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Contact Urticaria Syndrome: a comprehensive review

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Abstract:	Purpose of review: Contact urticaria syndrome includes contact urticaria and protein contact dermatitis. Underreport, underdiagnosis or misdiagnosis of entities within the contact urticaria syndrome are believed to be common, especially in the occupational setting. This review provides a structured overview of the entities comprised in this syndrome as well as the diagnostic work-up and management strategies. Recent findings: Contact urticaria syndrome has been described with the use of hand sanitizers in the context of COVID-19 pandemic. A declining trend in the evolution of CoU has been described for natural rubber latex (NRL) allergy due to the use of synthetic gloves. Prick test has been proposed as a screening method instead of the classical sequential scheme. Summary: Physicians should be aware of growing number of culprit agents leading to CUS. Clinical presentation may be challenging since it includes immediate urticaria and/or eczema, and even more generalized reactions. Diagnosis requires a high degree of suspicion, detailed occupational history and complementary tests, including skin testing. If the culprit agent is found, the best treatment is to avoid contact with the product and to implement preventive measures.

Contact Urticaria Syndrome: a comprehensive review

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Abstract:

Purpose of review:

Contact urticaria syndrome includes contact urticaria and protein contact dermatitis. Underreport, underdiagnosis or misdiagnosis of entities within the contact urticaria syndrome are believed to be common, especially in the occupational setting. This review provides a structured overview of the entities comprised in this syndrome as well as the diagnostic work-up and management strategies.

Recent findings:

Contact urticaria syndrome has been increasingly described due to personal protective equipment and hand sanitizers in the context of COVID-19 pandemic. The use of legal cannabis products has led to a rise in occupational cases of contact urticaria to cannabis. A declining trend in the evolution of contact urticaria has been described for natural rubber latex allergy due to the use of synthetic gloves. Prick test has been proposed as a screening method, particularly if multiple products are to be tested, instead of the classical sequential scheme.

Summary:

Physicians should be aware of the growing number of culprit agents leading to contact urticaria syndrome. Clinical presentation may be challenging since it includes immediate urticaria and/or eczema, and even more generalized reactions. Diagnosis requires a high degree of suspicion, detailed occupational history and complementary tests, including skin testing. The best treatment is to avoid contact with the culprit agent and to implement preventive measures.

Keywords: Contact urticaria – Immediate – Protein contact dermatitis – Occupational – Dermatitis – Angioedema – Inducible urticaria

Introduction:

The contact urticaria syndrome (CUS) includes several forms of immediate contact skin reactions (ICSR) to eliciting substances that can be accompanied with systemic involvement. Since its description by Maibach and Johnson in 1975, growing evidence has showed multiple triggering factors and varying clinical pictures. [1,2,3] CUS can present with CoU and/or protein contact dermatitis (PCD) after contact with the substance. CoU can even present with severe generalized symptoms. Early detection and prevention remain essential in its management.

Due to a lack of awareness by patients and providers, it is suspected that CUS is regularly underdiagnosed and/or misdiagnosed. [2] Previous publications have highlighted the importance of spreading knowledge on this entity among dermatologists and occupational health doctors. [2,4]

Epidemiology and occupational relevance:

To date, no precise data on CUS prevalence in the general population is available and current evidence is frequently obtained from occupational registers. Occupational CoU cases in European health care workers are estimated to have a prevalence between 5 and 10%, whereas in the general population data vary between 1 and 3%. [2,5] Due to the high frequency of immediate skin reactions in real dermatology practice, it has been hypothesized that CoU is more common than the data indicate outside the occupational setting. [2,5]

CUS is well-established in the occupational setting. [6] The classification of occupational dermatosis of the International Classification of Diseases-11 includes CoU. There are some occupational screening questionnaires including specific symptoms of CoU, such as the Nordic Occupational Skin Questionnaire (NOSQ-2002). [7] Both CoU and PCD are considered to have a favorable prognosis in comparison to occupational allergic contact dermatitis and occupational irritant dermatitis. [8]. However, in some reports, patients with PCD presented worse and more severe symptoms than patients with other diagnoses. [9]

The Finnish Register of Occupational Diseases showed that CoU was the second most common skin occupational condition (29.5%) after contact dermatitis. The three most common responsible agents reported in this register were cow dander, flour and grains, and natural rubber latex (NRL) [10]. In two German cohorts, the most frequent elicitors of CoU were cosmetics and NRL, respectively. [11] In an Australian study, the three most common occupations involved were health workers, food handlers and hairdressers due to NRL, foodstuffs and ammonium persulfate, respectively. [12]

A favorable trend has been observed with NRL allergy, considered to be the most common form of CUS among health workers. [13] Healthcare workers with latex allergy produce IgE specific for a 20 kDa latex peptide (prohevein), which can be found in latex gloves, powder and even in the air due to local transmission. The introduction of non-NRL or nonpowdered synthetic gloves, and progressive elimination of powdered gloves,

has enabled workers to avoid the air contamination. Consequently, the lowering of latex release has prevented new cases of sensitization, with subsequent observation of a declining trend in the evolution of CoU in different studies. [13, 14, 15]

An insight into pathophysiology:

The precise mechanisms that lie behind CUS remain unknown. An initial approach to improve its understanding may be to divide this entity into immunologic and non-immunologic urticaria.

Immunologic CoU is a type I hypersensitivity reaction which occurs in patients with specific IgE against a specific agent. Thus, immunologic CoU needs prior sensitization and only after repeated contact with the culprit agent will the patients present symptoms. The clinical translation of this suspected is evidenced when skin testing is performed, as positive tests will be seen in the affected patients, and will be negative in controls. Immunologic CoU may be caused by two types of agents. The former group includes high molecular weight proteins (10,000 kD or more), whereas the second includes hapten chemicals of low molecular weight (less than 10 kD). [5] A classification on the agents leading to immunologic CoU has been proposed and can be found in Table 1.

The main example of immunologic CoU is NRL, for which thirteen different allergenic proteins have been described, named Hevein (Hev) b1 to b13. [2] Allergy to NRL has allergic implications for patients, since latex-allergic patients show a high degree of cross-reactivity to other antigens, particularly present in fruits (banana, kiwi, avocado, chestnut), sometimes referred to as “latex-fruit syndrome”. [16] Latex Hev b 6.02 and class I chitinase (Hev b11) with a N-terminal Hev-like domain have been described as the main allergens responsible for cross-reactivity.[17]

In contrast, non-immunologic CoU occurs without prior sensitization. Therefore, a solitary contact with the agent may directly trigger the reaction. It is seen with a higher frequency than immunologic CoU but is not accompanied by systemic manifestations. [5] Among the substances that can induce non-immunologic CoU, cinnamaldehyde, benzoic acid, sorbic acid and nicotinic acid esters are to be enhanced. [2] However, the best example remains contact urticaria due to the stinging nettle (*Urtica dioica)*. Histamine is not believed to play a key role due to the therapeutic inefficacy of antihistamines. Contrary to immunologic CoU, skin testing may be positive in all individuals.

Table 1. Immunologic CoU classification of causative agents

Group I	Proteins of plant origin
Group II	Proteins of animal origin
Group III	Grains
Group IV	Enzymes

The pathogenesis of PCD is thought to be a co-occurrence of type I and IV hypersensitivity reactions against proteins, normally with a high molecular weight or even low molecular weight haptens, as described for immunologic CoU. Various foods such as fruits, vegetables, meats, and seafood or non-food proteins have been reported as responsible for PCD. [18]

Risk factors and association of immunological CoU and PCD also provide insight for CUS. Concomitant history of allergic or atopic disorders like asthma, eczema or hay fever is a risk factor for the former [5], whereas history of atopy can be found in up to half of the cases of PCD.[19]

Clinical manifestations of CUS:

CUS clinical symptoms are determined by the nature of exposure (form, duration and extent), properties of the allergen and the individual susceptibility. [2]

CoU mainly occurs within 10 to 30 minutes after skin contact with the eliciting agent, and disappears within minutes or hours (<24 h). It affects areas of the body interacting with the sensitizer, normally exposed areas. [2,4] Delayed onset of CoU has been occasionally described after repeated applications of the trigger substance. [20] It consists of erythema and swelling, rarely angioedema, associated with itch, sting, burning sensation and/or pain, at the site of the contact with the eliciting agent. The clinical appearance of the primary lesions does not differ from that of other types of urticaria.

Volatile proteins (e.g. flour) may cause conjunctivitis, rhinitis, or asthma if there is contact with conjunctival mucosa or respiratory tract. Systemic symptoms like abdominal pain, oral itching after ingestion (oral allergy syndrome), and diarrhea may develop if existing contact with the mucosa of the gastrointestinal tract. [5] Oral allergy syndrome is a form of contact urticaria that occurs within minutes of ingestion and presents as itching, burning, and swelling of lips, tongue, roof of the mouth, or throat, and it is particularly linked to hypersensitivity to fresh fruits.[21]

Spreading of urticarial lesions to generalized urticaria, or to extracutaneous symptoms is possible and the progression of symptoms in CUS has been summarized in four stages, which can be seen in table 2.

Table 2. Clinical staging of CUS

Stage	Symptoms
1	-Localized urticaria -Localized eczema / dermatitis -Non-specific symptoms (burning, itching)
2	-Generalized urticaria
3	-Systemic upper and lower airway and oropharyngeal manifestations (asthma, rhinitis, angioedema, lip swelling) -Systemic digestive manifestations (nausea, diarrhea) -Other allergic systemic manifestations (conjunctivitis)

4	-Generalized anaphylactic reaction, including anaphylactic shock

It is important to highlight that CoU may present as transient erythema, swelling and discomfort in the face. This setting has been described with the use of cosmetics. Before diagnosing "sensitive skin syndrome", "cosmetic intolerance syndrome", or "status cosmeticus", clinicians should assess the possibility of CoU to the products used by the patient. [22]

In contrast, PCD shows predilection for involvement of hands (especially the fingertips) and sometimes extends to the wrists and arms. Rarely, the face and other locations, have been reported to be involved. [23] Pruritus, erythema, wheals or angioedema are characteristic of the acute phase, occurring in a matter of minutes, followed by vesicles in the subacute phase. Examination after the acute phase shows chronic hand dermatitis (erythema, lichenification, fissures or sometimes residual scales), chronic paronychia, or fingertip dermatitis. [18] In the chronic phase, excoriations and lichenification are seen.

Agents responsible for CoU and CUS:

A vast myriad of compounds is thought to be responsible for both occupational and nonoccupational CUS including animal products, plants and plant derivatives, foods, fragrances, cosmetics, flavorings, medications, preservatives, disinfectants, enzymes or metals.

Both proteins of high molecular weight and low molecular weight haptens can induce immediate contact skin reactions in the setting of immunologic CUS. These substances may be found in plants or animal proteins, chemicals, metals, etc. Non immunologic CUS may also be seen due to preservatives, fragrances, chemicals and food products, among others.

Interestingly, there have been some emerging sources of CoU the past years in the context of COVID-19 pandemic and the increasing use of hand sanitizers and personal protective equipment. [24, 25, 26] Contact urticaria due to surgical masks and due to hand sanitizers have been reported, with a myriad of agents causing these reactions (polypropylene, ethanol). Another source of CoU to highlight are cannabis and its derivates. It has been suggested that the increasing use of legal cannabis products such as hemp and cannabidiol oil may increase exposure and hence sensitization, and recently some cases of occupational CoU due to cannabis have been reported. [27]

In contrast with the previous entities, PCD is mostly seen due to proteins from animal or vegetal origin.

Tables 4 to 6 show the most common causes of immunologic CoU, non-immunologic CoU, and PCD cited in the literature.

Table 4. Common causes of immunologic contact urticaria reported in the literature[2]

Category	Examples
Animals and their derivatives	-Caterpillars -Dander -Jellyfish -Placenta, saliva, serum of some animals -Silk -Spider mite
Drugs	-Ampicillin -Bacitracin -Benzoyl peroxide -Cephalosporins -Neomycin -Penicillin -Streptomycin
Food and food additives	-Seafood -Cheese -Eggs -Milk -Onion -Coffee bean -Asparagus -Tomato -Nuts -Mushroom -Mustard -Some seeds and grains
Fragrances	-Balsam of Peru -Wool alcohol
Other chemicals and metals	-Acetone -Acrylic monomers -Formaldehyde resin -Chromium
Plants and their derivatives	-Algae -Cannabis -Colophony -Eucalyptus -Ficus -Natural rubber latex -Poppy flowers -Tobacco -Tropical woods -Tulips
Preservatives	-Alcohols -Chlorhexidine -Gentian violet -Sodium hypochlorite

Table 5. Common causes of non-immunologic contact urticaria reported in the literature[2]

Category	Examples
Animals and their derivatives	-Caterpillars -Moths
Drugs	-Capsaicin -Chloroform -Dimethyl sulfoxide -Nicotinic acid esters -Tar extracts -Tincture of benzoin
Food and food additives	-Some fish products -Runner bean -Tomato -Benzaldehyde -Cinnamic acid -Menthol -Vanillin -Cayenne pepper
Fragrances	-Anisyl alcohol -Cassia oil -Coumarin -Eugenol -Geraniol -Hydroxycitronellal -Benzophenone-3 -Resorcinol
Other chemicals and metals	-Naphtha -Sulfur
Plants and their derivatives	-Nettle -Sea anemone -Coral -Turpentine
Preservatives	-Benzyl alcohol -Bronopol -Camphor -Chlorocresol -Sodium benzoate -Sorbic acid

Table 6. Common causes of protein contact dermatitis reported in the literature[28]

Category	Examples
Animals and their derivatives	*Crustaceans -Lobster

	-Shrimp -Scallops *Fish -Cod -Mackerel -Salmon *Dairy products *Meat -Beef -Horse -Liver -Mutton -Pork -Poultry -Suet
Food and food additives	*Nuts and seeds -Almonds -Cumin *Fruits -Apple -Banana *Vegetables -Carrots -Eggplants -Lettuce -Coriander -Parsley -Parsnips *Mushrooms *Spices -Cardamine -Curry -Paprika *Flours -Rye -Barley -Wheat *Enzymes

	-Amylase -Cellulase -Lactase
Plants and their derivatives	-Chrysanthemum -Cucumber leaf -Ficus -Lilac -Tulips -Natural rubber latex

Diagnosis:

Diagnosis of ICSR requires a full medical history and examination, followed by skin testing of the suspected substances. It is the authors' belief that a reason why both CoU and PCD are underdiagnosed could be that physicians may not ascertain the presence of immediate sting, itch or burning sensation – which leads to the attribution of immediate symptoms to diagnoses of the spectrum of sensitive skin syndrome. In terms of medical history, it is also of utmost importance to include the occupational history and habits. Some dermatologists may not take it into account and this may be a cause of underdiagnosing PCD, which is specially seen in this setting.

Physical examination is important to assess the nature of lesions (if present). Dermatologists need to be aware of the fact that in the case of PCD, eczema may be a manifestation of a previous type I hypersensitivity. Therefore, certain clinical scenarios (e.g., food handlers with chronic hand eczema who also complain of immediate symptoms) may prompt the need to interrogate for previous hives and erythema in the area in order to improve the diagnosis of PCD.

In vitro techniques may be available for a few selected allergens. For instance, NRL allergy may be studied with the use of basophil histamine release, radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA), and IgE immunoblots of peptides present in natural rubber. [20]

The investigation with *in vivo* procedures has to be performed with caution since severe systemic responses have been rarely described after testing. [2] A sequential order for skin testing procedures has been proposed, shown in Table 3. In the case of a positive reaction at any step, further studies are discouraged. Positive and negative controls are recommended. [30]

Table 3. Diagnosis scheme for ICSR starting with the open test

1. Open application on unaffected skin
2. Open application on affected skin
3. Occlusive application on unaffected skin
4. Occlusive application on affected skin
5. Intraepidermal administration (prick test, scratch test, scratch chamber test)

6. Intradermal injection

The initial cutaneous provocation test for ICSR is the open test, which entails rubbing the substance on normal-looking or slightly affected skin, either on the upper back or the extensor side of the upper arm. A positive result is defined as edema and/or erythema (typical of CoU), or tiny intraepidermal spongiotic vesicles (typical of acute eczema). Positive reactions will generally appear within 15-20 minutes. Immunologic CoU may show a delayed onset, although this is rare. [2,4]

If the open test results are negative, repetition with occlusion of the suspected products should be performed. If again negative, prick testing of the suspected allergen or prick-by-prick testing are often the method of choice for immediate contact reactions. Prick-by-prick skin may be a good option, particularly if the studied subject has experienced anaphylactic symptoms, as the amount of allergen is lower than in a prick test performed with the usual technique. In addition, it may also be used with low-molecular weight allergens [31] Prick-by-prick technique consists of pricking the skin first and then rubbing a piece of the suspected product (e.g., fruit, vegetable) to the area or rubbing the product first and then pricking the area. In our experience, normally the first procedure is more commonly used for prick-by-prick.

Scratch test and chamber scratch test (contact with a small aluminum chamber for 15 minutes) are less standardized than prick tests, but are useful when a non-standard allergen needs to be studied. When testing with poorly or non-standardized substances, control tests should be assessed on at least 20 people to avoid false positive interpretations. [2,4]

It is important to enhance that prick testing has been proposed as a screening method for immediate hypersensitivity. Prick testing may be a better diagnostic technique if there is a need to screen a large number of substances at the same time. If a patient needs skin and respiratory provocation tests, the open tests are preferred [31] However, to prevent systemic reactions, prick testing technique is to be commenced at very low concentrations. The open testing sequence remains the main diagnostic tool in the USA and Canada, as many physicians are not trained in prick testing.

It is important to note that the diagnosis of PCD lies in prick tests and/or scratch tests, as patch tests are rarely positive. [32] The diagnosis of PCD has historically been associated to positive prick reactions to protein containing materials. Further studies expanded our understanding of PCD to cases showing an additional type IV contact allergy to proteins. In this sense, isolated reports of non-occupational PCD and cases showing both positive prick-by-prick and patch tests have been reported. [33, 34] To date, the most helpful test to investigate PCD is considered to be prick test [28].

Figures 1 and 2 depict two positive prick-by-prick in two different patients

Many cases found in daily practice involve a differential diagnosis approach that may include other tests such as patch testing or photopatch testing. [35]

Treatment and prevention:

Discovering the responsible agent is a requirement to correctly avoid the eliciting trigger of CUS. Primary and secondary prevention are highly recommended. Considering their good safety profile, second-generation antihistamines should be considered the preferred first-line symptomatic treatment of immunologic CoU. Before considering alternative treatments, two to four-fold increase of the licensed dose of antihistamines should be used. If dermatitis is present in PCD, topical steroids are the first-line treatment. Severe cases of CUS may require a short course of oral steroids. [2,4]

Avoidance of further exposure improves occupational CUS. Occupational CoU seems to have a better prognosis than other occupational dermatitis, even if previous studies have shown that affected workers may lose their job. A Danish study on occupational CoU indicated a risk of prolonged sick leave. [36] In addition, job shift may occur during the first years after recognition of occupational CoU, and more often among patients with positive patch test reactions, or with a severe condition. [37]

Some guidelines advise that employers should remove or reduce the exposure to the agent causing occupational CUS, promote the use of afterwork creams, refer workers with occupational CUS to specialists, and provide appropriate gloves and cotton liners when it is not possible to remove the inciting agent. [38] In addition, health practitioners need to advise atopic workers to maximize safety measures, have a detailed study of history on the job and materials used at work when a worker is affected by CUS and confirm it with skin testing.

Additional treatment options may become available for CUS in the future, particularly if there is an improvement in understanding of the pathophysiology lying behind these underreported conditions. It could be hypothesized selected cases of immunologic CoU with difficulty in avoiding the allergen and without improvement with regular treatments may benefit from anti-IgE therapies. There is rationale for this, as IgE is considered to be one of the key mediators of immunologic CoU. On the other hand, taking into account the eczematous nature of PCD, and the common pathways with allergic contact dermatitis, PCD could potentially benefit from anti-IL-4 and IL-13 therapies. [39] In fact, there has been a case of occupational wheat protein contact dermatitis treated with omalizumab, with clear improvement, [40] which probably indicates common pathogenic mechanisms with CoU. In addition, in two patients with atopic dermatitis and PCD in the BioDay Registry have already been treated with dupilumab. [41]

Conclusions:

Immediate contact skin reactions pose an important challenge, as their occupational relevance has been seriously considered in very few selected countries. ICSR may present as urticaria and/or dermatitis. The identification of CUS requires a high level of clinical suspicion, detailed occupational history, physical examination and complementary tests (e.g., prick testing). Cosmetics, plants, vegetables and foods are

the most common agents. Avoiding the trigger factor is the best treatment. After symptom control, a global approach is required to treat ICSR. This includes appropriate and early diagnosis, occupational reporting, and the development of preventive measures.

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Figures:

Figure 1. Positive prick-by-prick to onion at 48 hours. The test was performed in the context of a cook who presented protein contact dermatitis to onion.

Figure 2. Immediate prick-by-prick to eggplant and tomato. Immediate reading at 15 minutes with two subtle papular wheals for tomato and eggplant in the center can be seen, accompanied by histamine and saline serum control. Posterior reading confirmed a positive result for eggplant, also in the setting of an occupational protein contact dermatitis.

Figure 1

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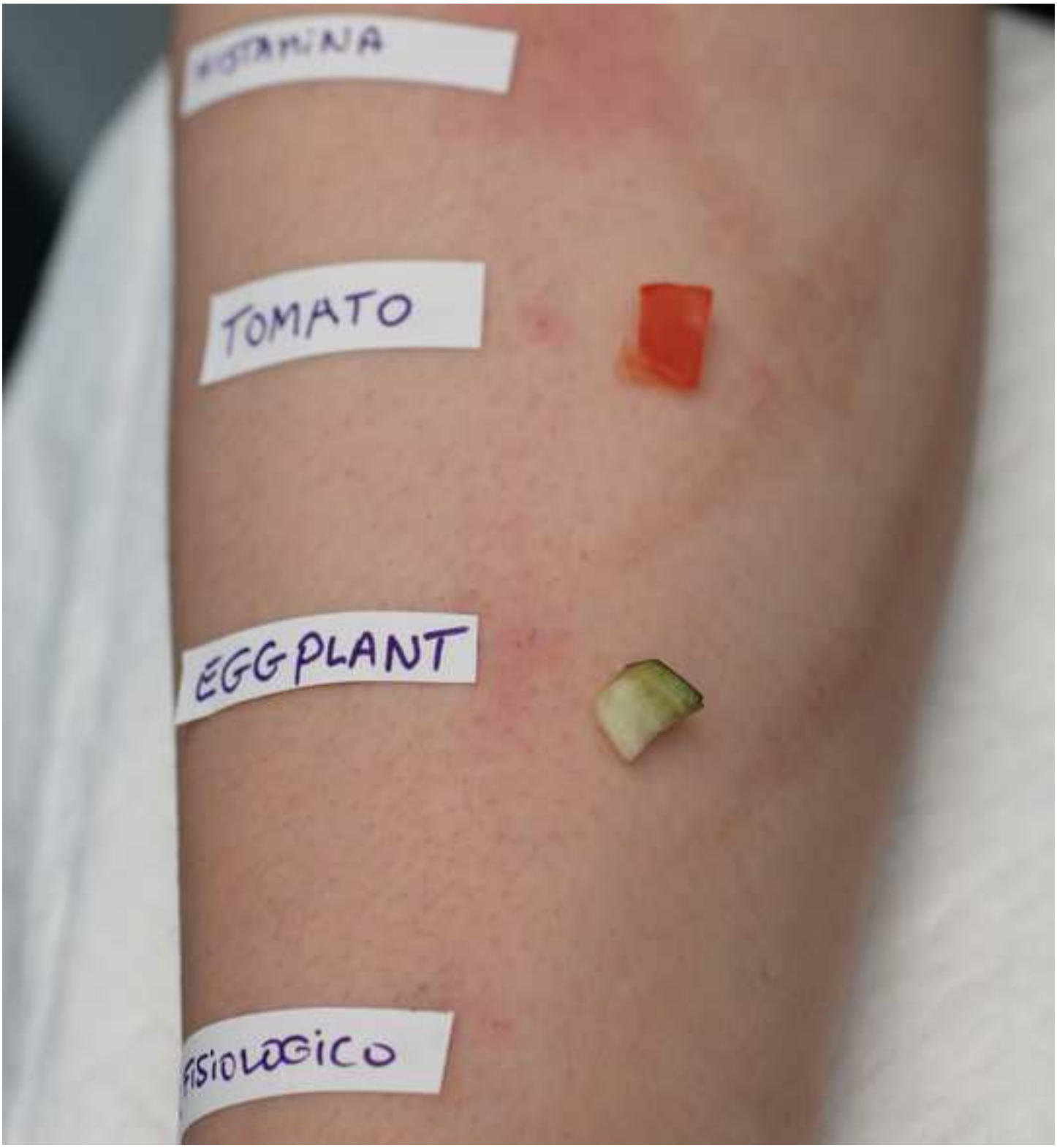

Figure 2

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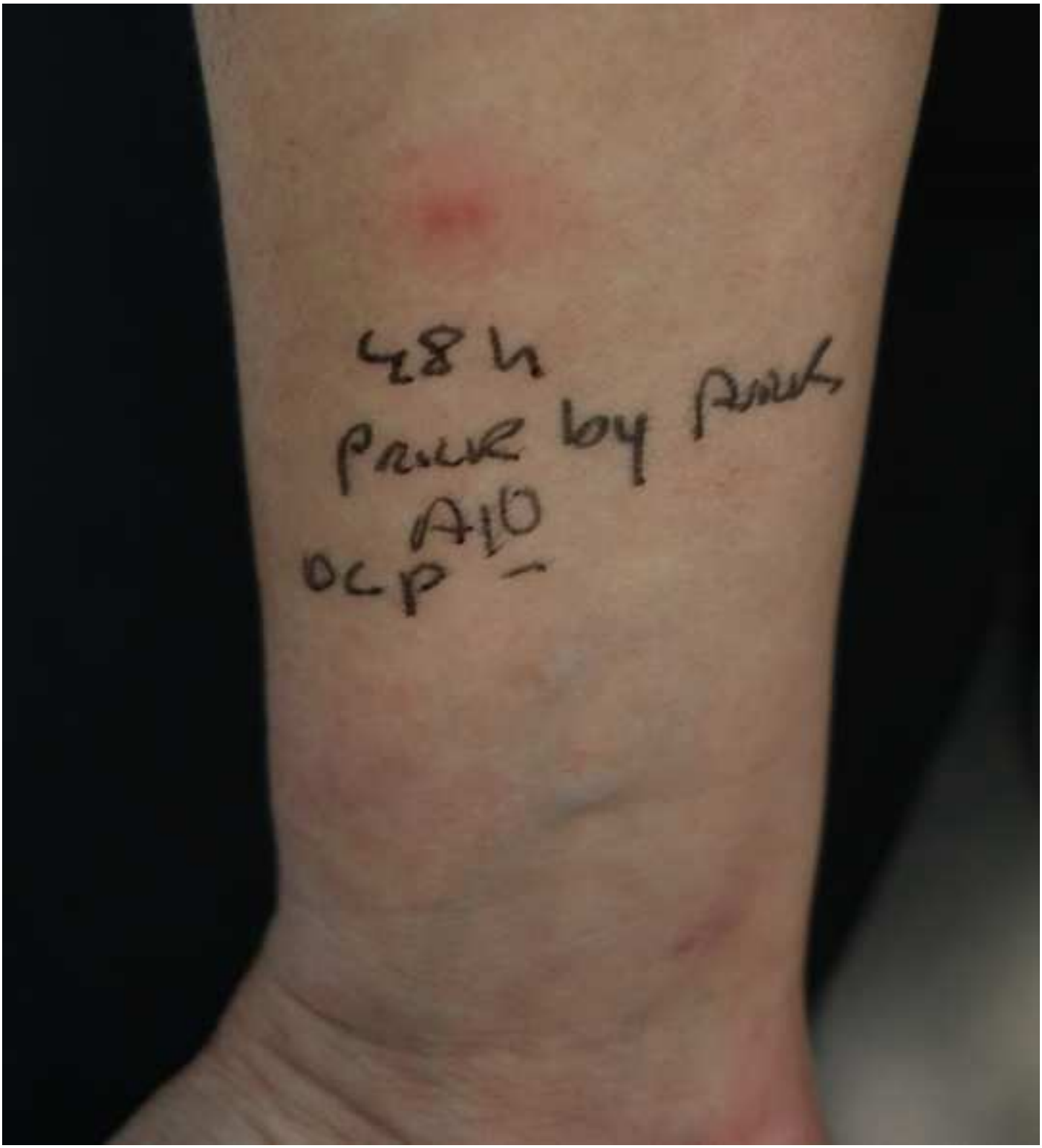

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