

PRIMARY CONTACT SENSITIZATION SITE

A Determinant for the Localization of a Diphenhydramine Eruption

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Abstract. Oral administration of diphenhydramine (Benadryl®, Parke, Davis & Company, Detroit, Mich.) to a patient was followed shortly by the appearance of a pruritic swollen eczematous plaque strangely localized to the right forearm. Subsequent history revealed that the patient had used Caladryl® lotion (containing diphenhydramine) to treat a dermatitis at that exact site 2 years previously. Patch testing showed a marked sensitivity to diphenhydramine on the forearm, with lesser degrees elsewhere. Uniform "challenge" of our patient's entire skin with minimal amounts of the antigen via the blood stream clearly brought out the unique sensitivity of the right forearm, later documented by regional patch testing. Noteworthy is the fact that the initial localization of this patient's drug eruption was precisely at the site of induction of the contact sensitivity 2 years earlier. These observations are compatible with the view that the skin has local intrinsic lymphoid immunocenters which are involved in delayed hypersensitivity and which account for local or fixed sites of hypersensitivity.

The hallmark of a drug eruption is its symmetry or generalized nature, thus attesting both to the fact that the antigen is blood-borne and that the degree of sensitivity is essentially uniform over the entire skin surface. An exception to this is the drug eruption occurring in individuals (6, 8) or animals (3) who have been initially sensitized to the compound as an external contactant. In these instances the initial or the most severe reaction occurs precisely at the site of the former eczematous contact dermatitis and hence may present in an unusual or asymmetric localization. In view of the paucity of documented examples of this in man, we wish to record the following experience wherein the clinical findings were totally obscure until one had the history of prior contact sensitization to the diphenhydramine (Benadryl®).

CASE REPORT

This 38-year-old white woman, hospitalized for myasthenia gravis, awakened complaining of pruritus sharply localized to the right forearm. During the course of the day the forearm became erythematous and swollen. Her attending physician prescribed diphenhydramine (25 mg orally). By the following morning the right forearm was markedly swollen, erythematous and eczematous. Her pruritus had become generalized and patchy eczematoid changes were seen more or less symmetrically distributed over the trunk, arms and legs, much as an id reaction.

Called in consultation, we elicited the fact that, 1) the patient had been given diphenhydramine (50 mg orally) as a soporific the evening before the eruption began; 2) two years ago after using Caladryl® lotion (containing diphenhydramine) for 1 week in the treatment of a poison ivy dermatitis of her right forearm, she had experienced a severe vesicular flareup of that exact area; 3) 1 year ago the use of Caladryl® lotion had also been followed by a local dermatitis.

Past history included a thymectomy at age 34. Physical examination disclosed moderate muscle weakness of the upper and lower extremities, and a 40% bilateral eyelid ptosis. Laboratory data: hemoglobin 13.6 g%, WBC 9 000/mm³, with 65% neutrophils, 33% lymphocytes, and 10% monocytes. Urinalysis, SMA-12, and serum electrolytes were all within normal limits. Serum protein electrophoresis was normal except for a slight elevation of the beta globulins. LE preps, ANA, latex fixation were all negative, and the RPR card test was non-reactive. A chest X-ray was normal (including tomograms of the anterior mediastinum) and EMG studies were consistent with a diagnosis of myasthenia gravis.

Following oral and topical steroid therapy the eruption subsided and had largely cleared within 5 days.

Subsequent closed patch tests (on unstripped skin) with diphenhydramine powder on the forearm gave a 4+ vesicular response whereas on the lower leg only a 1+ erythematous change was elicited. On the back, nothing appeared except some epidermal separation due to the tape trauma. Erythematous positive patch tests (1 to 2+) were seen at the sites tested with pyribenzamine, chlortrimeton and antistine. The following closed patch tests on the back were negative:

aminophylline	lanolin
arsenate, sodium	mercury bichloride
balsam of Peru	Mycolog cream®
benzocaine	nickel sulfate
DDT (dichlorodiphenyl trichlorethane)	paraaminobenzoic acid
dichromate potassium	pyrethrum
iodochlorhydroxyquin	resorcinol

DISCUSSION

Antihistamines are known to produce a variety of cutaneous reactions including urticarial, photosensitivity, angitic, eczematous and fixed (2, 4, 7, 10). Nonetheless, cutaneous eruptions following oral or parenteral diphenhydramine are uncommon (6). If a problem is to arise, it most likely will be eczematous in nature, and reflect the earlier induction of delayed hypersensitivity by local contact. Our patient presents just such a sequence. The repeated application of diphenhydramine, in an adequate concentration, to a local area of "open" dermatitic skin, induced specific contact sensitivity 2 years ago. This was confirmed clinically a year later by use of the same lotion. The patient's next challenge was not topical but rather systemic, in the form of a single oral dose.

It is the singularly localized response to this challenge which we are reporting and stressing. Only the right forearm erupted, at first, and even later the bulk of the response was entirely limited to this same site. Our feeling that this was indicative of a hypersensitivity localized to the original site of sensitization was in keeping with the patch test finding that the forearm was markedly more sensitive than other areas of skin.

It is established clinically and experimentally that contact type delayed hypersensitivity is an immune state involving the lymph nodes, and that the entire skin surface is accordingly capable of reacting. Yet gradually, peripheral sensitization (1, 9) and the special micro lymph organs within the skin itself (5) are being shown to play primary or auxiliary roles. In our patient the entire skin was uniformly exposed "internally" to the antigen at the time of oral challenge. Yet only the primary sensitization site responded.¹ In contrast,

had the regional lymph node mechanism been fully involved, the initial eruption would have been generalized. We suspect that the marked clinical response of our patient's forearm skin to the circulating diphenhydramine reveals the persistent functioning of local immunocenters within the skin itself.

Our case study thus illustrates several important items:

1) The initial site of an eczematous reaction to an oral or parenteral drug can be indicative of the site of primary contact sensitization.

2) The history of Caladryl® sensitivity should alert one to the possibility of a sensitivity to diphenhydramine and its antihistaminic congeners.

3) Patch testing for this type of drug sensitivity should be done at or near the area of response. In this regard the classic fixed drug eruption is an extreme example where tests will usually be negative unless done at the exact site of the dermatitis (11).

4) Patch tests may be quite meaningful in unraveling the nature of eczematous contact type dermatitis medicamentosa.

5) There is a growing awareness that nests of immunocytes within the skin contribute significantly to the response in contact dermatitis. Thus an oral inadvertent challenge with a contact antigen allowed us to suspect a peripheral sensitization based on a local lymphoid response within the skin. Such local skin sensitization, although it may occur regularly, is masked when the regional lymph nodes produce the commonly observed generalized sensitivity state.

In conclusion, it would seem that delayed hypersensitivity in the skin consists of a dual system of lymphoid response, 1) intracutaneous, and 2) intranodal. When only the primitive lymphoid organs within the skin are involved, the classic fixed drug eruption develops. Here, a single "clone" of sensitized lymphoid cells within the skin could explain the striking, circumscribed, round area of localized response to a given drug either by mouth or by "supra-lesional" patch test. In our patient, both immunologic systems apparently had responded, but the regional lymph node apparatus, to only a minor degree. This has allowed us to postulate the significance of the sensitized lymphoid cells in the skin of her right forearm, and hence the occurrence of a true peripheral sensitization state.

¹ We would cite personal knowledge of a laboratory technician who spilled penicillin solution on his chest, developed a streaked dermatitis in the area, which healed without trace, only to reappear dramatically on the same site ten years later—following oral penicillin therapy.

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Received February 14, 1972

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