin biopsy specimens revealed a combination of histological features of UV. These included leukocytoclasia (in eight patients), fibrin deposition (in eight patients), fibrinoid necrosis (in two patients), erythrocyte extravasation (in one patient), and vascular wall damage (in eight patients).

Two patients with HUVS had urticarial rashes accompanied by burning and soreness, as well as angioedema of the hands and facial skin. The urticaria resolved after 24 hours, leaving foci of hyperpigmentation. One patient exhibited anterior uveitis, a condition marked by involvement of the iris and ciliary body, accompanied by ocular discomfort, blurred vision, photophobia, and iris color alteration. At histological examination of skin biopsy specimens, leukocytoclasia

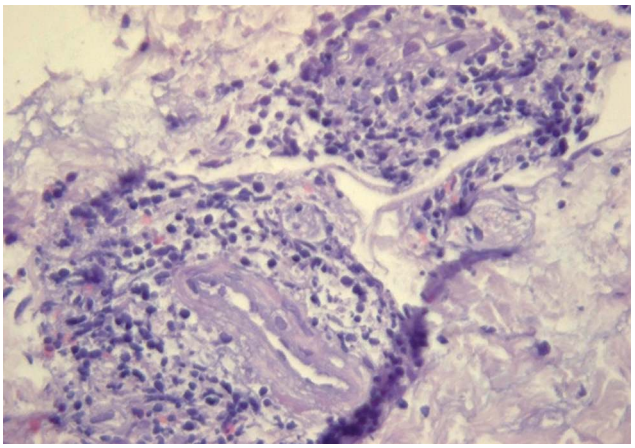

Fig. 3. Histological picture of urticarial vasculitis with signs of severe neutrophil infiltration, leukocytoclasia and fibrinoid necrosis. Hematoxylin-eosin staining, ×200.

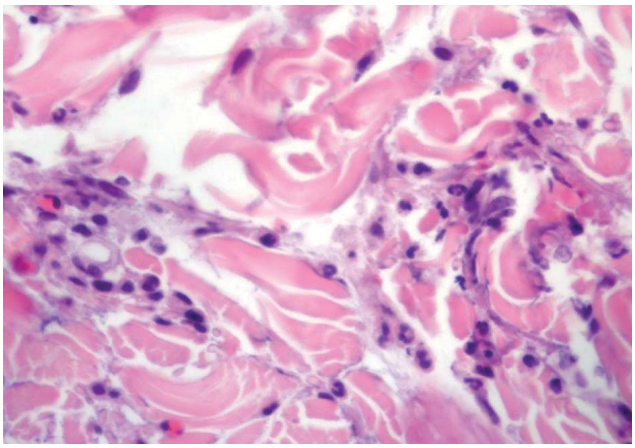

Fig. 4. Histological picture of urticarial vasculitis with signs of neutrophilic infiltration and leukocytoclasia. Hematoxylin-eosin staining, ×400.

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Table 3. Clinical characteristics of patients with urticarial rashes

Patient, No.	Gender	Age, years	Disease duration, months	Skin symptoms						Systemic symptoms	Lack of response to antihistamines	Associated diseases	UAS7	Therapy provided
				Blisters	Duration of existence of individual elements > 24 h	Pruritus	Burning and/or soreness	Residual phenomena	Angioedema					
Chronic spontaneous urticaria														
1	Ж	31	60	+	-	+	-	+	-	-	-	-	ND	Antihistamines
2	Ж	25	24	+	+	+	-	-	-	-	-	-	ND	Antihistamines
3	Ж	37	132	+	+	+	-	-	+	Fever, 39 °C	+	Autoimmune gastritis, celiac disease, hypothyroidism, and vitiligo	ND	Omalizumab
4	Ж	26	18	+	+	+	-	-	+	-	-	-	28	Antihistamines
5	Ж	36	3	+	+	+	+	+	-	-	-	-	2	Antihistamines
6	Ж	37	2	+	-	+	-	+	+	-	+	-	25	Omalizumab
7	Ж	61	24	+	-	+	-	+	-	-	-	-	ND	Antihistamines
8	Ж	37	21	+	-	+	+	-	-	-	+	Autoimmune thyroiditis	5	Dexamethasone
9	Ж	26	33	+	-	+	+	-	+	-	+	-	9	Omalizumab
Urticarial vasculitis														
10	Ж	47	24	+	+	+	-	-	+	Fever	+	-	ND	Prednisolone, dapsone
11	M	48	120	+	-	+	-	-	+	-	+	-	ND	Omalizumab
12	Ж	49	180	+	+	+	+	+	-	Arthralgia, neuropathy	-	-	ND	Antihistamines
13	Ж	24	7	+	+	+	-	-	-	-	+	-	ND	Methylprednisolone, methotrexate
14	Ж	34	60	+	-	-	+	+	-	-	+	-	7	Prednisolone
15	Ж	23	84	+	-	+	-	-	+	-	+	-	11	Prednisolone
16	Ж	26	9	+	-	-	+	+	+	-	+	Chronic thyroiditis	13	Omalizumab, dexamethasone
17	M	27	30	+	-	+	-	-	+	Fever	+	-	ND	Prednisolone, omalizumab
18	M	60	24	+	+	-	+	+	+	-	+	-	10	Omalizumab
Hypocomplementemic urticarial vasculitis syndrome														
19	Ж	41	24	+	+	-	+	+	+	Arthralgia, fever, polyneuropathy	+	Systemic lupus erythematosus, Sjogren's syndrome, thrombophilia	23	Dexamethasone
20	M	63	24	+	+	+	+	+	+	Uveitis	+	Monoclonal gammopathy	21	Dexamethasone

Note. М — male sex; Ж — female sex; НИ — no information.

was observed in two patients, along with marked fibrinoid necrosis with fibrin deposits in the vessel wall (in two patients) and moderate vascular wall destruction (in two patients) (Table 4).

Analysis of cellular infiltrate in skin biopsy specimens. In the case of CSU, neutrophils and eosinophils were observed in insignificant quantities. Of these, intravascular neutrophils were observed in two cases, while intravascular eosinophils were absent. In the perivascular infiltrate, eosinophils were slightly more common (in five patients) than neutrophils (in two patients). Conversely, neutrophils were more frequently observed in the dermis (in five patients) than eosinophils (in two patients).

Both neutrophils and eosinophils were observed in skin biopsy specimens of patients with UV, both within the perivascular infiltrate and in the dermis. Within the dermal vessels, neutrophils were observed in small, moderate, and significant numbers in four, two, and two patients, respectively. Similarly, eosinophils were present within the vessels in small and moderate numbers in five and two patients, respectively. In the perivascular infiltrate, neutrophils were observed in small, moderate, and significant quantities

Table 4. Data obtained from a histological examination of skin biopsies of patients with urticarial rashes

Patients, No.	Leukocytoclasia	Extravasation of red blood cells	Fibrinoid necrosis	Intravascular fibrin accumulation	Endothelial cell edema	Ectatic vessels	Blurring of the vascular wall boundaries	Dermal edema	Intravascular neutrophil count	Intravascular eosinophil count	Neutrophil count in perivascular infiltrate	Eosinophil count in perivascular infiltrate	Dermal neutrophil count	Dermal eosinophil count	Dermal mast cell count
Chronic spontaneous urticaria															
1	0	0	0	0	1	3	0	3	1	0	0	1	1	0	3
2	0	0	0	1	3	2	0	2	0	0	1	1	0	0	1
3	0	0	0	0	1	2	0	3	0	0	1	1	0	1	2
4	0	0	0	0	1	3	1	3	0	0	0	0	1	0	3
5	0	0	0	0	1	2	0	3	0	0	0	0	0	0	1
6	0	0	0	0	1	1	0	1	0	0	0	1	1	0	2
7	0	1	0	1	1	0	1	1	1	0	0	0	1	0	3
8	0	1	0	0	1	2	0	2	0	0	0	0	0	1	0
9	0	0	0	0	1	3	0	3	0	0	0	1	1	0	3
Urticarial vasculitis															
10	1	1	0	2	1	1	1	1	3	1	1	1	2	1	1
11	3	0	3	3	1	3	1	3	1	1	1	1	2	3	2
12	3	0	3	3	3	3	3	3	2	0	1	1	3	1	1
13	3	0		3	3	3	3	3	2	1	2	3	3	1	1
14	3	0	0	3	3	3	3	3	3	2	3	3	3	3	1
15	1	0	0	1	1	1	1	1	1	1	1	3	1	3	0
16	1	0	0	1	1	2	1	1	1	1	1	0	2	1	1
17	1	0	0	0	1	1	1	1	1	0	2	3	1	0	1
18	1	1	0	0	1	1	1	2	0	2	1	2	1	1	1
Hypocomplementemic urticarial vasculitis syndrome															
19	1	0	3	3	1	1	1	2	3	1	3	1	3	3	1
20	3	0	1	3	1	2	1	3	1	0	3	1	3	3	1

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in six, two and one patient, respectively, and eosinophils were observed in small, moderate, and significant quantities in three, one and four patients, respectively. In the dermis, neutrophils were observed in small (in three patients), moderate (in three patients), and significant (in three patients) quantities, whereas eosinophils were observed in small (in five patients) and significant (in three patients) quantities.

A marked neutrophilic cellular infiltrate was observed in two patients with HUVS. Neutrophils were present in significant numbers within the vessels (in one patient) and perivascular infiltrate (in two patients), while eosinophils within the vessels and perivascular infiltrate were noted in small amounts (in one and two patients, respectively). However, in the dermis, both neutrophils and eosinophils were visualized in significant numbers (in two patients).

Analysis of the number of mast cells in the dermis. Mast cells in the dermis were detected by toluidine blue staining in 18 patients with chronic urticarial rashes. In patients with CSU, mast cell accumulation was observed in small (in 2 patients), moderate (in 2 patients), and significant (in 4 patients) amounts, whereas in patients with UV, the number of mast cells was small (in 7 patients) and moderate (in 1 patient).

Therapy. Notably, four out of nine patients with CSU, eight out of nine patients with UV, and all patients with HUVS exhibited resistance to increased doses of non-sedative antihistamines (i.e., no effect of double and quadruple doses of antihistamines). In this context, six patients were treated with the biological drug omalizumab. Additionally, glucocorticosteroids were used in eight patients, with one case involving their combination with dapsone.

Adverse events

No adverse events were observed during the study.

DISCUSSION

Summary of the primary study results

This study presents the results of our own observations and analysis of clinical and histological features of patients with various diseases accompanied by urticarial rashes (CSU, UV, HUVS). The results obtained characterize the clinical experience of doctors of various specialties, including dermatologists, allergists-immunologists, and rheumatologists.

CSU was clinically characterized by a shorter duration of the disease and a shorter time of existence of separate elements. Standard or increased doses of antihistamines were effective in five of nine patients with CSU. Additionally, atypical signs of rashes were observed in patients with CSU, indicating a transitional group between CSU and UV.

Patients with UV and HUVS were significantly more likely to demonstrate clinical features such as prolonged blister duration, burning sensation and soreness, residual hyperpigmentation, and resistance to antihistamine therapy. Histological examination revealed that the main histological features for UV were leukocytoclasia, fibrin deposition, and vascular wall damage with fibrin deposition. Fibrinoid necrosis was rarely observed, and in combination with the aforementioned features, was present only in two patients with HUVS.

Perivascular and dermal neutrophil infiltration was insignificant in CSU, moderate in UV, and pronounced in HUVS. On the contrary, mast cells in moderate and significant amounts were much more frequent in CSU and in insignificant amounts in UV and HUVS.

Discussion of the primary study results

The differential diagnosis of urticarial rashes is of interest to physicians and researchers of various specialties, as it provides insight into the clinical and histologic characteristics of patients with this pathology. The data summarizes the interdisciplinary clinical experience of three institutions in working with patients with chronic urticarial rashes. This is a valuable resource for dermatologists, allergologists-immunologists, rheumatologists, and pathologists' clinical practice.

Our study indicates that the clinical differences between diseases accompanied by vascular involvement (UV and HUVS) include the duration of urticarial rashes, the presence of burning and soreness, residual phenomena, and systemic manifestations such as fever, arthralgia, and neuropathy. These findings are consistent with the results of a recent international prospective study [13]. Our study indicates that eight out of nine patients with established UV and all patients with HUVS were resistant to antihistamine therapy. However, given the indications for biopsy only in patients with atypical urticarial rashes, patients in the CSU group in our study may be classified as having a transitional form between CSU and UV, as previously described by R.R. Jones et al. [14].

The histological criteria for differential diagnosis have been widely studied over the past decades. A statistical analysis conducted by scientists from the Charité Clinic (Berlin, Germany) identified three key differentiation criteria, including leukoclasia, erythrocyte extravasation, and fibrinoid necrosis and/or fibrin deposition in the vascular wall [15]. These findings align with the results of our study. However, erythrocyte extravasation has also been observed in patients with CSU, potentially due to microvessel traumatization during skin biopsy.

In addition to the main histological criteria, the study of cellular infiltrate is of interest. The literature describes correlations with eosinophilic infiltrate and clinical indicators of greater severity in patients with urticaria [16]. Furthermore, there is data on the presence of hemosiderin hyperpigmentation in perivascular and interstitial infiltrate consisting of neutrophils, eosinophils, and lymphocytes in patients with CSU [17]. Our data indicates that patients with CSU exhibited perivascular and interstitial infiltrates

of eosinophils and neutrophils, suggesting the presence of a transitional group described in the study by R.R. Jones et al. [14]. This group was characterized by a dense perivascular infiltrate comprising mononuclear cells with a notable admixture of neutrophils and eosinophils, accompanied by minimal leukocytoclasia in the absence of other signs of vasculitis.

The study conducted by H. Bonnekoh et al. [18] indicated that neutrophilic infiltrates in skin samples were less pronounced in CSU and more pronounced in Schnitzler syndrome, with the formation of neutrophilic extracellular traps. Our data suggests that neutrophil infiltration, both perivascular and in the dermis, may also occur in patients with CSU, but these changes are more pronounced in patients with UV and HUVS.

The data obtained by counting mast cells, which play a key role in the formation of urticarial rashes, is noteworthy. A higher number of mast cells was more typical in patients with CSU, but they were absent in two patients. This may be associated with the degranulation process, which requires additional staining with special dyes and immunohistochemical examination. For example, immunohistochemical analysis in a previous study showed a three-fold increase in mast cells in skin samples from patients with CSU [19].

Clinical and histological correlations are important for optimizing the differential diagnosis of diseases accompanied by urticarial rashes. Significant clinical features of diseases with vascular involvement are resistance to high-dose antihistamine therapy, the duration of rashes, residual phenomena at their resolution, subjective sensations of burning and soreness, and systemic symptoms. Histologic features include leukoclasia, fibrin deposition in the vascular wall and/or fibrinoid necrosis, and a dense perivascular and interstitial neutrophilic and eosinophilic infiltrate in urticarial diseases accompanied by lesions of dermal microvessels (UV, HUVS). However, the issue of standardization of histological criteria, as well as additional criteria for the indication of histological examination, remains unresolved. In the differential diagnosis of diseases accompanied by urticarial rashes, a skin biopsy is of diagnostic value in patients with atypical characteristics of urticarial rashes. The necessity of a skin biopsy in patients with CSU in case of resistance to therapy with non-sedative antihistamines requires further investigation.

Study limitations

The study limitations include the inclusion of CSU patients with atypical urticarial rashes in the histologic analysis, in accordance with the indications for histologic examination in clinical practice. Consequently, it is challenging to assess the changes in the skin associated with typical CSU rashes. Furthermore, this study is limited by the use of semi-quantitative scales to assess the composition of the cellular infiltrate in skin biopsy specimens and the lack of assessment of the severity of urticarial rashes using clinical indices in the retrospective material. The findings have value for clinical practice and further mechanistic research, given the multicenter and multidisciplinary nature of the study, as well as the inclusion of rare medical conditions in the comparative analysis of urticarial rashes.

CONCLUSIONS

The differential diagnosis of chronic urticarial rashes represents a significant interdisciplinary challenge, given the considerable heterogeneity observed in both the clinical symptoms and histologic characteristics of these diseases. However, the clinical differences between UV and CSU included the duration of urticarial rashes, the presence of burning, soreness, and systemic manifestations. Histological findings more characteristic of UV included leukocytoclasia, fibrin deposition, and a dense neutrophilic infiltrate. In contrast, CSU was characterized by the absence of leukocytoclasia, as well as damaged vessels and fibrin accumulation, which were rarely observed. Neutrophils in perivascular infiltrates were present in low quantities, and mast cells were more frequently observed.

In histologic examination, the choice of generally accepted histologic criteria remains an important issue, as well as the use of international diagnostic criteria to verify the diagnosis of rare urticarial diseases associated with damage to the skin microvascular wall.

A promising area for further research of diseases accompanied by urticarial rashes is the role of effector cells in the pathogenesis of urticarial rash formation and vascular damage. Additionally, there is a need to identify novel biomarkers for differential diagnosis using cutting-edge genomic and post-genomic technologies.

ADDITIONAL INFORMATION

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