Pathomechanisms of phototoxic dermatitis

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A young lady applied herbal mask of common rue *(Ruta graveolens)* onto her face. After that, she took a nap on a balcony in the full sun. An hour later, she woke up with a burning sensation, erythema and oedema of the skin. A few hours later, painful erythema and oedema developed. Subsequently, she developed a bullous reaction, which became superinfected in the following days. After treatment of the secondary infection, the inflammation resolved within 5 days, however, postinflammatory hiperpigmentation persisted over 1 year of follow-up.
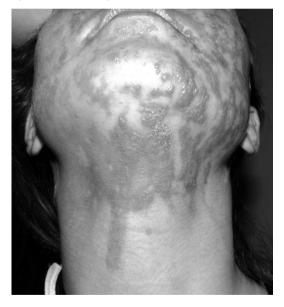

Figure 1. Phototoxic reaction to *Ruta graveolens*

This short clinical history demonstrates typical features of a phototoxic reaction:
• the reaction develops after applying a substance with phototoxic activity.

  Common rue contains 5-methoxypsoralen and 8-methoxypsoralen, which
  are potent phototosensitising agents [1],
- the second factor necessary for provoking the skin reaction is the
  subsequent exposure to sunlight (in case of psoralens, UVA is the active
  range of the sunlight),
- the reaction develops within hours (no involvement of time-consuming
  processes of immunological recognition by antigen-specific lymphocytes),
- phototoxic reactions occur also upon first exposure to phototoxic agent
  (no sensitization phase is necessary),
- in many cases, the reaction resolves with leaving postinflammatory
  hiperpigmentation.

What is a phototoxic reaction?
The terms "phototoxic reaction" and "phototoxicity" refer to an inflammatory
reaction of the skin, resulting from a direct cellular damage produced by the
photochemical reaction initiated by photoactive chemicals (photosensitizers)
and the active spectrum of radiation on the skin. The activation spectrum of
such photochemicals expands from the UVB to the UVA range [2], however,
in a vast majority of patients UVA is the causative factor [3].

There are three elements essential for a phototoxic reaction:
- the radiant energy,
- the chemical,
- the skin (substrate) [2].

Molecules capable of absorbing energy carried by the light are referred to as
chromophores. Photobiologic responses induced by reactions initiated by such
molecules include sunburn and photosensitivity to chemicals and drugs.
There are 2 main pathways of phototoxicity:

- the reactive oxygen species (ROS) pathway,
- the reactive nitrogen species (RNS) pathway.

The most common clinical manifestation of phototoxicity is an exaggerated
sunburn-like response in exposed areas. In many cases, this inflammatory
reaction is followed by localized hyperpigmentation [4]. In contrast to
"classical" sunburn, skin inflammation in the phototoxic reactions is provoked
by UV doses that normally are well tolerated by the skin [3]. In contrast to
photoallergy, no individual- or photosensitizer-specific predisposition is
prerequisite for phototoxic reaction. This means that phototoxicity will occur
already upon the first exposure in most persons of the same skin type, as
long as both the threshold concentration of the photosentising chemical and
the threshold dose of radiation have been reached.

In contrast to photoallergy, no mechanisms of adaptive immunity (specific
antibodies or lymphocytes) seem to be involved into phototoxic reaction.

However, an involvement of innate immunity mechanisms was suggested, such as activation of complement [5], proteases [6], and prostaglandin secretion [7].

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The inflammatory skin disease - photoallergic contact dermatitis (PACD), is a clinical expression of specific immune reactions that takes place in the skin, however, also extracutaneous structures (e.g. lymph nodes, circulating and resident lymphocytes) are involved at some stages of the reaction.

The initiation of the disease symptoms requires an interaction of three substantial elements:

- pre-existing contact hypersensitivity to a given photohapten in the exposed individual,
- exposure of the skin to the offending photohapten (via direct contact or blood-borne),
- subsequent exposure to the light with the wavelength capable of interacting with the photohapten (in most cases, UVA is the active spectrum).

Contact allergy (synonym: contact hypersensitivity) is defined as body's readiness to develop an inflammatory reaction against a specific low molecular weight substance (hapten) upon skin contact [1]. By analogy, photocontact allergy (PCA) can be defined as readiness to develop inflammatory response to a photohapten present in the skin upon subsequent exposure to light. The light supplies energy necessary for the conversion of precursors (prohaptens or prehaptens) into the actual sensitizing photohaptens, or for the initiation of binding between hapten and endogenous carrier protein (photobinding) into a full antigen. The term "photocontact allergy" refers to an altered reactivity of the immune system to a given substance, which is not a disease as such. Certain proportion of people with PCA will never develop clinical symptoms [1].

The aetiology of photoallergic reactions remains unknown: We still don't know, why one individual develops a hypersensitivity to a given photohapten, whereas most people tolerate it. It seems that this process is determined by an intricate interplay of multiple factors, including:

- individual susceptibility (large populations are continuously exposed to numerous photohaptens and light, but only a fraction will develop photoallergy),
- intrinsic properties of a photohapten (there is a relatively low number of substances that are the most frequent causes of photoallergy; an important role is ascribed to the chemical's ability to form photobonds - photosensitised chemical bonds with body's proteins; another important

intrinsic property of a hapten is its irritant potency and ability to trigger so-called "danger signals" in the skin),
- environmental and microenvironmental influences, which may play an important role as co-factors in the breach of immune tolerance to the photohapten that results in the development of PCA, e.g. co-existing infections, inflammation, substances with adjuvant properties.

The natural history of contact allergy (and most probably also of photocontact allergy) can be divided into 2 phases:
- induction phase, in which the hypersensitivity to a given (photo)hapten – photocontact allergy – is developed,
- elicitation phase, following the hapten (or photohapten and light) exposure in a sensitised person.

In the induction phase, usually numerous exposures to a hapten are necessary to induce contact allergy [2,3], depending on the hapten's sensitizing potency [4,5]. This altered reactivity may be acquired months or years before the first clinical contact allergic reaction takes place. A similar pattern could also be true for photocontact allergy, although the picture seems more complex due the involvement of the light into these processes: UV-induced damage of the skin may enhance penetration of photohaptens and leads to infammatory reaction that might have an adjuvant effect during the development of hypersensitivity. On the other hand, in everyday circumstances, photoallergy develops under influence of sunlight, which consists not only of UVA, but also of UVB, which is a potent immunosuppressive agent. An impairment of the induction of contact hypersensitivity (CH) to haptens applied to UVB-exposed skin was demonstrated in both animal and human experiments. It has been suggested that these immunosuppressive effects of UVB are primarily mediated by tumour necrosis factor-alpha (TNF-α) [6,7].

Haptens are low molecular weight chemicals too small to be recognised by the adaptive immune system. However, they can bind to endogenous proteins of the body, causing changes in their spatial conformation. This leads to a recognition of resultant molecules as "non-self" and to initiation of immune response. Such complexes are caught and processed by the Langerhans cells (LC) – dendritic cells resident in epidermis, which belong to "professional" antigen presenting cells. While processing the antigens, LC undergo activation and maturation and migrate along lymph vessels to local lymph nodes. During maturation/migration of LC, lipophilic antigens are transported (endocytosis) into the cell. After processing, antigenic epitopes are presented in the context of major histocompatibility complex I (MHC-I), similar to intracellular (e.g. viral) antigens. Hydrophilic antigens are presented in the context of MHC-II, similar to extracellular (e.g. bacterial) antigens. In the lymph node, LC present the antigens to thousands of lymphocytes passing

through the lymph node. This process is random, yet effective due to a very high turn-over of lymphocytes. If there exist naïve T lymphocytes with T-cell receptors (TCR) capable of specific recognition of the presented antigen, these will eventually encounter the LC, recognise the antigen, and start activation and proliferation into antigen-specific effector cells. Depending on the type of antigen and the context, in which the antigen is presented (MHC-I or MHC-II), respectively CD8(+) or CD4(+) lymphocytes will recognise the antigen and proliferate. This phenotype determines further immune reactions, correspondingly to the secretory profile and cytotoxic properties of respective T cell types, which may be Tc1, Th1, Tc2, Th2, possibly also NKT1, NKT2. In the lymph node, antigen-specific lymphocytes are also assigned to the respective target organ (the skin in the case of PACD). During this process, the cells acquire organ-specific "homing antigens", e.g. the cutaneous lymphocyte antigen (CLA). It seems that also chemokine receptors may play role as determinants of the target organ. This "addressing" of the lymphocytes is probably determined rather by soluble factors present in the lymph draining into the lymph node, than the type and origin of the antigen presenting cell itself [8]. After maturation, specific effector lymphocytes migrate to the skin site of the initial hapten penetration and may initiate an inflammatory response there. Some of the effector lymphocytes will turn into long-lived effector memory T cells that will circulate in the body as a part of immune surveillance. Some will reside in the skin, especially in the site of previous hapten exposure (local immune memory). These circulating and resident antigen-specific effector memory lymphocytes are the physical substrate of (photo)contact hypersensitivity.

Subsequent exposures to the offending photohapten and light will result in a cascade of processes referred to as elicitation of photoallergic contact dermatitis. The elicitation phase takes a significantly faster and more violent course. At this stage, the involvement of professional antigen presenting cells is no longer prerequisite. Sufficient for the initiation of the immune response is antigen presentation by keratinocytes (KC), which constitutively express MHC-I, moreover, they can also express MHC-II in a range of skin conditions. Notably, tumour necrosis factor alpha (TNF-α) – a potent stimulator of MHC-II expression on KC, is released in large amounts upon UVB irradiation, which may play an important role in the elicitation of photoallergic contact dermatitis [9].

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