Dermatological Manifestations of Toxic Agents

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ABSTRACT

A great variety of cutaneous disorders can be seen as reactions to toxic substances. To limit the extent of this review, cutaneous manifestations known to have an immunological mechanism are simply listed with pertinent references. The report has been focused to cover the cutaneous manifestations of toxic agents of non-immunological and unknown mechanisms. Entities discussed include acne, alopecia, dermatitis caused by spider bites, pityriasis rosea, and chemically-induced scleroderma.

Introduction

In general, the human body may develop toxicity to any chemical substance to which it might get exposed. Therefore, toxic reactions may be seen with medicinal agents, social drugs, pharmacologically active food constituents and environmental poisons.

Exposure to a given toxic agent may be accidental, suicidal or homicidal.

Dermatological manifestations of exposures to toxic agents may become apparent immediately or may take days, weeks or years to develop. Their severity may vary from mild to life threatening.

According to the mechanism of action, these toxic dermatologic reactions can be classified as immunologically mediated, non-immunologically mediated and by unknown mechanisms.

Cutaneous manifestations characteristic of immunological responses have been well studied and are listed in table I. The manuscript is limited to some of the cutaneous reactions caused by toxic substances by either non-immunological or unknown mechanisms.

The material selected is not inclusive but covers reactions seen that the present authors found to be most interesting for toxicologists and pathologists.

ACNE

Numerous substances are known to cause acne. Testosterone and chlorinated compounds may cause comedones and cysts similar to acne vulgaris. It is possible that chloracne is the most sensitive indicator of poisoning by chemical chlor-acnegens in humans. The malar and
TABLE I
Dermatological Manifestations to Toxic Agents by an Immunological Mechanism

| Urticaria24,37,47,51 |
| Morbilliform eruptions12,26 |
| Pruritus13,45 |
| Allergic cutaneous vasculitis (Leukocytoclastic vasculitis29) |
| Allergic contact dermatitis1,3,31,43 |
| Photoallergic eruptions14,43 |
| Granulomas34 |
| Erythema multiforme20,21,27 |
| Lupus erythematosus40,42,46 |
| Pemphigus25 |
| Toxic epidermal necrolysis38 |

Alopecia

The most common chemically-induced alopecia is that produced by antineoplastic drugs, especially bleomycin, cyclophosphamide, fluorouracil and vincristine. The hair loss is usually diffuse and of the anagen effluvium type rather than the telogen effluvium type. Fortunately, this effect is reversible after discontinuation of the drug, but the new hair may be of a different texture or color.16

Bullous Lesions in Drug-Induced Coma

This form was originally described in barbiturate coma; however, other comatose states can cause these bullous lesions. Generalized and localized hypoxia have been implicated as the etiologic mechanisms. Histologically intraepidermal and subepidermal blisters are associated with sweat gland necrosis.35

Dermatitis Caused By Spider Bites

The spiders are arthropods that belong to the class Arachnida; they are not insects. They are characterized by a cephalothorax, an unsegmented abdo-

**Figure 1.** Acneiform lesions caused by ingestion of corticosteroids.
men, four pairs of legs, and a pair of small leg-like appendages.

Pain, swelling, erythema, papule, bleeding, ulcers, and large necrotic areas may be seen as a response to a spider bite.

The most recognizable spiders are the Black Widow spider (Latrodectus mactans) which usually cause a mild reaction in the skin. This is accompanied, however, by excruciating pain and systemic symptoms. The treatment usually is symptomatic and rarely is the use of antiserum needed.48 The small, eight to nine mm long, brown house spider, Loxosceles reclusa, produces a gangrenous slough at the bite site. The recommended immediate treatment for this lesion is ice and immobilization.28 Heat is not recommended because the active enzyme in this spider venom is a lipase, sphingomyelinase D, which increases activity as the temperature rises.

There are other species reported as causing dermatological signs and symptoms as, for example, the sac spider Chiracanthium mildei30 and Wolf spider (Lycosidae).6

Lichenoid Eruptions

These reactions may be identical to lichen planus or slightly different not only clinically but also histologically.17,33 Gold salts, dapsone, furosemide and antimalarials have been implicated in lichenoid drug reactions.

Pityriasis Rosea-like Eruptions

Numerous drugs, including barbiturates, captopril, and isotretinoin, have been reported to produce pityriasis rosea-like eruption.36 Ten percent of the adverse reactions to gold therapy may have the appearance of pityriasis rosea. Clinically, however, there are slight differences from the classic form of pityriasis rosea. These two forms differ in the number of lesions and the size and distribution of the lesion; histologically, they are practically indistinguishable. Gold-induced pityriasis rosea-like eruption has a smaller number of lesions, but larger in size than the classic form, and associated oral lesions are more common.

Phototoxicity

A phototoxic reaction clinically appears as an exaggerated sunburn reaction. These reactions are dose-dependent on sunlight and toxic agents. While the great majority of photoallergic reactions are caused by external agents, most phototoxic reactions are caused by drugs after oral or parenteral administration, such as tetracyclines and chlorpromazine.50

Pigmentary Alteration

The variety of skin discoloration caused by toxic substances is limited. The most common colors are red, brown, black, blue-gray, yellow, and white.

The pigmentation is caused either by melanin, hemosiderin, lipofuscin, the toxic agent itself, or a combination of these.

Red discoloration is caused by carbon monoxide intoxication and also has been described after inadvertent administration of rifampin to children.4 Brown discoloration caused by increased amounts of melanin may be caused by adrenocorticotropic hormone (ACTH), arsenic, mercury, bromides, and antineoplastic agents, especially busulfan.

Black discoloration may be caused by deposits of iron as in therapy with minocycline.18,19 (figure 2). Blue-gray discoloration may be caused by deposition of heavy metals, gold (chrysiatis), silver (argyria) or bismuth (bismuthia).21 Melanin plays a role in the
Silver particles have preference for the lamina propria of sweat glands which are easily identified by light microscopy. Gold particles are present in the lysosomes of dermal macrophages, and their identification usually requires transmission electron microscopy or electron probe analysis.

Yellow discoloration may be caused by antimalarial drugs.

Hypopigmentation may be observed in arsenic intoxication.

Porphyria

Porphyria cutanea tarda may be caused by alcohol abuse or poisoning by hexachlorobenzene and other chemical substances. Skin lesions seen are photosensitive with blisters, hyperpigmentation, hirsutism, and pseudosclerodermatous thickening seen on exposed skin.

Purpura and Infarcts

Anticoagulant therapy with coumarin derivatives and indandione compounds has been described as causing petechiae, ecchymoses, and hemorrhagic infarcts with necrosis. Histologically, there is occlusion of dermal and subcutaneous blood vessels by fibrin and platelet thrombi without vasculitis (figure 3).
These findings are similar to those of disseminated intravascular coagulation.

Deficiency of protein C plays a role in vascular occlusion by Coumarin.\(^{36,52}\) Coumarin competes with Vitamin K causing a decrease of factor II, VII, IX, and X of the Vitamin K-dependent proteins C and S. Activated protein C cleaves activated factors V and VIII, destroying their procoagulant activity, and also stimulates fibrinolysis, most likely by activating plasminogen activator-inhibitor. Protein S is a co-factor for the actions of activated protein C.

When coumarin is administered to patients with protein C deficiency, the protein C levels fall more rapidly than the procoagulant factors IX and X and prothrombin. This imbalance causes thrombosis. Coumarin-induced thrombosis has not been reported to occur in protein S deficient patients. The difference may be due to the longer biological half-life of protein S compared with that of protein C.\(^{15}\)

**SCLERODERMA**

Scleroderma has been reported as a complication of silicone breast implants for augmentation mammoplasty.\(^{44}\) The disease is similar clinically to the spontaneously-occurring scleroderma (figure 4). The mechanism of production is not known, but an immunological mechanism is suspected. A probably mechanism that has been proposed is the conversion of silicone to silica perhaps by the nicotinamide adenine dinucleotide phosphate (NADP) pathway following macrophage phagocytosis.

Silica then will be the active ingredient with the capacity to cause scleroderma in some patients. The disease may or may not improve after removal of the implants. Silicone granuloma of the breast\(^{11}\) is less rare than this complication.

The toxic oil syndrome is a new chemical-induced scleroderma which appeared in Spain in 1981 and is produced by consumption of cooking oil.\(^{2}\) The exact toxic agent has not been identified; however, trichloroethylene and perchloroethylene found in some of the oil samples are suspected of having pathogenic implications.

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**References**


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