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Case Report



Allergic Contact Dermatitis, Angioneurotic Edema and Conjunctivitis in a Patient with Autoimmune Thrombocytopenia – A Clinical Case

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Abstract

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BACKGROUND: Allergic contact dermatitis (ACD) is common in clinical practice, but the aetiology of this disease is quite varied. A leading pathogenetic mechanism is a cell-mediated immunity. The combinations of ACD with other allergic and systemic autoimmune diseases are relatively rare, but these conditions are undoubtedly a professional challenge for practitioners.

CASE REPORT: We present a case of ACD combined with other immune-allergic conditions. Aetiology and pathogenesis in these cases are not well understood.

CONCLUSION: Based on the data from the general and targeted allergic history, patient's subjective complaints, clinical picture, allergenic status, paraclinical results, and the presented photo material, the final diagnosis is as follows: Contact allergic dermatitis-acute form.

Introduction

Contact dermatitis is the most common skin allergic disease with professional aetiology [1]. The disease is Type 4 allergic reaction after Coombs and Gell (delayed type hypersensitivity) [1] [2]. According to literature, symptomatology in most of the cases is triggered and occurs in skin areas exposed to direct contact with allergens from the work environment [1] [2] [3]. The clinical picture is characterised by burning and itchy exanthema in allergen contact areas of the skin. Sometimes the rash also involves more distant non-contact areas [1]. Angioneurotic oedema is defined as a state of pathological fluid retention in the

subepidermic interstitium [1] [4]. Swelling is a symptom that occurs in many different diseases. Oedema is a condition where there is pathological fluid retention in the interstitial, i.e. in the extravascular part of the extracellular space. Pathogenetic mechanisms that determine the onset of swelling are increased hydrostatic pressure in the capillaries, decreased oncotic plasma pressure found in hypoalbuminemia, increased capillary permeability and worsened lymphatic drainage [4]. Drug oedema is most commonly caused by calcium antagonists, ACE inhibitors, angiotensin-2 receptor antagonists – sartans, diuretics (aldosterone), NSAIDs, corticosteroids, antidepressants (AD). Angioedema is an acute swelling of the deeply located connective

tissue most commonly located on the eyelids, lips, tongue, pharynx, thigh, and larynx. It rarely occurs on limbs. Several pathogenetic forms of angioedema are known: allergic IgE mediated angioedema (Oedema Quincke), non-allergic drug-induced angioedema (aspirin, ACE inhibitors, sartans), angioedema in parasitic diseases (echinococcosis, larva migrans), physical angioedema (cold, pressure, vibrations, etc.). A particular form of angioneurotic oedema is hereditary angioedema, a rare disease associated with congenital or acquired deficiency of the C1 esterase inhibitor [1]. Diagnosis of angioedema requires a lot of effort, clinical experience and in-depth knowledge. It includes a detailed history, physical examination and modern clinical and immunological tests. Differential diagnosis (DD) of angioedema includes various conditions. Localisation and the nature of the swelling focus attention on the diseases that will result in a differential diagnosis. These include immunopathological diseases such as autoimmune thrombocytopenia, immune-allergic vasculitis, malignant hematopoiesis and others. Some cases in children and adults have been reported in the literature [5] [6] [7] [8] [9].

Material and Methods

A source of information is the data from the clinical and paraclinical examinations carried out in pre-hospital and hospital care, reflected in the patient's medical records, as well as photos voluntarily provided by the patient herself.

Clinical Case

The patient is a young female aged 29, hospitalised urgently for diagnosis and treatment in the Department of Occupational Diseases and Clinical Allergology of the University Hospital "St. George" in Plovdiv at 2017. Our participant signed voluntary informed consent after a detailed explanation of all procedures and the ethics of this study. We have followed the Declaration of Helsinki and European Medicines Agency Guidelines for Good Clinical Practice.

The woman is admitted to the clinic for a rash and a heavy itching on her neck and behind her ears. Gradually, the exanthem spreads over the whole body. The patient associates the appearance of allergic symptoms with body lotion (a frequent contact allergen).

The patient reports a similar incident from a year ago, also after using a cosmetic product (face

cream). The complaints are an urticarial rash on the face, neck and behind ears, concomitant episodes of pruritus in the eyes with profuse, non-exogenous conjunctival secretion, and angioneurotic swelling of the soft tissues of the face and neck several weeks previously and resolving spontaneously.

After an outpatient clinic consultation with an ophthalmologist, allergic conjunctivitis was diagnosed (Table 1).

Table 1: Haematological and biochemical tests

Haematology	Differential blood count	Biochemistry
HGB – 136 g/l	Neut. – 77.4 %	gluc – 5.1 mmol/l
RBC – 4.66 T/l	Lymph. – 16.5 %	t.prot – 70.0 g/l
HCT – 0.397 pg/l	Eos. – 0.1 %	alb – 45.0 g/l
MCH – 29.1 pg	Mono – 4.4 %	urea – 3.3 mmol/l
MCV – 85 fl	Baso – 0.3 %	crea – 78 mmol/l
WBC – 8.74 G/l		AST – 16 u/l
		ALT – 22 u/l
PLT – 153 G/l		
ESR – 22 mm/h		

There are currently no data on food, medication and insect allergy. The patient has no addictions and is not in domestic or professional contact with animals and birds.

Comorbidity of autoimmune thrombocytopenia was objectively diagnosed with immunological tests before the occurrence of the above-described mucocutaneous symptoms (Table 2).

Table 2: ANA profile3 (14Ag, PCNA)

Antigen	Method	Result
RNP/Sm	immunoblot	+++
SS-A native (60kDa)	immunoblot	+
Ro-52 recombinant	immunoblot	++
Nucleosomes	immunoblot	+
Histones	immunoblot	0
Sm	immunoblot	0

The patient is observed by a haematologist. Serum immunoglobulins and complementary fractions were added to the medical documentation during an asymptomatic period. They are in reference values (Table 3).

Table 3: Scale for interpretation of Immunoblot

Intensity	Class	explanation
0-5	0	negative
6-10	(+)	borderline
11-25	(+)	positive
26-50	(++)	strong positive
51-256	(+++)	strong positive

Family history: a mother with a drug allergy to penicillin.

The patient works as a doctor of clinical immunology at University Hospital "St. George" and Plovdiv Medical University. This does not link the triggering of allergic manifestations to work environment factors.

General condition – good. Clear consciousness. Adequate. Afebrile. White skin. Pale-pink, visible mucous membranes. Language and speech – normal.

Local status: maculopapular rash on the neck (Figure 1), behind the ears and on the abdomen, against the background of pronounced erythema (Figure 2), accompanied by intense itching.



Figure 1: Maculopapular rash behind ears and neck

Peripheral lymph nodes are not palpable in accessible areas. Respiratory system: chest with proper form. Clear percussion tone. On auscultation – pure vesicular breathing without wheezing.



Figure 2: Rash on the upper body

Cardiovascular system: Rhythmic, nor frequent cardiac activity. Heart rate 80 beats/minute. Clear heart tones without pathological noises. Arterial pressure 120/70 mmHg. Succusio renalis bilateral (-) rep. Abdomen – at the level of the chest, soft and painless in palpation. Liver and spleen not enlarged upon palpation. Bone-muscle system – properly developed for the age.

The haematological and biochemical tests of the patient were within the reference range, except for the differential count, which showed an increase in

neutrophil granulocytes with lymphopenia at normal leukocytes (Table 1). Tables 2, 3 and 4 present the results of immunological tests which confirm autoimmune thrombocytopenia and have relevance to the interpretation and differentiation of the angioedema type.

Table 4: Immunological parameters

Test	Method	Result	Reference value
Tot. IgE	ELISA	12 IU/ml	0 – 100 IU/ml
C 3	nephelometry	1.44 g/l	0.9 – 1.8 g/l
C 4	nephelometry	0.18 g/l	0.1 – 0.4 g/l
C1 esterase inhibitor (Ag)	RID	31.2 mg/dl	sera 21.0 – 39 mg/dl plasma 18.0–32 mg/dl
C1 esterase inhibitor (func)		113 %	70 – 130 %

Systemic corticosteroids, antihistamines and H2 blockers at doses adequate for the clinical picture for 3 days. On the third day after admission, the patient was discharged in good general condition with a complete reversal of the exanthema. The case history points out given recommendations.

5: Skin-allergic samples with a panel of plant and animal allergens

Grass	20 min	Micro ticks	20 min
688 (5 kinds of grass)	(-)	314 (D. farinae)	(-)
687 (4 wheat)	(-)	315 (D. pteronissimus)	(-)
Trees		Allergens of animal origin	
696 (Beech)	(-)	507 (Cat)	(-)
702 (Birch)	(-)	509 (Dog)	(-)
701 (Willow)	(-)	506 (Feathers)	(-)
Weeds		Controls	
604 (Ambrosia)	(-)	Positive control (histamine)	8/5
605 (Plain wormwood)	(-)	Negative control	(-)
665 (Plantain)	(-)		
714 (Atripliceae)	(-)		

To clarify the aetiology of the skin-mucous toxo-allergic syndrome, further studies are recommended to be performed on a "pure background" and in the absence of contraindications. The volume and duration of treatment with H1- and H2-blockers has been specified. Use of cosmetic products should be discontinued.

Table 6: Epicutaneous test with European standard series for epicutaneous testing (European Environmental and Contact Dermatitis Research Group)

No	Allergen	48h	72h
1	Potassium dichromate	+++	+++
2	4-phenylenediamine base (PPD)	-	-
3	Thiuram mix	-	-
4	Neomycin sulfate	-	-
5	Cobalt (II) chloride hexahydrate	-	-
6	Benzocaine	-	-
7	Nickel sulfate hexahydrate	-	-
8	Clouquinol	-	-
9	Colophony	++	+
10	Paraben mix	+++	++
11	N-Isopropyl-N-phenyl-3-phenylenediamine (IPPD)	-	-
12	Lanolin Alcohol	++	+
13	Mercurio mix	-	-
14	Epoxy resin	-	-
15	Balsam Peru	-	-
16	4-tert-Butylphenolformaldehyde resin	-	-
17	2-Mercaptobenzothiazole (MBT)	-	-
18	Formaldehyde	-	-
19	Fragrance mix I	+++	++
20	Sesquiterpene lactone mix	-	-
21	Qua ternium 15	-	-
22	2-methoxy-6-n-pentyl-4-benzoquinone (Primin)	-	-
23	5-chloro-2-methyl-4-isothiazolin-3-one (Kathon CG)	-	-
24	Budesonide	-	-
25	Tixocortol-21-pivalate	-	-
26	Methyl-dibromoglutaronitrile	-	-
27	Fragrance mix II	-	-
28	Lyril (alpha-hexyl cinnamal)	+++	++

Based on the data from the general and targeted allergic history, patient's subjective complaints, clinical picture, allergenic status, paraclinical results, and the presented photo material,

the final diagnosis is as follows: Contact allergic dermatitis-acute form. Status after angioneurotic oedema. Accompanying diseases: autoimmune thrombocytopenia and allergic conjunctivitis.

The results of the additional diagnostic procedures performed to determine the patient's immuno-allergic diseases have been reported in Table 5 and Table 6.

Discussion

The combination of allergy-related reactions, though less common, is not an isolated phenomenon in practice. We have described similar cases [10] [11] [12] [13] [14] [15] [16]. Some of them have an interesting aetiology, especially those related to risk factors in the work environment [10] [11] [14] [16]. In others, rare associations of allergic with non-allergic mechanisms are described, which explains the combined pathology in the same person [17] [18]. Similar clinical cases are also described in hereditary angioedema (HAE) type 1 and type 2 patients [19] [20]. There have also been reports of autoimmune hematoopoiesis associated with allergic syndromes [21].

Discussion questions are whether diseases, demonstrated in the case described, are an expression of allergy, what is the relationship between them and how autoimmune hemopathy is connect with angioedema and ACD.

The allergic aetiology of angioedema in the case described is questioned because of normal blood eosinophil levels and total serum IgE (biomarkers for allergy and atopic predisposition) [1]. The same applies to negative skin-allergic specimens with a set of indoor and outdoor allergens that are a proven method in the diagnosis of allergic diseases [1].

The normal levels of the C1-esterase inhibitor (both quantitative and qualitative) and C4 (the "golden" standard in the diagnosis of HAE), as well as the negative family history, practically exclude HAE type 1 as a cause of oedema in the case described. It is probably an acquired autoimmune thrombocytopenic form of angioedema that can explain the increased consumption of C3 in immune complexes. This explanation does not contradict the normal values of C3 because the study is done in a period of clinical and immunological remission of the disease. Regarding the causes of conjunctivitis certain facts should be taken into account. Negative results from specific allergy tests do not support allergic mechanisms. Given the clinical symptoms typical of allergic conjunctivitis, the possibility of the person being sensitised to an allergen that is missing in the

panel with which it was tested and the fact that no specific IgE antibodies have been tested, the allergic cause of conjunctivitis is highly probable. This is also supported by the conclusion of the ophthalmologist.

Benchmarks for the diagnosis of ACD are the results from the history, the clinical manifestations and the positive results of epicutaneous testing with the European Environmental and Contact Dermatitis Research Group.¹⁷ The result of the patch-test is positive for Colophony, Lanolin Alcohol and highly positive for Paraben mix, Fragrance mix I and Lyrall (alpha-hexyl cinnamal). Epicutaneous testing objectively targets allergic reactions in the 4th (cell-mediated) type. The patch test is considered a "golden" standard in the diagnosis of ACD [1], a disease that illustrates the fourth type of allergic reactions by Coombs and Gell.

As to the analysis of the compounds (allergens) from the epithelial samples carried out, some of them are components of the cosmetics used by the patient [22]. Benzocaine and rosin are used in the manufacture of nail polish, makeup, spirals, eye pencils, shades, lipsticks, blush and creams. This also applies to Paraben mix 4 chemicals. Individually or in combination, they are used as preservatives for the production of various cosmetic preparations (lotions, creams, makeup, lipsticks, shampoos, soaps, gels). The same applies to other allergens in the series to which the patient is objectively sensitized – Lanolin, Fragrance mix I and Lyrall. Fragrance Mix I is a multi-component allergen that contains cinnamic alcohol, cinnamic aldehyde, hydroxycitronellal, amyl cinnamaldehyde, geraniol, eugenol, Isoeugenol. These compounds are a component of the fragrance of a range of cosmetic products (perfumes, deodorants, soaps, shampoos, shower gels). Wool alcohols is an essential ingredient in a range of cosmetic products (creams, lotions, lipsticks, lipsticks, shampoos).

The sensitising effect of the cosmetic products used by the patient is made by contact route. It should be taken in mind that, depending on the mode of use, cosmetic products can affect the body through different mechanisms. For example, aerosols and vapours are irritants, and some of them have a direct toxic effect on the skin and the lining of the eyes and the upper respiratory tract.

Regardless of the technology of production, the sensitising effect of these substances is preserved. Moreover, they are added to other preparations with contact-irritant and toxic-chemical action-fillers, stabilisers, preservatives, flavours, colourants. Deviations in neutrophil and lymphocyte counts in normal white blood cell counts are not a specific indicator for a specific disease state, including immune-allergic pathogenesis. The professional aetiology of immune-allergic diseases in the case described is not commented because there is no causal link between the occurrence and the clinical

manifestation, with exposure to a certain risk factor in the working environment. There are no disease-specific laboratory parameters to verify the performance of professional allergens. The occupation of the patient coincides with the diagnosed immuno-allergic pathology, which does not meet the requirements and criteria for acceptance of professional aetiology [23] [24] [25], which in turn do not correspond to the normative regulations for the administration of occupational diseases in the Republic of Bulgaria.

We present this specific clinical case because it is:

1. A rare combination of clinically proven diseases with the skin-mucosal syndrome.
2. A combination of various etiological factors and pathogenetic mechanisms.
3. The profession of the patient-an immunologist.

Although it may rarely occur in a patient, there may be symptoms of various diseases manifested by skin-mucosal syndrome, with diverse aetiology and pathogenesis. In these cases, both immune and non-immune factors and mechanisms are involved. Good knowledge of etiological factors is crucial for the timely and accurate diagnosis of immune-allergic diseases and is a key to their effective treatment.

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