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Лекарственно-индуцированные крапивница и ангиоотёк

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АННОТАЦИЯ

Крапивница и ангиоотёк относятся к наиболее распространённым проявлениям лекарственной гиперчувствительности и вызываются лекарственными средствами, различающимися по химической природе и механизмам действия. Основой патогенеза лекарственно-индуцированных крапивницы и ангиоотёка могут быть как иммунологические, так и неиммунологические реакции. Иммунологическая (аллергическая) крапивница и сочетающийся с нею ангиоотёк чаще всего развиваются в результате IgE-опосредованных реакций. Неиммунологическая гиперчувствительность обусловлена прямым действием лекарства-агониста на клетки-мишени с последующим высвобождением широкого спектра медиаторов и цитокинов воспаления или влиянием лекарственных средств на метаболизм ряда биологически активных веществ, стимулирующих клетки воспаления. Изолированный ангиоотёк (не сопровождающийся крапивницей) может быть признаком лекарственной аллергии, но чаще обусловлен различными неиммунологическими реакциями, тем или иным путём активирующими мастоциты и базофилы. Другой распространённый вариант лекарственного изолированного ангиоотёка не связан с дегрануляцией клеток-мишеней, а развивается по иным механизмам, приводящим к избыточному накоплению брадикинина. Наконец, некоторые лекарства могут усугублять патологию системы комплемента у больных с наследственным или приобретённым ангиоотёком.

В представленной лекции с современных позиций рассматриваются этиология, патогенез, клиническая картина, диагностика, принципы терапии и профилактика различных вариантов лекарственно-индуцированных крапивниц и ангиоотёков.

Ключевые слова: лекарственная гиперчувствительность; неиммунологическая гиперчувствительность; аллергическая крапивница; гистаминовый ангиоотёк; брадикининовый ангиоотёк.

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Drug-induced urticaria and angioedema

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ABSTRACT

Urticaria and angioedema are the most common manifestations of drug hypersensitivity and are caused by drugs that differ in chemical nature and mechanisms of action. The pathogenesis of drug-induced urticaria and angioedema can be based on immunological and non-immunological reactions. Immunological (allergic) urticaria and associated angioedema most often develop due to immunoglobulin E-mediated reactions. Non-immunological hypersensitivity is caused by the direct action of an agonist drug on target cells, followed by the release of a wide range of inflammatory mediators and cytokines, or the effect of drugs on the metabolism of several biologically active substances that stimulate inflammatory cells. Isolated angioedema (not accompanied by urticaria) may be a sign of drug allergy but is more often due to heterogeneous non-immunological reactions that activate mastocytes and basophils in various ways. Another common variant of drug-induced isolated angioedema is not associated with target cell degranulation but develops according to different mechanisms, leading to excessive bradykinin accumulation. Finally, some drugs may exacerbate the pathology of the complement system in patients with hereditary or acquired angioedema.

Here, the etiology, pathogenesis, clinical picture, diagnosis, principles of therapy, and prevention of heterogeneous variants of drug-induced urticaria and angioedema are considered from modern positions.

Keywords: drug hypersensitivity; non-immunological hypersensitivity; allergic urticaria; histamine angioedema; bradykinin angioedema.

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List of abbreviations

AE — angioedema
ACE — angiotensin converting enzyme
ASA — acetylsalicylic acid
ARB — angiotensin-II receptor blocker
GCS — glucocorticosteroids
ACEI — angiotensin converting enzyme inhibitors
ICCA — iodine-containing contrast agent
DH — drug hypersensitivity
HAE — hereditary angioedema
NSAIDs — nonsteroidal anti-inflammatory drugs
AAE — acquired angioedema
DPT — drug provocation test
COX-1 — cyclooxygenase 1
C1, C3a, C5a — complement components

INTRODUCTION

The most common adverse drug reactions involving the skin are urticaria and angioedema (AE) [1, 2], the occurrence of which is linked to the provoking action of a wide range of drugs. Despite the clinical similarity of different pathogenetic variants of urticaria and AE, the mechanisms of these reactions' development are heterogeneous. The heterogeneity of drug-induced urticaria and AE necessitates distinct approaches to diagnosis and treatment.

Urticaria is a group of diseases characterized by the development of itchy blisters and/or AE [3–5]. Histologically, with blistering rashes, edema of the upper and middle layers of the dermis and dilatation of postcapillary venules and lymphatic vessels are described. A mixed perivascular infiltrate of neutrophils or eosinophils, macrophages, and T-cells is found in the affected skin, while the vascular wall is unaffected.

Angioedema is manifested by edema of the skin, subcutaneous tissue, and mucous membranes of various organs and systems (respiratory, digestive, urinary, etc.). Moreover, AE can occur alone or in conjunction with urticaria (wheals) [3, 6, 7].

According to modern definitions, **drug hypersensitivity** (DH) **refers to reactions caused by a drug's unintentional and adverse stimulation of immune or inflammatory cells** [2]. To put it another way, DH is a phenomenon that includes both drug-induced immunological responses (drug allergy) and non-immunological inflammatory reactions (outdated synonym is "pseudo-allergy"). Allergies are caused by processes initiated by specific antibodies or hyperactivation of the immune system's T-cell link. Non-immunological or non-allergic hypersensitivity results from an agonist's direct action on target cells, followed by the release of inflammatory mediators and cytokines, or from the effect of drugs on the metabolism of a number of bioactive substances that stimulate inflammatory cells. P. Gell and R. Coombs, who identified four types of reactions, developed the most commonly used allergy classification in clinical practice back in 1968. The first three (I, II, III) types of allergic reactions are humoral and mediated by antibodies, while the fourth is due to delayed-type hypersensitivity. According to this theory, urticaria and AE are caused by a type I immune response (IgE-dependent) [1–3]. Another classification distinguishes two DH phenotypes: immediate (the response manifests within 1–6 hours of drug exposure) and delayed (symptoms manifest 6 hours or more after drug administration to a sensitized organism). Simultaneously, the immediate phenotype, which includes urticaria and AE, can develop via immunological and non-immunological mechanisms [8].

It is important to note that urticarial rashes and AE can be symptoms of other clinical forms of DH, such as anaphylaxis, serum sickness/serum sickness-like reaction, and vasculitis, which can manifest as isolated skin lesions and systemic involvement, with skin involvement being one component of multiorgan vascular inflammation. In addition, a number of drugs can cause urticarial rash and AE in mastocytosis and mast cell activation syndromes [9].

Table 1 shows the clinical forms, pathogenetic mechanisms, and main causes of urticaria (urticarial rashes) and AE associated with drug action.

Isolated AE (without blisters) may be a sign of drug allergy, but it is more commonly caused by non-immunological hypersensitivity reactions that lead to mast cell activation in some way. Another common type of isolated AE caused by ACE inhibitors (ACEI) is not associated with degranulation of mast cells and basophils but develops through different mechanisms. Finally, in patients with hereditary (HAE) or acquired (AAE) angioedema, some drugs can "reveal" the complement system pathology [6, 7].

In this lecture, drug-induced urticaria and AE will be treated as separate diseases.

PATHOGENESIS AND DRUG CAUSES IN DIFFERENT VARIANTS OF URTICARIA AND ANGIOEDEMA

Allergic urticaria and associated AE are classic examples of type I immunological reactions that are elicited by foreign proteins (complete antigens with molecular weights >1000 daltons) or hapten–endogenous protein complexes. Low molecular weight drugs (haptens) can covalently bind to "host" proteins (plasma, extracellular,

Table 1. Clinical forms, pathogenesis, and underlying drug triggers of urticaria and/or angioedema (adapted from [1–13])

Clinical forms	Pathogenesis	Drugs
Urticaria and/or angioedema	Immunological hypersensitivity: predominantly IgE-mediated, in rare cases IgG-dependent reactions	Complete antigens: recombinant proteins (cetuximab, rituximab, etc.); blood products, serums, vaccines, enzymes, protamine, insulin and other hormones; herbal treatments, latex, bee venom in apitherapy, etc. Haptens: β-lactams and other antibiotics, sulfonamides, acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), pyrazolones, iodine-containing radiopaque agents (ICCAs), etc. Drugs with functional multivalence: succinylcholine and other muscle relaxants, carboxymethyl cellulose
	Non-immunological hypersensitivity: • direct activation of mast cells/basophils	Narcotic analgesics (opiates), ICCAs, fluorescein dyes for angiography, sulfites, dextrans, fluoroquinolones, vancomycin, some chemotherapy drugs, etc.
	• complement activation via alternative pathway and formation of anaphylatoxins C3a and C5a	Human plasma, blood products, immunoglobulins, dextrans, ICCAs
	• inhibition of cyclooxygenase type 1 (COX-1)	ASA, NSAIDs, pyrazolones
Isolated angioedema	Non-immunological hypersensitivity: mechanisms are the same as in urticaria	Same causes as for non-immunological urticaria
	Excessive accumulation of bradykinin due to decrease in its degradation	Angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, renin inhibitors, dipeptidyl peptidase-4 inhibitors, streptokinase, alteplase
	Unknown	Amlodipine, nifedipine, diltiazem, verapamil
Drug-induced urticaria and/or angioedema as manifestation of other forms of drug hypersensitivity		
Anaphylaxis	Immunological IgE-mediated or (less frequently) IgG-mediated reactions	Causes are the same as for urticaria/angioedema
	Non-immunological hypersensitivity with various mechanisms (direct activation of mast cells/basophils; complement activation via alternative pathway; inhibition of COX-1)	Causes are the same as for urticaria/angioedema
Serum sickness	Immune complex IgG-mediated reactions	Heterologous sera and immunoglobulins, recombinant immunopreparations, organ preparations, streptokinase, vaccines, apitherapy bee venom and other heterologous proteins

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Table 1. Ending

Clinical forms	Pathogenesis	Drugs
Serum sickness-like reaction	Immune complex IgG-mediated reactions	Human plasma and immunoglobulins. Haptens: β-lactams and other antibiotics, furazolidone, metronidazole, NSAIDs, drotaverine, rivaroxaban, bupropion, mirabegron, iodine drugs, gold drugs, etc.
Vasculitis	Immune complex IgG-mediated reactions	β-lactam antibiotics, macrolides, sulfonamides, including diuretics, isoniazid, rifampicin, allopurinol, NSAIDs, propylthiouracil, penicillamine, gold drugs, phenytoin, atorvastatin, metformin, beta-blockers, warfarin, etc.
	ANCA-associated reactions (anti-neutrophil cytoplasmic antibodies)	Propylthiouracil, thiamazole, tumor necrosis factor alpha (TNF-α) inhibitors
Trigger action of drugs in chronic diseases of various nature involving the skin		
Chronic spontaneous urticaria	Pathogenesis is unknown, possibly autoimmune. One of drug hypersensitivity mechanisms is non-immunological inhibition of COX-1	ASA, NSAIDs, pyrazolones
Mastocytosis Mast cell activation syndromes	Proliferation of mast cells and their infiltration of the skin and other organs Primary syndrome–hyperactivation is associated with clonal mutation of mast cells Idiopathic syndrome–pathogenesis unknown Secondary syndrome is associated with IgE-dependent allergy (atopy)	Morphine, codeine, vancomycin, ASA, ketorolac and other NSAIDs, ICCAs, muscle relaxants
Hereditary angioedema	Genetically determined deficiency and/or decrease in C1 inhibitor functional activity or other mutations. Mechanism of adverse drug reaction (ADR)–additional increase in bradykinin levels	ACE inhibitors, estrogens
Acquired angioedema	Type I–excessive C1-inhibitor consumption (more common in lymphoproliferative diseases) Type II–formation of C1 inhibitor autoantibodies (registered in autoimmune diseases). Mechanism of ADR is additional increase in bradykinin levels	ACE inhibitors

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or intracellular), resulting in drug antigen formation (hapten-peptide complex). During the sensitization period, IgE specific to the drug determinant is produced, and antibodies bind to high-affinity Fc-receptors of mast cells and basophils. When a drug with similar determinants is administered again, a cascade of cellular activation occurs, resulting in the release of pre-existing mediators (histamine, tryptase, etc.) and the synthesis of new ones (leukotrienes, prostaglandins, kinins, cytokines, etc.). Within minutes, histamine causes blistering, itching, flushing, and edema, while cytokine-driven inflammatory erythematous response develops after several hours (the time required for protein synthesis and recruitment of other immune cells).

The causes of allergic urticaria/AE vary (see Table 1). Aside from well-known protein drugs and low molecular weight haptens, chemicals with so-called functional multivalence represent a small number of drugs. These include non-protein macromolecules with numerous repeating epitopes. Despite their small size, these drugs can cross-link antibodies and cause immediate reactions. Synthetic polymer carboxymethyl cellulose (stabilizing agent in injectable drugs for intramuscular injection) and quaternary ammonium compounds used as neuromuscular blockers in general anesthesia (succinylcholine, etc.) are two well-known examples [10].

In non-immunologic urticaria/AE, triggers of inflammatory cascade are fueled by direct degranulation of mast cells/basophils caused by drug stimulation of G protein-coupled membrane receptors or complement activation and formation of complement components such as anaphylatoxins C3a and C5a, which cause the release of mediators from mastocytes and basophils [8]. In patients with acute urticaria and AE who have a cross-reactive response to drugs with different chemical structures, inhibition of type 1 cyclooxygenase (COX-1) causes hypersensitivity to acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), and pyrazolones. At the same time, potent COX-1 inhibitors cause symptoms in all patients, while less potent inhibitors, such as paracetamol, cause acute urticaria and/or AE in only 25% of patients, primarily at high doses (⩾1000 mg). These patients generally tolerate selective COX-2 inhibitors (coxibs) well. It is also possible that NSAIDs have a direct effect on the membranes of basophils and mast cells, causing the release of various mediators [7, 8, 11].

Isolated AE develops primarily through non-immunological pathways and is classified into two types: AE caused by excessive bradykinin accumulation and mediated by mast cell/basophil mediators ("histamine" AE). The pathogenesis and triggers of AE caused by direct mastocyte/basophil degranulation are similar to those seen in non-immunologic urticaria. Another common mechanism linking non-allergic urticaria and isolated AE is COX-1 inhibition by non-selective NSAIDs and ASA.

The occurrence of AE in the skin and small intestine during treatment with calcium channel blockers of various classes, such as amlodipine, nifedipine, diltiazem, and verapamil, has been described; however, the pathogenesis of this AE variant is unknown. Furthermore, isolated AE can be caused by sirolimus, everolimus, amiodarone, metoprolol, risperidone, paroxetine, etanercept, and other biological agents, despite the absence of convincing evidence of IgE-dependent allergy to those drugs [7, 8, 10, 11].

Bradykinin AE is more commonly caused by ACE inhibitors, but it can also be caused by angiotensin II receptor blockers (losartan, valsartan, etc.), hypoglycemic drugs (sitagliptin, saxagliptin, linagliptin), and selective renin inhibitors (aliskiren). Bradykinin accumulates in AE caused by ACE inhibitors and other drugs because its degradation is inhibited. ACE inhibitors are the most common cause of AE in critically ill patients (30%–50% of the time). AE is reported in 0.1%–0.7% of ACE inhibitor patients. The risk of developing AE is independent of whether the drug belongs to the ACE inhibitor group or the dose [7, 10, 12, 13].

CLINICAL MANIFESTATIONS

IgE-dependent urticaria/AE develops 1–2 weeks after the start of drug use in previously unsensitized individuals. Non-immunological reactions, as well as the introduction of an allergenic drug into an already sensitized organism, cause mast cell and basophil degranulation to occur very quickly — within 15–20 minutes, and sometimes within 1–2 hours. Blisters of various sizes can form and merge into vast fields with "geographical" contours. At the same time, the blisters are short-lived and usually vanish without a trace within 24 hours, but with continued drug exposure, more and more rashes appear, also vanishing over time without transformation into papules, hemorrhages, or leaving any pigmentation (Fig. 1). Itching is always present with urticarial rash. When urticaria is combined with AE, there may be swelling of the tongue, lips, or face, as well as other parts of the body and mucous membranes. The transformation of urticaria and AE into a systemic reaction, anaphylaxis, is possible with massive degranulation of mast cells and involvement of blood basophils.

Isolated histamine AE occurs within a few minutes, less frequently a few hours (usually within six hours), accompanied by mild or moderate itching, but can occur without itching because the edema is localized in deep dermal and hypodermal layers, where there are no irritant receptors. The skin over the edema is typically slightly hyperemic, occasionally pale, and warm to the touch. The face, hands, feet, and external genital organs are the most common sites for AE associated with mast cell degranulation; various mucous membranes are frequently involved. The regression, like urticaria, lasts about 24 hours, but if the edema is severe, it can take 36–48 hours. This AE variant responds well to glucocorticosteroids (GCS) and antihistamines (AGS). Under the influence of these drugs, the edema may disappear faster [3–5, 12, 13]. If histamine AE has a recurring clinical

course (e.g., with intermittent use of NSAIDs), then edema localization may change during different episodes, and previously unseen urticarial rashes may appear.

Bradykinin AE is distinguished from histamine AE by more pronounced involvement of the face, lips, tongue, pharynx, and larynx, as well as a higher risk of progression; it can pose a real threat to life due to asphyxia. There is no urticaria or itching. The edema is pale and dense (Fig. 2), slowly resolving (from 24 to 72 hours or more), and not responding to systemic GCS and antihistamine therapy. Because ACE inhibitors can cause intestinal edema, sudden onset of abdominal pain, diarrhea, nausea, and occasionally vomiting in the elderly may be associated with their use. It should be noted that AE symptoms caused by ACE inhibitors do not appear immediately after taking the drug, as they do with exposure to drug allergens or drugs that cause direct degranulation of mast cells/basophils. Symptoms may appear several weeks/months/years beginning ACE inhibitors and recur with varying frequency, ranging from several times per year to weekly episodes [3, 7, 10, 12, 13].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The combination of urticaria and AE is one of the most common manifestations of DH, and in most cases, the vivid clinical presentation combined with anamnesis does not make the disease difficult to diagnose. When reviewing the anamnesis, consideration is given to whether the symptoms were acute or recurring, as well as the type of drug suspected of causing the edema (complete antigen, hapten, or non-immunological trigger). A thorough family history is taken, which is especially important when making a differential diagnosis with HAE.

During the physical examination, the doctor looks for signs of urticaria and edema. In the case of face or tongue AE, a careful assessment of airway patency is required to rule out life-threatening edema before deciding on emergency treatment tactics. Upper respiratory tract involvement is indicated by stridor, voice change and hoarseness, as well as difficulty swallowing. If a physical examination reveals swelling of the tongue, particularly its root and soft palate, there is a high-risk of developing laryngeal and airway AE, which may necessitate immediate intubation or cricotomy. In contrast, if the edema is limited to the lips, intubation is usually unnecessary [3, 7, 10, 12, 13].

In the case of abdominal pain in an ACE inhibitor patient, it is necessary to rule out visceral edema: for this, non-invasive imaging — ultrasound and computed tomography — are used, which in most cases aid in diagnosis by revealing dilated intestinal loops, thickening of the mucosal folds, mesenteric edema, and free fluid in the abdominal cavity. Endoscopic procedures are used less frequently.

Blood pressure, heart rate, and lung auscultation are all required. The combination of physical examination findings

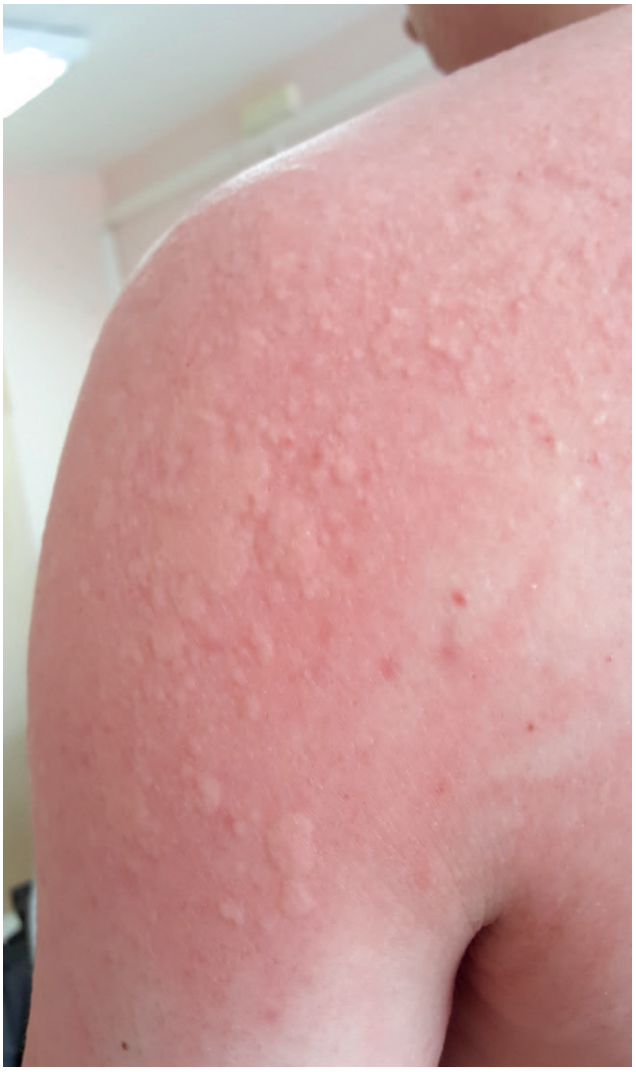

Fig. 1. Urticaria caused by Tempalgin. Multiple wheals of various sizes on erythematous background. (Photo from authors' archive).

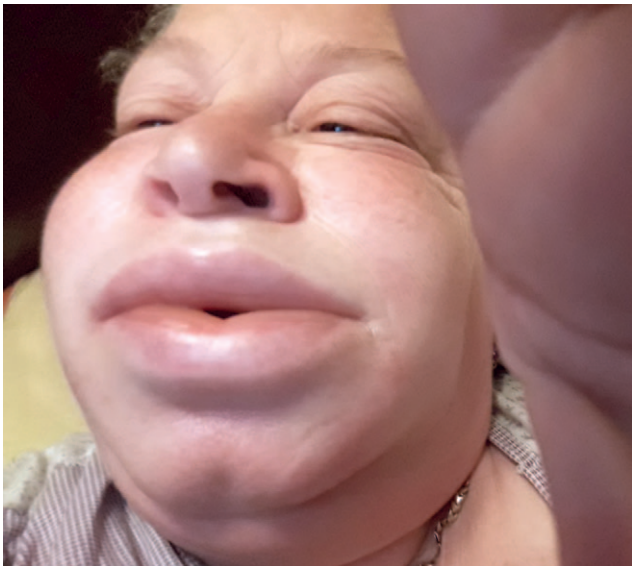

Fig. 2. Bradykinin angioedema caused by ACE inhibitor. (Photo from authors' archive).

with sharp decrease in blood pressure, bronchospasm, vomiting, abdominal pain, urge to defecate, urge to urinate, and bloody discharge from the vagina in patients with acute urticaria and AE is a sign of anaphylaxis [3, 4].

Urticaria/AE caused by drug administration may be accompanied by general symptoms such as low-grade fever, headache, and myalgia as a result of inflammatory cytokine exposure. Because urticaria / AE may be signs of a systemic process due to DH (serum sickness/serum sickness-like reaction, systemic drug-induced vasculitis), it is critical not to overlook lymphadenopathy, splenomegaly, arthritis, or involvement of other organs in patients with a torpid course of the disease. Body temperature must be measured daily and its fluctuations monitored throughout the day.

Bloodwork may show leukocytosis with moderate neutrophilia, sometimes moderate eosinophilia, indicating the possible involvement of IgE-mediated allergic reactions in urticaria and drug-induced AE. General urinalysis, biochemical blood tests, and other examinations are performed if clinically indicated to rule out the systemic nature of DH process and other causes of urticaria and AE.

Differential diagnosis of drug-induced urticaria

If fever and other general symptoms persist despite discontinuation of the suspected drug, and signs such as lymphadenopathy, arthritis, maculopapular, hemorrhagic, or bullous rashes appear, or hyperpigmentation or other unusual manifestations are observed, differential diagnosis with a number of diseases, both drug-induced and those not associated with DH, is required [10]:

- urticaria as a component of serum sickness/serum sickness-like reaction and drug-induced vasculitis;
- maculopapular drug exanthema;
- erythema multiforme;
- hypocomplementemic urticarial vasculitis and other immunocomplex lesions of small skin vessels;
- urticaria as a symptom of systemic autoimmune or autoinflammatory diseases.

Table 2 shows the main clinical and diagnostic signs of various manifestations of DH involving the skin, as well as some autoimmune or autoinflammatory diseases that can be classified as urticaria. Significant differences should be noted between acute drug urticaria and other isolated skin lesions in DH–maculopapular exanthema and erythema multiforme: urticarial rashes vanish without a trace, without peeling or pigmentation, and never evolve into target-shaped papules or bullous elements.

Skin vasculitis is typically characterized by palpable purpura–slightly elevated hemorrhagic rashes (bright red or burgundy colored). Urticarial vasculitis is another variant that manifests as persistent blisters lasting more than 24 hours with residual hyperpigmentation. Histologically, drug-induced allergic isolated skin vasculitis is most often characterized as a leukocytoclastic variant with small vessel involvement [10]. The only way to accurately diagnose vasculitis is through biopsy. Fibrin and inflammatory infiltrates in the vessel wall, as well as leukocytoclasia (neutrophil fragmentation), are the main pathological criteria for leukocytoclastic vasculitis.

Drug-induced leukocytoclastic vasculitis of the skin is a benign disease that can be treated with early detection and withdrawal of the offending drug. Drug-induced vasculitis of the skin, on the other hand, is not always isolated. When vessels are damaged, other organs, in addition to the skin, are frequently involved, as is typical for serum sickness and sometimes for serum sickness-like reactions, as well as systemic drug-induced vasculitis (see Tables 1 and 2).

Differential diagnosis with drug-induced urticaria also includes vasculitis of unknown origin (probably autoimmune), in which drugs, along with other factors, serve as triggers, and clinical presentation of vascular inflammation may manifest not as classic bright purpura but as rashes similar to persistent blisters, which can lead to diagnostic errors. Leukocytoclastic variants with immunocomplex-related damage of small vessels in the skin include hypocomplementemic urticarial vasculitis, IgA-mediated vasculitis, and cryoglobulinemic vasculitis.

It is widely acknowledged that there is currently a high level of drug consumption due to both medical prescriptions and self-medication. If symptoms occur in the context of pharmacotherapy, they may be signs of adverse drug reactions, among other things. Doctors often make "fashionable" diagnosis of drug allergy, ignoring the possibility of a simple coincidence of drug intake and manifestation of another disease that mimics DH skin manifestations. This is true for urticaria and serum sickness-like reactions caused by rarer diseases. Consider systemic juvenile idiopathic arthritis and adult Still's disease as examples (see Table 2): these forms are distinguished by a chronic relapsing course and "transiency" of rashes. In contrast to DH, careful collection of pharmacological anamnesis with chronological comparisons reveals that exacerbation and subsidence of symptoms are not associated with drug appointment and withdrawal.

We must not overlook acute rheumatic fever, which can present with rashes in the form of annular erythema, which is mistaken for urticaria in some cases. Since patients usually present with migratory arthritis and significant joint swelling, a serum sickness-like reaction is often suspected. However, a recent history of streptococcal infection (tonsillitis) and increased levels of specific serological markers allow for accurate diagnosis. However, if tonsillitis was treated with antibiotics, then the possibility of developing serum sickness-like reaction should be considered.

Various rare autoinflammatory syndromes with rashes (urticarial or maculopapular), fever, and arthritis must be ruled out in children and young adults [4, 5]. However, unlike DH, drug withdrawal does not lead to recovery. In the case of chronic relapsing diseases, a more thorough examination is required.

We should also consider the possibility of drug-induced urticaria being confused with a condition known as "contact

Table 2. Differential diagnosis of urticaria. Main clinical manifestations in various drug hypersensitivity reactions and some autoimmune/autoinflammatory diseases (adapted from [1, 3–5, 10] with additions)

Clinical form	Chronology of symptoms after repeated drug exposure	Main clinical manifestations
Urticaria	From minutes to 6 hours Rapid evolution and disappearance of individual elements (<24 h)	Pale pink (sometimes bright) itchy blisters surrounded by erythematous border. Localization: torso, face, or entire skin. Often mucosal involvement (angioedema)
Maculopapular exanthema	From 6 to 72 hours Resolution of rashes in 7–10 days	Spots, papules, sometimes merging. With involution, pigmentation and peeling are not uncommon. Localization: trunk, limbs or diffuse rash
Erythema multiforme	From 24 to 48 hours Resolution within 1–3 weeks	Erythematous papules round in shape with dark target-like center. There may be vesicle or blister in the lesion center. Localization: more frequently limbs, including palms, torso. Pigmentation may occur with involution
Isolated skin vasculitis	From 6–12 hours to 3–5 days Resolution within 2 weeks	*Palpable purpura*–slightly raised hemorrhagic rashes or urticarial vasculitis –persistent blistering rashes that persist for more than 24 hours with residual hyperpigmentation
The main manifestations in systemic drug allergy syndromes		
Serum sickness (serum sickness-like reaction)	From 6–12 hours to 3–5 days Resolution for mild form within 2 weeks	Common eruption: *persistent urticaria* or *urticarial vasculitis*, or maculopapular rash, or palpable purpura. Fever, lymphadenopathy, arthralgia/arthritis, myalgia, weakness
Systemic drug vasculitis	Gradual development within 1–3 weeks from the start of drug administration Resolution for non-severe forms within 2–4 weeks	Palpable purpura, or petechial rash, or urticarial vasculitis Low-grade fever, weakness, arthralgia and myalgia Damage to the kidneys (glomerulonephritis), lungs (alveolar hemorrhages), and nervous system (neuropathy), with varying frequency and intensity
Maculopapular or urticarial exanthems associated with autoimmune/autoinflammatory diseases		
Juvenile idiopathic arthritis and adult-onset Still's disease	No obvious association with drug use	Rapidly disappearing salmon-pink maculopapular or *urticarial* rash that appears simultaneously with recurrent fever. The rash presents predominantly on the trunk and extremities, including palms and soles, sometimes affecting the face Arthralgia, myalgia, arthritis, periarthritis
Acute idiopathic cutaneous lupus erythematosus	No obvious association with drug use	Widespread morbilliform exanthema, predominantly on the outer surface of arms and hands. Onset of the disease or it's exacerbation under the influence of ultraviolet radiation are characteristic

urticaria–protein contact dermatitis." As the name implies, allergic protein contact dermatitis is induced by proteins, as opposed to the classical variant caused by low molecular weight substances–haptens. Clinically, it is distinguished by morphological elements typical of allergic contact dermatitis: edematous erythema, papules, vesicles, and, later in the disease's progression, lichenification, cracks, and peeling. In the case of relapses caused by unintentional provocation by a protein contact allergen, dermatitis symptoms appear quickly — within a few minutes, making it similar to urticaria. Protein contact dermatitis may begin with a picture of contact urticaria, i.e., blistering rashes at the site of protein exposure; however, at the onset of the disease, only prominent local edema and bright erythema are observed, accompanied by severe itching, and then, in the absence of allergen elimination, transformation into a local eczematous process occurs [14].

The mechanisms underlying protein contact dermatitis are unknown, but it is thought that IgE-dependent allergy, T-cell hypersensitivity, and/or delayed reactions mediated by IgE-bearing Langerhans cells are involved. 56%–68% of patients with protein contact dermatitis have a history of atopy. This type of contact dermatitis is more commonly seen as an occupational disease in people who come into contact with food proteins, latex, plants, animal proteins, and so on. At the same time, topical medications containing proteins from various sources can cause the disease. If a protein allergen enters the bloodstream in any way, it causes systemic dermatitis or generalized urticaria, as well as anaphylaxis in rare cases. At the same time, rashes may resemble papules rather than wheals, and the involution of rash elements is slower than in classical urticaria (Fig. 3).

Another issue in differential diagnosis is distinguishing between acute drug-induced urticaria and trigger action of drugs in chronic diseases of various types involving the skin (see Table 1). This primarily entails spontaneous chronic urticaria and AE with exacerbations induced by ASA and

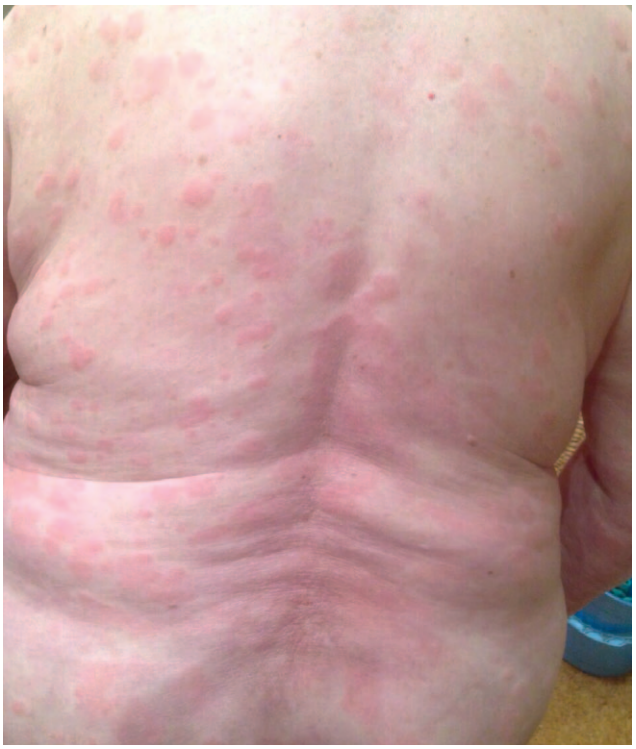

Fig. 3. Protein allergic contact systemic dermatitis caused by bee venom in medicine "Sofya Balm." Rubbing was done along the spine in the lower thoracic region and sacrum, which has the most pronounced confluent rashes are observed. The patient has history of contact urticaria when using "Apizartron" ointment, which also contains bee venom. (Photo from authors' archive).

NSAIDs. Over the last four decades, a number of studies based on sufficient clinical evidence have shown that ASA, NSAIDs, and less often pyrazolones can be a trigger factor in 10%–30% of patients with chronic urticaria and AE. For a long time, this disease was known as aspirin-induced chronic urticaria and AE, but it was discovered that it is characterized by broad cross-reactivity with non-selective NSAID inhibitors and COX-1, COX-2. As a result, NSAID-exacerbated cutaneous disease (nonsteroidal anti-inflammatory drug-exacerbated cutaneous disease) is now commonly used [11]. The severity of reaction to ASA and non-selective NSAIDs in this disease is dose-dependent; additionally, selective COX-2 inhibitors are well tolerated by the majority of patients. Non-immunological hypersensitivity to ASA and NSAIDs has been observed not only in patients with spontaneous chronic urticaria, but also in other types of urticaria, such as cholinergic urticaria. Patients with aspirin-induced spontaneous chronic urticaria experience rashes on a regular basis without any obvious triggers, but when ASA and NSAIDs are used, the disease worsens: the number of blisters and their size increase, and swelling of the tongue, lips, or face, as well as other parts of the body, may occur. Shortness of breath, wheezing, and chest tightness may appear in addition (for the first time in the patient's life). Anaphylactic shock occurs very rarely.

Urticaria and AE symptoms typically appear 30 minutes to 6 hours after taking NSAIDs, though both immediate (within 15 minutes) and delayed (more than 6 hours) reactions have been described. Skin rashes usually go away within a few hours, but they can last for several days. The severity of the exacerbation is determined by the drug dose. The more active the course of the disease, the more severe the exacerbation: during periods of remission or during treatment for chronic urticaria and AE, manifestations of DH are minor or absent.

In mastocytosis and all variants of mast cell activation syndrome (see Table 1), histamine liberator drugs are described as triggers for the appearance of urticarial rash and AE: most frequently morphine, codeine and other opiates, vancomycin, ASA, NSAIDs, iodine-containing contrast agents (ICCA), and muscle relaxants.

Mast cell pathology necessitates a multidisciplinary approach, including consultations with dermatologists, hematologists, and allergologists-immunologists. Diagnostic algorithms for such conditions have been developed, based on clinical signs evaluation, serum tryptase levels assessment, and exclusion of secondary mast cell hyperactivation syndrome (IgE-mediated allergy and other hypersensitivity conditions). One of the diagnostic criteria for mastocytosis and mast cell activation syndrome is a persistent increase in tryptase levels above 20 ng/ml (primary and idiopathic). In aggressive systemic mastocytosis, tryptase levels are typically elevated (greater than 200 ng/mL). In adult patients, skin biopsy is required to confirm the cutaneous form of mastocytosis, and sternal puncture and immunogenetic study to identify mast cell clonality are performed in cases of systemic mastocytosis symptoms and to verify primary mast cell activation syndrome [9].

Diagnosis and differential diagnosis of isolated angioedema

In isolated AE it is necessary first of all to determine its variant–histamine (i.e., associated with mast cell degranulation) or bradykinin AE. Bradykinin edema further requires its differentiation between ACEI-induced AE without complement deficiency or dysfunction, and HAE or AAE, i.e., forms caused by complement system pathology (see Table 1; Table 3).

When distinguishing between histamine and bradykinin AE, the focus is on a set of features that are more characteristic of either AE type. Urticarial rash elements are not associated with bradykinin AE. Isolated swelling of the earlobes is almost always found in the histamine AE variant. In contrast, abdominal pain associated with edema of the intestinal walls is most characteristic of HAE, but it can also be seen in ACEI-induced AE in patients without complement system deficiency; however, the pain is less severe in this case. In most cases, histamine AE progresses quickly, peaking after 30–60 minutes and accompanied by tingling or moderate itching. Histamine AE usually resolves within 12–24 hours and responds well to treatment with glucocorticoids (GCS) and antihistamines. Bradykin AE associated with ACEI develops more slowly, peaking in 6 hours on average but can

Table 3. Diagnostic differences between types of angioedema (adapted from [6, 7, 12])

Type of angioedema	Main trigger drugs	Family history of recurrent angioedema and/or abdominal pain/asphyxia	Association with urticaria	C1-inhibitor concentration	C1-inhibitor function	C4 concentration
Histamine	Antibiotics, NSAIDs, opiates, ICCAs, dextrans, muscle relaxants, etc.	-	Characteristic	Normal	Normal	Normal
AE-ACEI	ACEI	-	Non-characteristic	Normal	Normal	Normal
HAE type I	ACEI, estrogens (+)	++	Non-characteristic	Normal	Low	Low
HAE type II	ACEI, estrogens (+)	++	Non-characteristic	Normal or high	Low	Low
HAE with nC1inh	ACEI, estrogens (++)	++	Non-characteristic	Normal	Normal	Normal
AAE type I и II	ACEI, estrogens (+)	-	Non-characteristic	Low	Low	Low

Note: "+" — frequent or typical; "++" — very frequent or very typical; "-" — rare or unusual. AE — angioedema; AE-ACEI — angioedema caused by angiotensin converting enzyme inhibitors; ICCA, iodine-containing contrast agents; HAE, hereditary angioedema; nC1-inh, normal content of 1st complement component inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; AAE, acquired angioedema; C1 and C4, 1st and 4th complement components.

be delayed for up to 24 hours. Simultaneously, pronounced laryngeal edema can develop quite quickly, much earlier than in the soft tissue area. The resolution of bradykinin edema is slow (from 24 to 72 hours or more), and systemic GCS and antihistamines have no effect [6, 7, 12, 13].

In the case of bradykinin AEs, it is important to note that ACE inhibitors and other drugs can act as triggers for HAE and AAE, revealing C1-inhibitor deficiency or dysfunction. There is a basic increase in bradykinin levels with these AE variants, which increases to an even greater level when affected by a number of drugs. The most common provocateurs are ACE inhibitors, but other drugs may also cause isolated bradykinin AE in patients who do not have initial complement system abnormalities (see Table 1). The use of estrogen-containing drugs causes the onset or exacerbation of HAE in women with normal C1-inhibitor levels (former name — HAE type III).

Although it is well-known that mechanical injuries frequently cause AE attacks in patients with HAE type I-II, there are times when disease exacerbation after dental procedures is misdiagnosed as a manifestation of drug allergy to local anesthetics. When making a differential diagnosis of histamine and bradykinin AE, patients with HAE may develop marginal erythema, which are rose-red rashes that do not rise above the skin surface, without itching or peeling, and disappear within a few hours to two days. Such symptoms could be a separate manifestation of the disease or a precursor to AE [6]. Erythema marginalis is frequently confused with urticaria.

AAE attack may be triggered by ACE inhibitors and, less commonly, by estrogens. AAE type I is more common in lymphoproliferative diseases, when there is constant activation of the classical complement pathway with excessive consumption of C1 inhibitor and its subsequent depletion. AAE type II is associated with formation of autoantibodies to C1 inhibitor (noted in autoimmune diseases) [7].

To diagnose different types of AE, clinical signs, the patient's personal and family history, underlying diseases, and laboratory parameters such as C1 inhibitor levels and function, as well as C4 levels, are examined (see Table 3). Normal levels of C1 inhibitor and C4 are measured in patients with drug-induced AE as an independent disease, including variants caused by any ACE inhibitors and angiotensin receptor blockers. Isolated drug-induced AE can also be distinguished from idiopathic forms, such as histamine and bradykinin AE. Idiopathic AE is a diagnosis of exclusion; the possibility of any other (non-drug) triggers is investigated.

In addition, as the practice of many national and nondomestic clinics shows, in some cases incorrect diagnosis of drug-induced AE occurs in "coinciding circumstances," when a patient takes drugs to treat chronic or acute disease, and at the same time he has a pathology that includes tissue edema as one of its manifestations. Examples of such pathologies are:

- contact dermatitis (irritant and allergic);
- local infection (furuncle, phlegmon, acute cheilitis glandularis, hordeolum);

- erysipelas;
- superior vena cava syndrome;
- heart failure;
- nephrotic syndrome;
- hypothyroidism;
- other diseases accompanied by edema.

It should also be taken into consideration that AE in combination with high eosinophilia can be a sign of parasitic invasion, manifesting inflammatory tissue edema (for example, with trichinosis), a manifestation of hypereosinophilic syndrome, and Gleich's syndrome (episodic angioedema with eosinophilia, currently considered to be a variant of hypereosinophilic syndrome) [4, 5].

Specific diagnosis of drug hypersensitivity in patients with drug-induced urticaria and angioedema

Standard allergological methods are used for etiological diagnosis of drug-induced urticaria and AE: analysis of pharmacological and allergic anamnesis, skin tests and provocation tests, and laboratory diagnostic methods, which are positioned as preferred methods in comparison with in vivo tests from the standpoint of patient safety [3, 10, 15, 16].

In most cases, anamnesis data and elimination effect are sufficient: symptoms of urticaria and AE do not recur after offending drug withdrawal and exclusion of subsequent intake of cross-reactive drugs. The situation with ACE inhibitors is more complicated, since the effect of their elimination can be delayed due to the pathogenesis of this AE variant. For example, one of long-term studies showed that more than 80% of patients during the first month after discontinuation of ACE inhibitors experienced relapses of AE, and in some cases, symptoms reappeared for 6 months or more [17]. However, in a situation where episodes of edema recur for several weeks or months in the absence of drug administration, it is possible that the disease is either not associated with ACE inhibitors at all, or these drugs were triggers for manifestation of other forms of bradykinin AE.

A number of in vitro tests are currently being developed to diagnose type I allergic reactions to drugs and non-immunological hypersensitivity. Specific IgE to certain drugs and their metabolites (primarily penicillins) are determined in cases of immediate allergic DH, and various modifications of the basophil activation test are used for IgE-mediated allergy and non-immunological hypersensitivity. These tests are available in some highly specialized clinics and laboratories, but their sensitivity and specificity have received mixed reviews from experts, so they are not yet recommended for widespread use. The detection of specific IgE to native drug molecules has a low sensitivity and, in most cases, is not informative (a negative result does not rule out allergy) [3, 8, 10, 11, 15].

In real-life clinical practice, if the cause of urticaria and AE has not been reliably established (which happens when the disease develops against the background of polypharmacy), and these drugs are necessary for continuous use or may be required in the future, and they cannot be replaced by drugs of different structure or mechanism of action, then after recovery the patient is recommended specific drug skin tests and / or provocation tests. It is preferable to carry out testing with drugs 4–6 weeks after an acute reaction, since at this time the highest sensitivity to tests is observed, but positive results can be obtained after several months and even years [1, 3, 10, 15].

For the diagnosis of immediate drug allergy, there are two types of **skin tests**: prick tests and intracutaneous tests. Contraindications must be considered, and medications that reduce skin reactivity and cause false negative results are investigated. Skin tests, which are simple to perform and inexpensive, are used to demonstrate immunological response to certain drugs. However, their advantages, such as ease of use and low cost, are offset by disadvantages, the most notable of which are the low sensitivity and specificity of most drug tests. Many drugs, especially when administered intradermally in undiluted solutions, can cause irritative effects (nonspecific skin irritation manifested by hyperemia/erythema). As a result, for skin tests, non-irritative drug concentrations are used [15, 16, 18].

It should be emphasized that skin tests can only be performed by allergy-immunology specialist (or trained nurse under physician's supervision) in allergological room after the patient has signed informed consent. Prick test is considered safe when taking into account it's contraindications, and intracutaneous test in rare cases can lead to fatal consequences (especially with history of immediate allergy to beta-lactams), so it is recommended to perform it in a hospital [3].

Positive wheals and hyperemia response within 15 to 20 minutes in prick test and intracutaneous test indicates the presence of drug-specific IgE on patient's mast cells and confirms type I reaction. However, in addition to the simple irritative effect that any drug can cause, a number of drugs (for example, opioids, fluoroquinolones, and vancomycin) induce non-immunological (i.e., without the participation of IgE antibodies) release of skin mast cell mediators, leading to the development of a classic wheal with pseudopodia and severe hyperemia (Fig. 4), particularly during intracutaneous testing [10]. At the same time, no urticaria/AE manifestations were observed during provocation testing or subsequent therapeutic use of the drug.

Skin testing with a drug uses the native (non-metabolized) form of the drug, which can reveal allergies in only a subset of patients. The full range of metabolites and intermediate forms that stimulate the development of allergies has not been determined for most drugs, and no test reagents are available. The only exception to this rule is penicillin, which has metabolites and metabolite-protein complexes that are required for the most accurate identification of allergy patients. However, diagnostic allergens containing these determinants are not currently available for clinical use in the majority of countries [10].

In addition to penicillin, a number of drugs with native (non-metabolized) form have been identified. With these drugs skin tests turned out to be informative for diagnosis of immediate allergy [10, 15]:

- other beta-lactam antibiotics (cephalosporins and imipenem);
- neuromuscular blockers and blue dyes used to localize lymph nodes during surgery;
- carboplatin and other platinum drugs;
- pyrazolones such as metamizole;
- local anesthetics;
- thiobarbiturates (e.g., thiopental sodium);
- therapeutic monoclonal antibodies.

Testing begins with a prick test, and if the results are negative or indeterminate, the transition is made to an intracutaneous test, which has higher sensitivity (but lesser specificity). For prick tests and intradermal tests, sterile drug solutions are used. In most cases, a skin reaction appears after 15–20 minutes, but a wheal and erythema can develop more slowly — within 1 hour. Papules may form after 2–6 hours of intradermal administration of the drug, indicating the late phase of IgE-dependent allergy caused by secondary effector cells — eosinophils and neutrophils. The appearance of a papule after 24–72 hours is indicative of delayed T-cell hypersensitivity. When non-irritating drug concentrations are used, an immediate response (within 1 hour) indicates IgE-mediated allergy. Negative result does not exclude allergy, as the patient may have immunological reaction to drug metabolites. In other words, under the clinical conditions during treatment with this drug, the occurrence of a reaction induced by the binding of the drug to IgE cannot be completely excluded. Skin tests can also be false negative if done too soon after an acute allergic reaction.

The drug provocation test (DPT) involves gradually increasing doses of a suspected drug and is based on the idea that a certain amount of drug is required for the onset of symptoms. DPT is widely regarded as the gold standard in the diagnosis of DH when all possible studies (skin and laboratory tests) have been performed but the cause remains unknown [1, 3, 15]. However, informative specific laboratory tests are not widely available for allergological practice, and skin tests with many drugs have low specificity and sensitivity, owing in part to their ability to only diagnose immunological reactions. In cases of non-immunological DH, skin tests are not used, therefore, specific diagnosis of DH is immediately started with DPT, if anamnesis data are insufficient for this purpose [1, 10]. In case of allergy, which could not be proved using skin tests, the advantage of DPT is its possibility of confirming or excluding the reaction to drug metabolites, since immunological response to native drug is determined by skin tests.

There are generally accepted indications, contraindications and limitations for DPT. The causes of false positive and false negative results have also been described [1, 10, 15, 16].

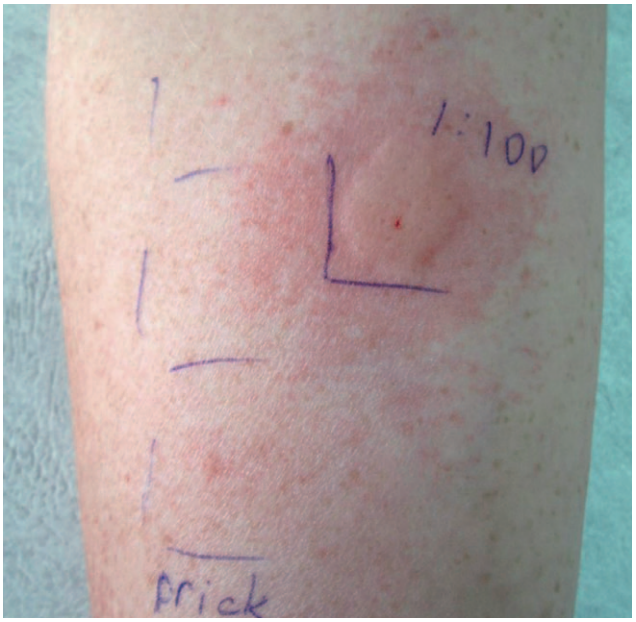

Fig. 4. Skin tests with levofloxacin. The prick test with whole solution (5 mg/1 ml) is ambiguous. IT at a dilution of 1:100 with a volume of 0.02 ml: after 20 minutes, a giant wheal with pseudopodia appeared, which resolved within 1 hour. There were no late skin reactions or systemic clinical manifestations the day after IT. IT was regarded as a false positive, owing to non-immunological mediator raised from skin mast cells. The intravenous provocation test with levofloxacin the next day was negative. Prior to coaxial arthroplasty surgery, an examination was carried out. The patient had a history of anaphylaxis during penicillin administration and urticaria during treatment with azithromycin. Prior to the skin test, no levofloxacin was administered. Following the examination, the patient given levofloxacin in the postoperative period, and no hypersensitivity was observed. (Photo from authors' archive).

The main indications for urticaria and AE:

- exclusion of DH with uncertain (unclear) anamnesis data;
- exclusion of cross-reactivity of drugs that are similar in structure/action to drugs that previously caused manifestations of DH in the patient;
- proof of safety of drugs that are pharmacologically and/or structurally unrelated to drugs that have previously caused true manifestations of DH in the patient; especially relevant for patients with anxiety and depression.

Certainly, any in vivo drug testing, including DPT, is conducted with strict justification for the necessity of suspected drug use now or in the future. When there is a convincing history of DH, as well as positive skin tests, the specificity of which is undisputed, DPT is not performed.

Contraindications for DPT with immediate DH [1, 10]:

- urticaria and AE as manifestation of anaphylaxis (in rare cases, provocation is possible after analyzing the risk/benefit ratio);
- suspected drug is unlikely to be needed in the future and there are structurally unrelated alternative drugs;
- severe or uncontrolled comorbidity and pregnancy; the exceptions include cases where the appointment of drugs is required for life-saving indications.

Several key points should be highlighted. In many cases, DPT is used to rule out DH rather than confirm it, i.e., when a drug-induced reaction is unlikely to occur. Negative DPT results allow you to persuade both the patient and the referring physician of the safety of the suspected drugs, the possibility of using local anesthesia, the need for a contrast X-ray, the absence of cross-reactions with drugs from another class (or even within the same group, but with different pharmacological structure: for example, beta-lactams with different side chains), and so on. DPT is performed under the close supervision of an allergologist after the patient has signed informed consent and only in a hospital where immediate assistance and intensive care are available if necessary.

Main reasons for false negative results of DPT are [1, 10]:

- testing during administration of antiallergic drugs, when the cancellation of them is impossible;
- difficulty or impossibility of modeling the effects of other factors such as viral infection, fever, ultraviolet radiation, exercise, etc. on DH;
- insufficient duration of test drug exposure and/or follow-up;
- insufficient or excessive time interval since DH reaction;
- insufficient provocative dose of the drug;
- development of desensitization during DPT.

Execution of DPT [1, 10]. Commercial therapeutic drugs are commonly used as provocative agents, as there are no standardized dosage forms for DT. Preference should be given to those dosage forms that do not contain ingredients capable of causing hypersensitivity (gelatin, lactose, etc.), and it is also not recommended to use combined drugs (e.g., amoxicillin + clavulanic acid or articaine with epinephrine).

For patient safety reasons, it is preferable to start the test with minimal doses taken orally. However, if the supposed "offender" was previously used parenterally and will be used in the same way in the future, then DT is completed in conditions maximally similar to this normal exposure.

Provocative tests are performed under placebo control on patients with anxiety and other subjective reactions that were interpreted as "drug allergy" by other specialists and served as the basis for referral to allergologist in order to establish DH diagnosis. This is required to rule out false positive results in patients with specific personality types and unintentional neurotic reactions to taking various drugs, which frequently arise as expectation neurosis after a disturbing experience with previous treatment, which resulted in the development of either true DH or other significant side effects. The placebo response assures both the clinician and the patient that the previous response was not caused by the suspected drug (one or more). Generally, after the entrance provocative test with placebo and psychotherapeutic conversation with the patient, further gradual stepwise increase in the dose of the required drug passes without complications.

Commonly used standardized protocols include DT with ASA, local anesthetics, and beta-lactam antibiotics [1, 10, 11, 16].

TREATMENT

To begin, the offending drug must be discontinued and, if necessary, replaced with a drug that has no cross-reactivity, i.e., has no common antigenic determinants in IgE-dependent allergies, or that does not similarly affect non-immunological mechanisms of DH (for example, potent COX-1 inhibitors in aspirin / NSAID-dependent non-allergic urticaria or any ACE inhibitor if one of them caused AE) are excluded.

Urticaria and associated AE symptoms are relieved in accordance with the general treatment principles for these conditions [3, 4]. Antihistamines are commonly positioned as first-line drugs that can be used as monotherapy for non-severe, non-life-threatening forms of urticaria and AE. Since the withdrawal of the offending drug already has an effect, this treatment is usually sufficient. The safest use of antihistamines II generation is orally in age-specific therapeutic doses.

More intensive antihistamine treatment is used in generalized urticaria in conjunction with AE. Parenterally administered drugs of the first generation have a rapid onset of action (clemastine or chloropyramine). Given the variety of side effects of these drugs, treatment is switched to second-generation antihistamines after the most severe manifestations are controlled.

Systemic corticosteroids are administered intravenously in severe cases of the disease, similar to anaphylaxis [4]. The GCS dose is determined on an individual basis based on the initial severity of clinical manifestations and response to therapy. It should be noted that severe urticaria in conjunction with AE could be a symptom of anaphylaxis, for which epinephrine is the first-line treatment. Even if there are no signs of involvement of other systems or hypotension, epinephrine is used if the patient has symptoms of laryngeal AE. A 0.01 mg/kg dose of epinephrine (adrenaline) solution at a concentration of 1 mg/ml is injected intramuscularly into the middle of the anterolateral thigh, with a maximum dose of 0.5 mg for adults and 0.3 mg for children. In case of larynx AE development with ineffectiveness of conservative therapy, emergency intubation or tracheostomy is recommended [3, 4].

Therapy for isolated AE depends on its pathogenetic variant. Histamine AE is treated according to the same principles as urticaria, and in case of laryngeal edema, the patient is immediately treated as a patient with anaphylaxis. First of all, epinephrine is administered intramuscularly, if necessary, injections are repeated every 5–15 minutes. In patients with AE of upper respiratory tract, in case of ineffectiveness of antihistamines and GCS in urgent situations, it can be difficult to exclude HAE or AAE, so it is recommended to administer fresh frozen blood plasma (it contains a C1 inhibitor) [3, 6, 12]. With further progression of larynx AE, intubation or tracheostomy is required.

Acute drug-induced adverse events associated with impaired bradykinin degradation (see Table 1) have yet to be treated. There is a widespread belief that GCS and antihistamines are

ineffective in this type of AE because there are no inflammatory mediators that antiallergic drugs affect. The commonly observed gradual improvement in AE caused by ACE inhibitors is thought to be due to the action of GCS and antihistamines, rather than the withdrawal of the offending drug. In the absence of improvement, frozen plasma, as in HAE or AAE, may be administered. In severe cases of drug-induced bradykinin AE (e.g., larynx AE or AE with abdominal involvement), use of bradykinin receptor antagonist, kallikrein inhibitor, and administration of C1 inhibitor have been studied in small groups. The data on effectiveness of these drugs is mixed, and when clinically indicated, the most important intervention is airway management. Although fatal outcomes in ACEI-associated AE have been described, they are very rare [12, 13].

If the drug-induced a relapse (attack) of AE in patients with known HAE diagnosis, then exacerbation therapy is carried out in accordance with clinical recommendations [6].

PREVENTION

It is necessary to include clinical diagnosis and information about the patient's DH, possible cross-reactivity, and recommendations for adequate replacement of offending drug with other, safer drugs in the patient's medical records [3]. It is critical to educate the patient and his family.

In cases of IgE-mediated urticaria and AE, where a repeated course of treatment or permanent therapy is necessary, the simplest option for further management of a patient with confirmed DH is to take a safe and effective unrelated drug. Second-line therapies, on the other hand, may carry additional risks, such as toxicity and higher costs. Penicillin allergy is a good example of these issues. Patients with this diagnosis are usually prescribed non-beta-lactam antibiotics that can be more expensive, cause serious side effects, and in some cases are less effective. Patients usually take quinolones, macrolides or vancomycin, but the use of these broad-spectrum antibiotics contributes to the development and spread of antibiotic resistance [10, 19].

In the case of penicillin allergy, the exclusion of all beta-lactam antibiotics, or at least cephalosporins, has recently been recommended. This approach has now been modified: it was discovered that side chains of penicillins and cephalosporins, rather than the beta-lactam ring, can be cross-antigens. It has been demonstrated that if treatment with a drug with a similar chemical structure is required, it can be carefully selected using skin tests and/or DPT, and this does not only apply to beta-lactams [10, 19].

If an IgE-mediated allergy to a specific NSAID is diagnosed, the patient can use chemically unrelated drugs safely. However, if tolerance to other drugs is doubtful based on anamnesis, prescription of NSAIDs from a different group is possible after DPT [11].

In cases of allergic urticaria/AE, if it is necessary to administer a vital drug, to which the patient supposedly or definitely has DH, and there are no safer and equally effective drugs as the "offender," desensitization is possible. The first successful desensitization in its modern form started with penicillin. To date, protocols have been developed and published for other antibiotics, co-trimoxazole, HIV drugs, ASA, insulin, allopurinol, omeprazole, cancer chemotherapy drugs, as well as biological drugs [10, 11, 20–22].

To avoid exacerbations of spontaneous chronic urticaria with non-immunological DH to NSAIDs, avoid high doses of ASA and all non-selective NSAIDs, while strict exclusion of these drugs has no effect on the disease's main clinical course. If an NSAID is required in conjunction with a specific drug (including COX-2 inhibitors), a placebo-controlled DPT should be performed. The majority of patients (75%–90%) tolerate selective COX-2 inhibitors such as meloxicam and nimesulide, as well as paracetamol. Opioids can be used as an alternative analgesic, but they are nonspecific histamine liberators and can worsen chronic urticaria and AE in some cases. This is why some patients with severe disease course require DPT with opiates. In case of developing a mild reaction to any or many of mentioned drugs and in case of strict justification for their prescription, antihistamines are used prior to drug administration [5, 10, 11].

Primary and secondary prevention of arterial thrombosis in cardiovascular diseases may become an issue in patients with aspirin-dependent chronic urticaria and AE, because drugs containing ASA are most commonly used due to their favorable cost-effectiveness ratio. Low doses of ASA as an antithrombotic agent are generally well tolerated by this group of patients with chronic urticaria and AE. If a reaction to low doses of ASA occurs, it is possible to replace it with ticlopidine or clopidogrel. In contrast to aspirin-induced respiratory disease, the effectiveness of ASA desensitization in chronic urticaria/AE is debatable [7, 10, 11].

Isolated cases of chronic urticaria and histamine AE provocation have been described in women taking estrogen-containing drugs; in such cases, the issue of their withdrawal must be addressed [7].

The prevention of immediate reactions to ICCA is a current issue.

In recent years, studies have been conducted to increase understanding of the possibilities of a differentiated approach to patient management when appointing contrast-enhanced X-ray examination [23]. As a first step, it is advised to assess the likelihood of developing a hypersensitivity reaction. Patient history and clinical assessment of comorbidities that may be a risk factor for DH are used to stratify patients:

- high-risk patient: history of DH reaction to ICCA;
- low risk patient: no history of DH to ICCA, but has comorbidity–uncontrolled asthma, active urticaria/AE, mastocytosis;
- very low risk patients include persons with history of hypersensitivity reactions to food and to any drugs, including iodine-containing antiseptics (povidone-iodine, etc.).

Assigning a patient to one or another gradation determines further tactics of their management.

1. High-risk patients

Alternative imaging methods or other diagnostic methods (e.g., ultrasound) are recommended for high-risk patients first. If a diagnosis cannot be made without the use of contrast-enhanced X-rays, magnetic resonance imaging and a new class of contrast agents containing gadolinium instead of iodine should be used (gadopentetic acid, gadoxetic acid, gadodiamid, etc.). These medications have a significantly lower ability to induce DH.

If a contrast-enhanced X-ray examination using ICCA is not possible, then tactics vary depending on the urgency of the situation. If the examination is routine, skin testing is recommended to assess the pathogenesis of previous reactions (immunological or non-immunological), followed by ICCA selection based on skin test data and cross-reactivity (if the "offending" drug is known). When replacing with alternative ICCA, risk of reaction still remains, therefore, oral premedication with GCS (40 mg of prednisolone or equivalent) is used 12 hours and 2 hours prior to examination. Additionally, 10 mg of cetirizine is taken 1 hour before contrast injection.

When an ICCA test is not possible and the drug that caused the hypersensitivity reaction is known, the drug is replaced with another, taking into account cross-reactivity. If the "offender" drug cannot be identified, the least reactogenic drug is chosen (non-ionic monomeric ICCAs group). Premedication is accomplished through an intravenous drip infusion of 200 mg hydrocortisone and antihistamines (clemastine or chloropyramine in therapeutic dose). To obtain a protective effect, these drugs should be taken no later than 60 minutes before the examination. ICCA is administered during vital function monitoring. If the previous reaction was urticaria/AE or bronchospasm, an anesthesiologist should be immediately available to attend an emergency. In the presence of an anesthesiologist and resuscitation equipment, a contrast-enhanced X-ray examination is performed in patients with a history of anaphylaxis.

The efficacy of the two described premedication regimens, depending on the urgency of the situation, has been demonstrated in clinical trials with a high level of evidence [23].

2. Recommendations for patients with concomitant disease (uncontrolled asthma, active urticaria/angioedema, mastocytosis)

If the situation is not urgent, postpone the examination and instead prescribe or strengthen basic therapy until the underlying disease is controlled. Then, using non-ionic monomeric ICCA or gadolinium-containing contrast agents, perform a contrast-enhanced X-ray study. When using ICCA as a contrast agent, oral GCS and antihistamine premedication is used to reduce the risk of reaction [3, 23].

In emergency situations, when there is not enough time to control concomitant disease, premedication is performed, similarly to the high-risk group: intravenous administration of hydrocortisone and antihistamines. Asthmatic patients should also take a short-acting 2-agonist 30–60 minutes before the study.

3. Very low risk patients

Persons with a history of hypersensitivity reactions to food or drugs, including iodine-containing antiseptics, pose the least concern. It has recently been demonstrated that allergic contact dermatitis caused by iodine-containing topical antiseptics is not a risk factor for ICCA hypersensitivity [23, 24]. In particular, in a domestic study, application test with iodine-containing antiseptics in patients with history of contact allergy showed positive result, and skin tests (application test, prick test, intracutaneous test) with various ICCAs yielded negative results. Following that, all patients in this group underwent various contrast-enhanced X-ray examinations with no adverse reactions [24].

There are no special recommendations for patients with a history of extensive skin manifestations and systemic DH syndromes caused by various drugs for the prevention of ICCA reactions proven by evidence-based studies. According to empirical evidence, these patients usually tolerate ICCA well. The same is true for patients who have food allergies. In real-life clinical practice, however, if food allergy is manifested by recurrent urticaria and/or AE, premedication with oral GCS and antihistamines is performed to reduce the risk of nonspecific histamine release from basophils under the influence of ICCA [3, 23].

If the patient is taking β-blockers, the risk of bronchospasm and anaphylaxis increases with the introduction of ICCA, and ACE inhibitors can be triggers for development of AE. As a result, if contrast-enhanced X-ray examination is performed routinely, the supervising doctor should also consider drug cofactors, and, accordingly, consider the issue of replacing β-blockers and ACEIs with alternative drugs in advance.

Prevention of drug-induced bradykinin angioedema

With AE caused by ACE inhibitors, all drugs of this group should be avoided; lowering the dose does not result in significant improvement, despite the non-immunological mechanism of development. It is necessary to inform the patient that AE symptoms may recur for some time after ACEI withdrawal. If any other ACE inhibitor is prescribed after the AE manifestations have disappeared, then the disease usually returns, and the afflictions become more severe.

Recommendations for the substitution of ACE inhibitors with other drugs in patients with cardiovascular pathology are pertinent. Although ACE inhibitors and angiotensin receptor blockers (ARBs) have many common cardioprotective effects, the mechanism by which AE develops as a result of ARB use is unknown. Data on AE incidence with ARB treatment is rather contradictory [25]. For example, in a large study involving 467,313 patients who started ARB treatment, 288 cases of

AE (or 0.006%) were registered, but the frequency of this adverse drug reaction was similar for β-blockers. In a meta-analysis of 19 studies, the overall incidence of AE with ARB treatment was not significantly different from placebo. There are current recommendations for patients with ACEI-induced AE who require ARB treatment in the absence of HAE or AAE types 1 and 2 signs. Treatment with these drugs is possible if patients are carefully monitored to assess possible adverse drug reactions. Another approach is to wait at least 4 weeks after discontinuing ACEI therapy before beginning ARB treatment. However, this is only acceptable if the patient can safely manage without drugs for a specified period of time or a replacement has been made with drugs of other groups. Taking into account possible contraindications, β-blockers, diuretics, calcium channel blockers, and other antihypertensive drugs can be considered [25].

Patients should avoid using ACEIs, ARBs, estrogens, and thrombolytic therapy with recombinant human tissue plasminogen activator (alteplase) to prevent drug-induced relapse of HAE, AAE, and idiopathic AE [7].

CONCLUSION

Drug-induced urticaria and AE have various forms that differ in etiology and pathogenesis but are often clinically difficult to distinguish. A thorough history is helpful in determining the etiology of the condition, skin tests may be informative with IgE-mediated allergies, and DPT may be informative in both immunological and non-immunological DH, if strictly indicated. To begin treatment, the "offender" drug must be removed and, if necessary, replaced with a drug that does not have cross-reactivity.

The most important preventive measures for recurrent episodes of urticaria and AE are to the update the patient's medical records with information about the patient's DH, potential cross-reactivity, and recommendations for adequate replacement of the offending drug with another, safer one.

Adult patients and relatives/guardians of children with DH must be educated.

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