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# Is chronic urticaria or urticarial vasculitis a diagnostic dilemma?

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**Introduction.** Urticarial vasculitis (UV) is a rare disease that has two components: clinical manifestations of urticaria and histopathological signs of cutaneous leukocytoclastic vasculitis of small vessels, predominantly involving postcapillary venules. This condition is characterized by chronic or recurrent episodes of urticaria, each element of which lasts more than 24 hours and is accompanied by a feeling of pain and burning.
**The aim** is to reveal the key points of pathogenetic mechanisms, differential diagnosis and therapeutic tactics of UV based on a clinical case.
**Clinical case.** A clinical case of a 17-year-old boy with normocomplementemic UV is described. The patient's main complaint was a long-lasting rash (more than three weeks) with itching. From the anamnesis it is known that the provoking factors for the onset of the disease were an insect bite and the start of taking a new drug, namely vitamin K (two days before the onset of the disease). Throughout this time, the child was examined by various specialists and received treatment. Alternative diagnoses: bacterial folliculitis, viral exanthem, unspecified urticaria. There was no positive effect from the received treatment. The diagnosis of UV was made in the sixth week of the disease using a punch biopsy. Regression of the skin syndrome was achieved using a combination of antihistamine and antileukotriene drugs.
**Conclusions.** Performing a punch biopsy, which is currently the gold standard for diagnosis, allows us to solve the diagnostic dilemma: «UV or chronic urticaria». Timely diagnosis helps to avoid false diagnoses and, as a result, incorrect treatment of UV. The description of this clinical case is a contribution to the disclosure of this globally complex problem.
The research was carried out in accordance with the principles of the Declaration of Helsinki. The informed consent of the child and child's parents was obtained for conducting the research.
No conflict of interest was declared by the authors.
**Keywords:** urticaria, vasculitis, autoantibodies, children.

## Хронічна кропив'янка чи уртикарний васкуліт — діагностична дилема?

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Уртикарний васкуліт (УВ) це рідкісне захворювання, що має дві складові: клінічні прояви кропив'янки та гістопатологічні ознаки шкірного лейкоцитокластичного васкуліту дрібних судин, переважно із залученням посткапілярних венул. Цей стан характеризується хронічними або рецидивуючими епізодами кропив'янки, кожен з елементів якої існує понад 24 години та супроводжується відчуттям болю і печіння.
**Мета** — на підставі клінічного випадку розкрити ключові моменти патогенетичних механізмів, диференційної діагностики та лікувальної тактики УВ.
**Клінічний випадок.** Описано клінічний випадок 17-річного хлопчика із нормокомплементемічним УВ. Основною скаргою пацієнта була тривала висипка (більше ніж три тижні) зі свербежем. З анамнезу відомо, що провокаційними факторами початку захворювання були: укус комахи та початок прийому нового препарату, а саме вітаміну К (за два дні до дебюту хвороби). Протягом усього часу дитина проходила обстеження в різних спеціалістів та отримувала лікування. Альтернативні діагнози: бактеріальний фолікуліт, вірусна екзантема, кропив'янка неуточнена. Від отриманого лікування не було позитивного ефекту. Діагноз УВ було встановлено на шостому тижні хвороби за допомогою панч-біопсії. Регрес шкіряного синдрому було досягнуто за допомогою комбінації антигістамінних та антилейкотрієнових препаратів.
**Висновки.** Проведення біопсії шкіри, яке на сьогодні є золотим стандартом діагностики, дає змогу вирішити діагностичну дилему: «УВ чи хронічна кропив'янка». Своєчасна діагностика допомагає уникнути помилкових діагнозів та як результат — неправильного лікування УВ. Опис даного клінічного випадку є внеском у розкриття цієї складної у всьому світі проблеми.
Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення досліджень отримано інформовану згоду дитини та її батьків.
Автори заявляють про відсутність конфлікту інтересів.
**Ключові слова:** кропив'янка, васкуліт, аутоантитіла, діти.

## Introduction

Urticarial vasculitis (UV) is a rare disease that has two components: clinical manifestations of urticaria and histopathological signs of cutaneous leukocytoclastic vasculitis of small vessels, predominantly involving postcapillary venules [2,8,9,13]. This condition is characterized by chronic or recurrent episodes of urticaria, each element of which lasts more than 24 hours and is accompanied by a feeling of pain and burning [6,12]. UV can primarily affect the skin or spread systemically, affecting various organs, including the musculoskeletal, renal, respiratory, gastrointestinal, and visual systems [6]. UV has been described in children, the youngest

patient was reported at the age of one year [13,15]. UV accounted for 9% of cases in a study of children with leukocytoclastic vasculitis [7].

At the moment, there are no uniform clinical recommendations, and approaches to the diagnosis and treatment of UV are different [8,9,13]. First of all, this is due to the variety of skin, systemic and serological signs, which make it difficult to establish a diagnosis. Therefore, the lack of generally accepted criteria for UV and the difficulty of differential diagnosis with other vasculitis remains a relevant topic nowadays.

**The aim** of the work is to reveal the key points of pathogenetic mechanisms, differential diagnosis and therapeutic tactics of UV based on a clinical case.

We have analyzed the clinical case of a 17-year-old *boy K.*, who was examined and treated at the Municipal Institution «Regional Medical Center of Family Health (RMCFH)» of Dnipropetrovsk Regional Council» with a clinical diagnosis «Urticarial vasculitis, normocomplementemic, Antinuclear antibodies (ANA) test — positive. Associated diagnosis: Secondary arterial hypertension (AH) 1st degree. Raynaud's phenomenon. Chronic tonsillitis».

The informed consent of the child and child's parents was obtained for conducting the research.

## Clinical case

*Boy K.*, 17 years old, consulted an allergist with complaints of a rash that has been bothering him for three weeks and is accompanied by itching. The patient associated the onset of the disease with the bite of an unknown insect two days before the onset of the rash. From the anamnesis of the disease, it is known that two days before the appearance of the rash, the patient started taking vitamin K and multivitamins, several months before the rash, he had COVID-19. Originally the rash appeared on the legs, and on the next day it spread to the abdomen and upper limbs, accompanied by unbearable itching without an increase in temperature. The boy was consulted by a dermatologist, who establish the diagnosis: bacterial folliculitis, viral exanthem. After prescribing symptomatic treatment (fexofenadine hydrochloride, silicon dioxide), no improvement was observed. On the contrary, the rash continued and spread throughout the body. The child's condition temporarily improved after adding dexamethasone to the treatment at a dose of 4 mg intramuscularly once a day and calcium gluconate. After one day, at night, there was swelling of the face and difficulty breathing. Therefore, it was necessary to call an ambulance. Intramuscular injection of additional 4 mg of dexamethasone and prescription of chloropyramine (4 pills per day) temporarily improved the condition.

*Objective status*: the general condition of the boy is relatively satisfactory. Body temperature — 36.6°C, heart rate — 100/minute, respiratory rate — 16/minute, blood pressure — 135/80 mmHg (which corresponded to AH 1st degree). Weight — 90 kg, height — 180 cm, body mass index (BMI) —

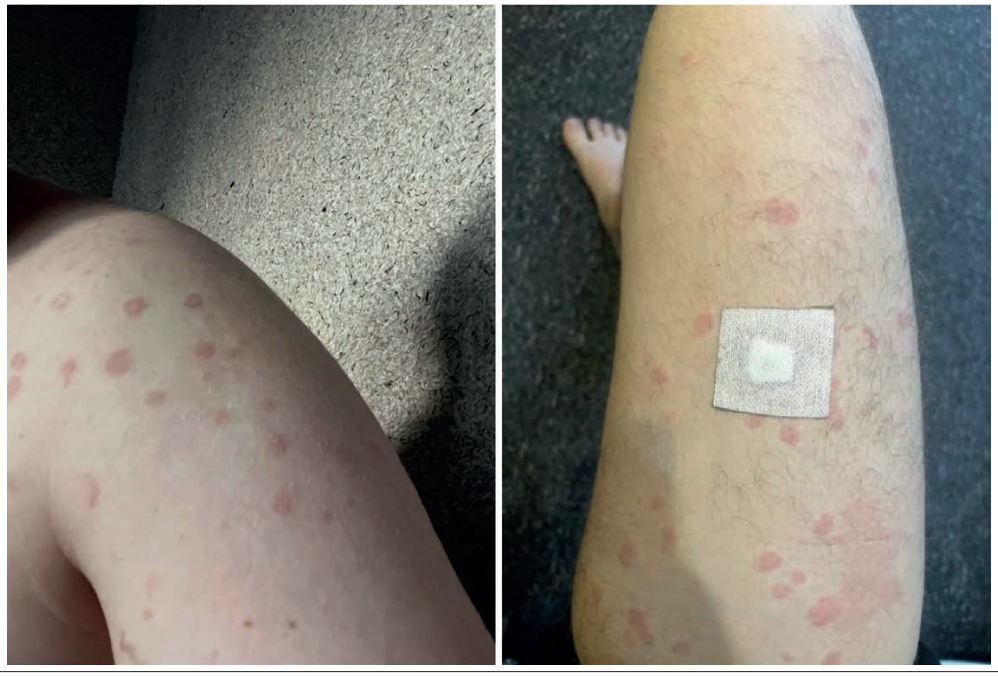

***Fig. 1.*** Urticarial rash in *patient K.*, 17 years old, on the lower limbs (before treatment)

27.8 kg/m$^2$ (overweight). The upper and lower limbs are cold to the touch, moist, red-blue in color like gloves and socks (Raynaud's phenomenon). An urticarial rash on the skin of the abdomen and limbs (Fig. 1), without a tendency to merge, striae on the lower part of the abdomen, back, upper limbs.

*Scoliotic posture*. The mucous membrane of the oral cavity is pale pink and clean. The breathing is vesicular in the lungs. There are no wheezes. Heart sounds are weakened, systolic murmur in the projection of the mitral valve. The abdomen is swollen, painful on palpation. The liver and spleen are not palpable. Physiological functions are not impaired.

An ophthalmologist's examination revealed angiospasm of retinal vessels in both eyes.

Results of additional examination methods: General blood analysis: erythrocytosis — $5.51\times10^{12}$/l, lymphocytosis — 43.7%. Common urine analysis: within normal limits. Biochemical analysis of blood: albumin 47.3 g/l, alanine aminotransferase (ALT) — 60 Units/l, direct bilirubin — 5.25 μmol/l, antistreptolysin O (ASLO) —156 IU/ml, complement C3 — 1.37 g/l and C4 levels — 0.15 g/l — corresponded to the normative values. The level of total IgE is less than 1 IU/ml (normal), eosinophil cationic protein (ECP) — 15.1 ng/ml (normal), diamine oxidase (DAO) — 13.33 U/ml (normal), allergy explorer 2 (ALEX-2) test — no sensitization was detected. ANA — 1:100 (positive test). The coagulogram blood test corresponded to normative values: prothrombin time — 11.9 seconds, prothrombin according to Kwik — 105.6%, international normalized ratio — 0.97, activated partial thromboplastin time — 28.8 seconds, thrombin time — 18.7 seconds, fibrinogen — 2.186 g/l, D-dimer — 0.36 μg.

An ultrasound examination of kidneys revealed pyelectasis of the left kidney. According to the results of ambulatory blood pressure monitoring, elevated systolic blood pressure during the day and night and diastolic AH of the 1st degree was registered. An ultrasound examination of the extracranial brachiocephalic vessels revealed a hyperkinetic type of blood circulation with a normoresistant component, S-shaped deformation of the carotid arteries.

*Established diagnosis*: Unspecified urticaria. Secondary AH 1st degree. Raynaud's phenomenon. Chronic tonsillitis.

It was planned to modify the therapy by adding double-dose rupatadine, but since the drug was not available, the decision was made to prescribe double-dose ketotifen and cardiotrophic therapy (carnitine, vitamins $B_{12}$, $B_1$, $B_6$) and following a diet.

While taking ketotifen, the child's condition began to improve, the rash gradually regressed, occasional rash elements remained on the limbs, but three days later the skin rash appeared again on the limbs and trunk, and the itching of the skin increased. A decision was made to perform a skin punch biopsy, and to add montelukast 10 mg per day to the therapy. Such a change in therapy led to significant positive dynamics in the form of stabilization of the child's condition, elimination of skin itching, regression of the rash. However, isolated elements on the limbs still appeared periodically (once every 2–3 days).

According to the results of the performed punch biopsy, it was established that the epidermis has a typical structure. At all levels of the dermis, a weakly expressed perivascular infiltration by lymphocytes is observed, in the lumen of vessels there is a parietal arrangement of segmented nuclear

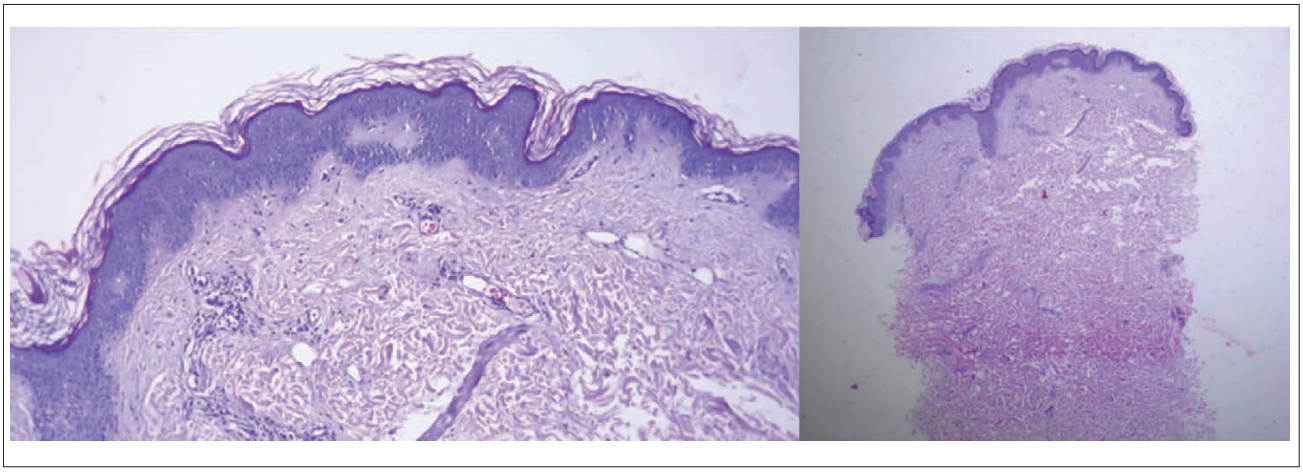

***Fig. 2.*** Histological picture of a punch biopsy of *patient K.*, 17 years' old

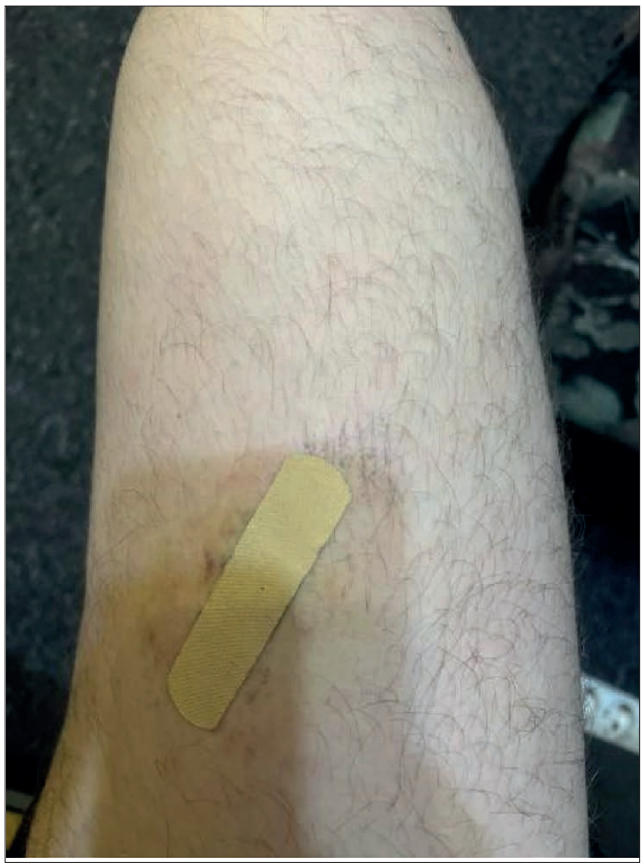

***Fig. 3.*** Lower limb of *patient K.*, 17 years old (during treatment)

neutrophils, focally located in the interfibrous spaces, single extravasated erythrocytes are present (Fig. 2).

Thus, the histological picture made it possible to assign dermatosis to the group of perivascular with lymphocytic infiltrate, and taking into account the areas of erythrocyte extravasation, morphological changes were more characteristic of UV. This gave reason to establish the *final clinical diagnosis:* urticarial vasculitis, normocomplementemic, a positive ANA test. *Associated diagnosis:* Secondary AH 1st degree. Raynaud's phenomenon. Chronic tonsillitis.

After stabilization of the patient's condition in 3 months and complete regression of the skin syndrome (Fig. 3), montelukast was discontinued. After this, 2 months later, with a preliminary gradual reduction in dosage, ketotifen was also discontinued.

## Discussion

UV is a rare form of leukocytoclastic vasculitis. It can be normocomplementemic or hypocomplementemic, and if it is not limited to the skin, but also has systemic manifestations, it is called hypocomplementemic urticarial vasculitis syndrome (HUVS) [2,4]. Patients often complain of rash or arthralgia several months before diagnosis. In our clinical case, the main complaint was an itchy rash that bothered the patient for three weeks before going to the hospital.

Urticaria that persists or recurs for more than 6 months is present in all patients. Angioneurotic edema is also common and present in approximately half of patients. Our patient had one episode of angioedema, which was resolved by dexamethasone administration. Constitutional symptoms such as fever, fatigue and malaise are quite rare, while arthralgia and arthritis are common [16]. From the perspective of the constitutional syndrome, in this patient it was manifested by an increase in temperature to subfebrile levels and signs of general fatigue.

Factors that provoke UV are various drugs, in particular, cimetidine, diltiazem, fluoxetine and nonsteroidal anti-inflammatory drugs, as well as infectious diseases: streptococcal infection, tuberculosis, hepatitis A, B and C, mononucleosis, mycoplasma pneumonia, flu, trichomoniasis, histoplasmosis, Lyme disease, and COVID-2019 [6]. In our opinion, the latter probably provoked the development of UV in our patient.

**Pathogenesis.** UV is now considered an immune complex-mediated disease and, when reacting to a known antigen such as a drug, can be classified as a type III hypersensitivity reaction [5,9]. The pathophysiology of urticarial vasculitis is summarized in Figure 4.

The hyperactive adaptive immune response determines the production of antibodies against several exogenous and/or endogenous antigens, which leads to activation of the complement cascade through the classical pathway and production of C3a, C5a and C5b-9. The presence of perivascular deposits of complement immunoglobulins and/or fibrinogen and circulating immune complexes confirms this theory [11].

It is important that autoantibodies against C1q play a key role in the development of hypocomplementemic UV. In normocomplementemic UV (in the minority of cases of hypocomplementemic UV without autoantibodies against C1q), antibodies are produced against trigger factors such as drugs, bacteria, or viruses. Afterwards, the classic pathway of complement is activated, which in its own way means the development of anaphylatoxins C3a and C5a, which are responsible for the activation of mast cells and the production of neutrophils and eosinophils. Activat-

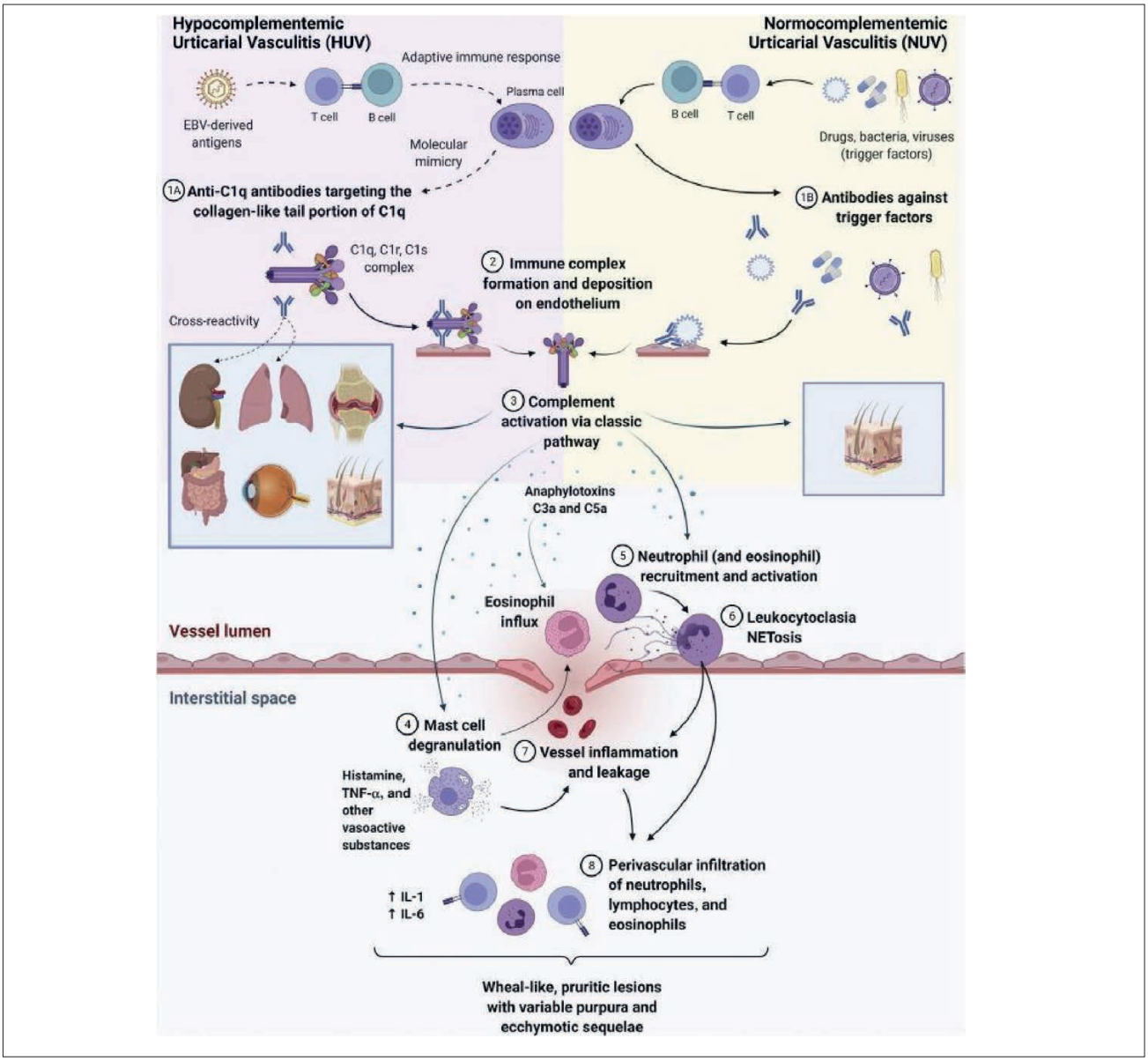


***Fig. 4.*** Modern understanding of the pathophysiology of hypocomplementemic and normocomplementemic UV [11]

ed NET-neutrophils mediate the destruction of the vessel wall, leading to the histological picture of leukocytoclasia and inflammation of vessels. Vasoactive molecules (for example, histamine) and TNF-α, increase the penetration of blood vessels and absorb more eosinophils. Perivascular infiltration of neutrophils, lymphocytes and eosinophils is eliminated and results in a clinical picture of HF with skin lesions, variable purpura and ecchymosis lesions [11].

One of the by-products of classical pathway activation is C5a, which can enhance the expression of adhesion molecules on the endothelium and increase vascular permeability. Anaphylaxin C5a is a specific chemoattractant for neutrophils and monocytes/macrophages, and it can cause mast cell degranulation, leading to the release of histamine and pro-inflammatory molecules. This may explain the presence of angioedema and true urticaria-like lesions (erythematous blisters lasting <24 hours) in approximately half of patients [11].

**Terminology.** UV is characterized by various cutaneous, systemic and serological features, which has led to confusion in the name of the disease [4]. UV appears to be a collection of diseases ranging from urticaria with minimal vasculitis to life- or organ-threatening systemic vasculitis [14]. Low complement levels are features associated with more severe course of the disease and systemic involvement. In comparison, patients with normal complement levels are more likely to

have a mild form of the disease (sometimes referred to as normocomplementemic urticarial vasculitis) [14]. Urticarial vasculitis is sometimes discussed as a clinical feature that is part of another diagnosis, and sometimes as a primary diagnosis or syndrome. Based on the levels of complement and the presence and/or absence of specific systemic signs, the terms that appear with UV as a separate diagnostic entity are HUVS, normocomplementemic urticarial vasculitis, hypocomplementemic urticarial vasculitis [12,13].

Hypocomplementemic urticarial vasculitis syndrome has been recognized as a specific autoimmune disorder characterized by six or more months of urticaria with hypocomplementemia in the presence of various systemic manifestations [4,8]. Clinical signs include: arthritis or arthralgia, glomerulonephritis, uveitis or episcleritis, periodic abdominal pain. HUVS can occur independently or be associated with other diseases [15].

Normocomplementemic UV is a hypersensitivity vasculitis of often unknown etiology, a benign self-limiting process with a normal level of complement components of an acute or chronic course [12]. This is exactly the option that was established for the patient whose clinical case is being considered.

Hypocomplementemic UV is a term used to describe patients with UV and hypocomplementemia who do not meet the diagnostic criteria for HUVS. In general, patients with hypocomplementemic UV have skin diseases and few or no systemic manifestations [14].

**Differential diagnosis.** UV shares many clinical features with autoinflammatory diseases, including urticaria, arthralgia, and systemic involvement. Since IL-1 plays a key role in autoinflammatory diseases, its pathogenetic contribution has also been suggested for UV. There may be high levels of IL-1Ra and IL-6 in patients with UV with a sharp decrease after treatment with canakinumab versus IL-1β mAb. Not surprisingly, a decrease in IL-6 levels was observed after administration of canakinumab [8].

The uncertainty of the pathogenesis of the disease does not facilitate differential diagnosis with other conditions, especially SLE and cryoglobulinemia. Distinguishing urticarial vasculitis from urticaria is usually not difficult because the skin lesions last more than 24 hours (usually 2–3 days), they are sometimes painful or «burning» and may have residual bruising or hyperpigmentation of the skin [1,5,13]. But in our clinical case, the rash periodically disappeared and reappeared, leading to an incorrect and prolonged initial diagnosis.

Skin biopsy usually reveals leukocytoclastic small-vessel vasculitis involving postcapillary venules. However, nonspecific findings such as lymphocyte and eosinophil infiltrates appear to be relatively common in biopsies of «old» lesions. Multiple biopsies, predominantly of the blister, less than 12 hours after the rash are often needed to make a diagnosis of leukocytoclastic vasculitis [10]. In our clinical case, the diagnosis was established during the first biopsy.

**Histology.** Histological findings in UV include the following [4]: damage and swelling of endothelial cells, usually postcapillary venules, extravasation of erythrocytes, fragmentation of leukocytes with nuclear debris (leukocytoclasia), fibrin deposition in and around vessels, perivascular infiltrate consisting mainly of neutrophils (Fig. 5) [4].

There is a continuum in the amount and type of inflammation of blood vessels observed histologically in UV, ranging from a rare perivascular infiltrate without leukocytoclasia to a dense infiltrate

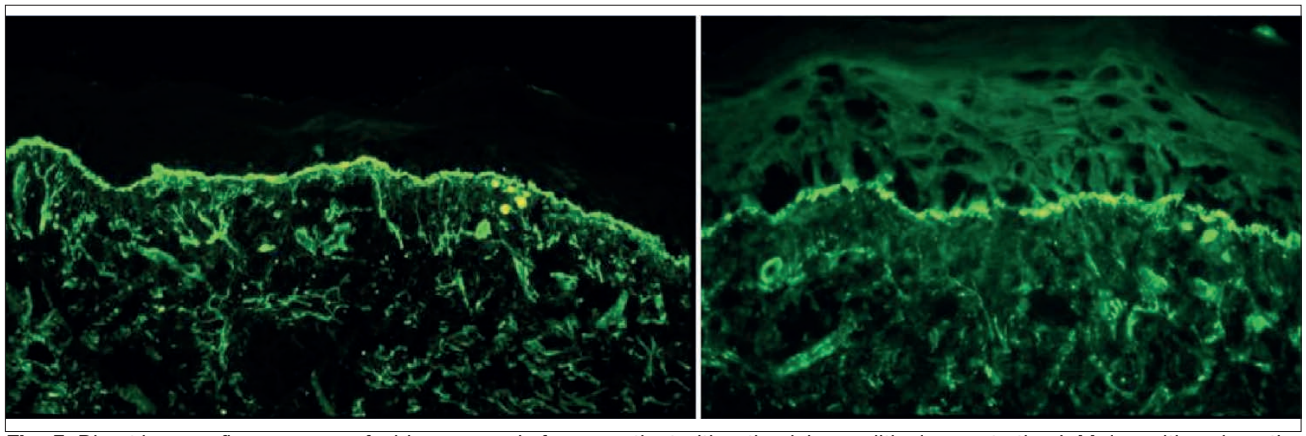

***Fig. 5.*** Direct immunofluorescence of a biopsy sample from a patient with urticarial vasculitis demonstrating IgM deposition along the dermolepidermal junction and involvement of dermal blood vessel walls

with pronounced leukocytoclasia and fibrin deposition in the most severe forms. Traditionally, these more serious signs with neutrophilic infiltrate, are observed in patients with hypocomplementemic UV syndrome [3,4]. According to the results of the punch biopsy in our clinical case, when examining the dermis, a weakly expressed perivascular infiltration with lymphocytes was observed, in the lumen of the vessels — a parietal arrangement of segmented neutrophils, which were focally located in the inner fibrous spaces and also the presence of single extravasated erythrocytes. These changes related to the histological picture of the UV.

Direct immunofluorescence detects immunoglobulin, complement, or fibrin deposits around blood vessels in most patients with UV. Deposits can also be present in the basement membrane zone of the dermoepidermal junction. Active urticarial lesions give a positive result for the deposition of immunoglobulin and complement in approximately 80% of cases. These findings are not specific for UV and are also frequently observed in patients with systemic lupus erythematosus. Therefore, identification of immunoglobulin and complement deposits in the basement membrane area should prompt consideration of both diagnoses [4].

**Treatment.** Taking into account the rarity of the disease and the wide range of manifestations, there are currently no uniform recommendations for treatment. Recent reviews have shed some light on treatment options and their effectiveness. We believe that applying this knowledge to the treatment of each patient will help individualize treatment.

The different treatment options and their effectiveness are summarized in a recent systematic review of 789 patients with urticarial vasculitis by Kohlkir et al. Corticosteroids are the most widely used method of treatment, which leads to remission of skin lesions in more than 80%. Immunosuppressive and immunomodulating factors were used as steroid-sparing drugs. In cases limited to the skin, hydroxychloroquine, dapsone, colchicine is used with satisfactory response; in patients with systemic disease, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, tocilizumab and anti-IL factors, in particular rituximab, are used [6,8].

In our clinical case, regression of the rash was achieved using a combination of first-generation antihistamine and antileukotriene drugs.

## Conclusions

The diagnostic dilemma: «urticarial vasculitis or chronic urticaria» is solved by performing a skin biopsy, which is currently the gold standard of diagnosis. Timely diagnosis helps to avoid false diagnoses and, as a result, incorrect treatment of UV. The description of this clinical case reveals the complexities of the diagnosis of UV and is a contribution to the disclosure of this globally complex problem. Further research will improve the diagnosis and treatment of UV.

*The authors declare no conflict of interest.*

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