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CLINICAL REPORT

Fixed Drug Eruption: Primary Site Involvement on Maximal Points of Head's Zones

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The principles behind the primary localization of lesions in fixed drug eruption are still unknown. Studies investigating the predilection areas indicated drug-related, trauma-related or inflammation-related specific site involvement in fixed drug eruption. This study presents new findings of primary site involvement on the maximal points of Head's zones. In the 3 cases reported here, fixed drug eruption lesions were located at specific sites; the so-called maximal points of Head's zones, which are known to be the most active dermatomal areas of an underlying visceral pathology. An underlying internal disturbance was found in all 3 patients, corresponding to the organ-related maximal point of Head's zones in each case. In conclusion, the primary location of the fixed drug eruption lesions on the maximal points of the Head's zones according to the well-known neurophysiological map is an important observation in studying the predilection areas. ***Key words: fixed drug eruption; Head's zones; localization; primary site involvement; viscerocutaneous reflex; site preference.***

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Fixed drug eruption (FDE) is characterized by the development of recurrent site-specific lesions on the skin and/or mucosae during treatment with the drug responsible. There have been worthy advances in understanding the immunopathology of the site-specificity in FDE, but there is little information about the primary localization of lesions in FDE. It is not known why FDE lesions initiate at a particular site in a given case. There are a few studies investigating drug-related site involvement in FDE (1–3), and some anecdotal reports on trauma-related localization or on the role of previous inflammation in FDE (4, 5). This paper describes the new finding of 3 cases with FDE with primary site involvement on maximal points of Head's zones. Head's zones are known as cutaneous areas of referred pain due to visceral pathology via the viscero-cutaneous reflex route. In the cases described here, it appears that the primary locations of FDE lie within the reflectorially most active parts of viscero-cutaneous referral from a diseased visceral organ (ureter, adnexes or oesophagus), the so-called maximal points of Head's zones.

CASE REPORTS

Case 1

A 16-year-old Turkish girl presented with 2 round- to oval-shaped indurated violaceous plaques, 3 cm and 1 cm in diameter on the left inguinal area and the trunk, respectively, following ingestion of a 275 mg tablet of naproxen sodium. This was her third episode of development of plaques following naproxen intake during the last 6 months. She was treated with methylprednisolone, 40 mg/day i.m., for 3 days. Within one week the lesions cleared, leaving residual hyperpigmentation. She declined to undergo a systemic provocation test with naproxen. The diagnosis of FDE was made according to the history of 3 site-specific attacks definitely following naproxen intake.

The patient reported recurrent urinary tract infection and a chronic pelvic inflammatory disease of 8 months and 2 years duration, respectively.

According to the diagram of maximal points of Head's zones (Fig. 1) (6, 7), the lesion on the left side of the trunk was consistent with Th9 (Thoracic 9)-maximal point on the ventral side of the body (Fig. 2), the known projection point of the kidney and ureter (7, 8). The lesion on the left inguinal region was consistent with L1 (Lumbar 1)-maximal point, designated as projection point of the kidney, ureter, urinary bladder, adnexes, and uterus to the skin via the viscero-cutaneous reflex route (7, 8).

Case 2

A 35-year-old Turkish woman presented with an oval-shaped, violaceous plaque of 3 cm diameter on the right femoral area, on exactly the same site as in an episode two months previously. Histopathological examination was consistent with a diagnosis of FDE. Cotrimoxazole, dipyrone, and diclofenac potassium were the drugs she had taken occasionally during the last 5–6 years because of recurrent urinary infection and lumbar pain

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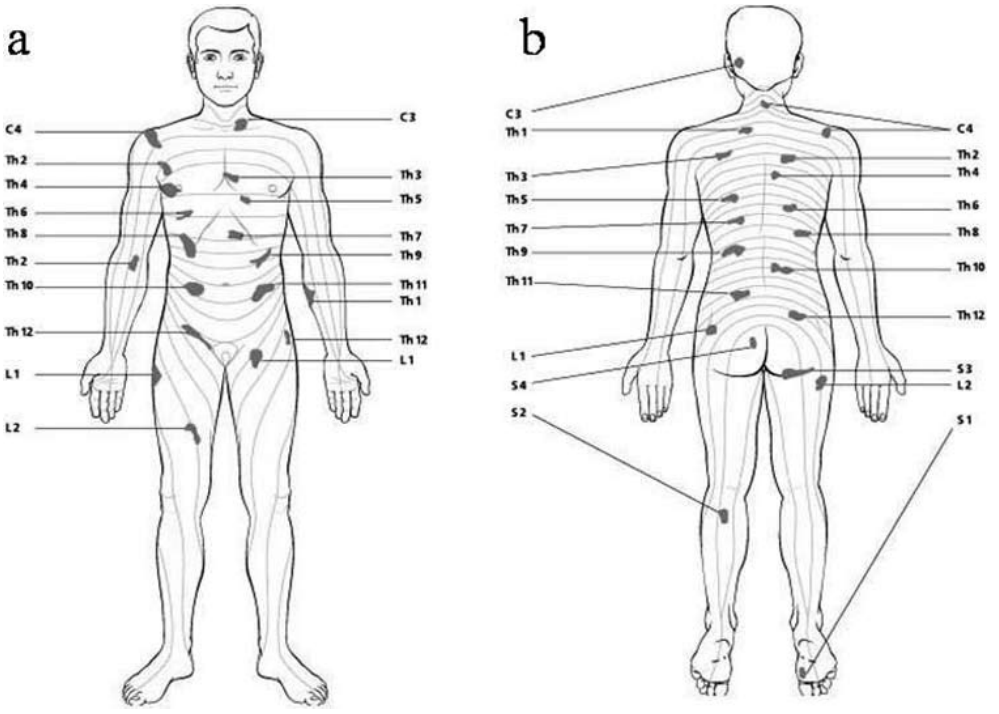

Fig. 1. Dermatomal distribution of the maximal points of Head's zones (modified according to Hansen & Schliack): (a) ventral side of the body; (b) dorsal side of the body (with kind permission of Professor Güneş).

due to stenosis of the right ureter. Within one week of withdrawal of the suspected drugs, the lesion cleared, leaving residual hyperpigmentation. Four weeks later, an oral challenge with one-eighth of a single cotrimoxazole dose led to complete reactivation of the previous lesion, whereas no reaction could be achieved upon systemic provocation with each full dose of dipyrone and diclofenac potassium. The case was diagnosed as cotrimoxazole-induced FDE.

The location of the lesion on the right femoral area was consistent with the L2-maximal point on the right side ventral (Fig. 3), the known projection point of the right ureter (7, 8).

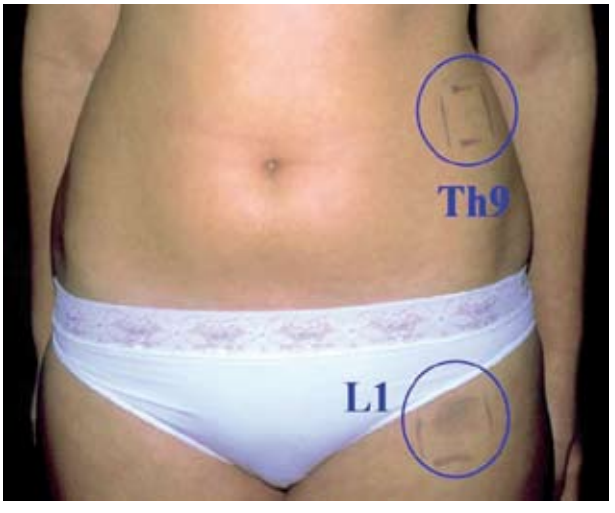

Fig. 2. Case 1. Naproxen-induced fixed drug eruption (FDE) on Th9 and L1-maximal points (left side ventral). Recurrent urinary tract infection and chronic pelvic inflammatory disease (corresponding Head´s zones for kidney and ureter: Th9–L3; urinary bladder: Th11–L3, S2–S5; adnexes: Th10–L4; uterus: Th10–L3, S1–S4).

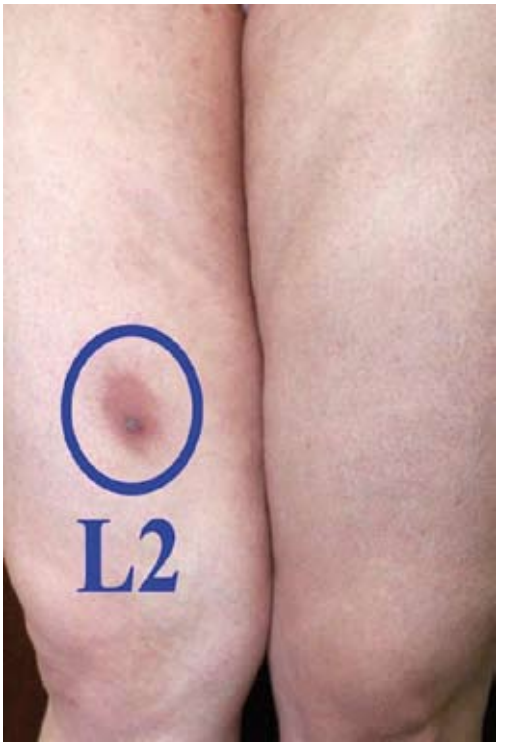

Fig. 3. Case 2. Cotrimoxazole-induced fixed drug eruption (FDE) on L2-maximal point (right side ventral). Right ureter stenosis and recurrent urinary infection (corresponding Head´s zones for kidney and ureter: Th9–L3; urinary bladder: Th11–L3, S2–S5).

Case 3

A 55-year-old Turkish woman presented with an ill-defined hyperpigmented macular lesion, 1 cm in diameter, on the skin of her back, which had developed over the previous 6 months. The patient reported monthly reactivation of the lesion, with marked redness and oedema, which healed spontaneously within 5–7 days, leaving hyperpigmentation. Histopathological examination was consistent with the diagnosis of FDE.

She had been taking esomeprazole 20 mg p.o. daily for the last 2 years because of gastro-oesophageal reflux and oesophagitis due to oesophageal spasm, with the typical radiographic finding of "corkscrew" oesophagus. In addition, she occasionally took piroxicam tablets (20 mg) for headache.

Upon oral provocation with one-eighth of a tablet (20 mg) of piroxicam the hyperpigmented lesion re-activated with marked redness and oedema, confirming the diagnosis of piroxicam-induced FDE.

The location of the lesion on the skin of the patient's back was consistent with the Th7-maximal point on the left side dorsal, the known projection point of the oesophagus and upper gastrointestinal organs (7, 8).

DISCUSSION

FDE is a distinctive drug eruption characterized by the development of recurrent lesions in the same location each time the responsible drug is taken. There have been recent advances in studying the immunopathogenesis of the disease, showing the role of the persistent intra-epidermal effector-memory CD8+ T-cells in the reactivation, and the role of the regulatory CD4+ T cells, transiently migrating into the epidermis of active FDE lesions, in the resolution of FDE (9–11). However, little is known about the site preference in FDE. It is a mystery why a FDE lesion comes to its primary manifestation in a certain part of the skin.

Attempts to understand the site preference in FDE led to studies investigating the drug-related site involvement in FDE (1–3). Summarizing these few studies, several statistically significant correlations were found between the localization of FDE and the inducer drug. For example, FDE on the male genitalia was significantly related to tetracycline in India (1, 2), but to co-trimoxazole in Turkey (3). FDE on lips (predominantly in females) was significantly related to naproxen (3).

On the other hand, some authors reported the role of a previous trauma in the site preference of FDE (4, 5, 12). Patients were reported in whom FDE lesions initially appeared at exactly the same site as a previous trauma, such as BCG (Bacillus Calmette-Guérin) vaccination (4), burn scars, insect bites, and venepuncture (5), whereas the interval between the original trauma and the initial onset of FDE within this area might vary from days to years, e.g. 22 years in one case (5).

Moreover, it was pointed out that previous inflammatory processes like infections, such as herpes zoster, herpes simplex, or cellulitis, might also determine the site of the primary lesions in FDE (12–14). It was hypothesized that virus-specific memory CD8+ T cells retained in sites of viral infections could be activated by non-specific stimuli, such as cross-reacting drug antigens. Activation of skin-resident T cells by drugs would then result in FDE localized in previously inflamed skin sites (14).

The primary location of dermatoses in certain parts of the skin, i.e. Head's zones, had been first recognized in the 1960s (6, 8, 15, 16). Head's zones are the well-known projection areas of visceral organs to the skin via the viscero-cutaneous reflex route (16–18). The reflectorially most active parts within these areas were defined by Hansen & Schliack as maximal points of Head's zones (Fig. 1) (6, 7).

It was claimed that, in case of a visceral pathology, a reflectorially induced optimal alteration in the terrain could arise within the corresponding Head's zones and especially on their maximal points; thus providing a preferential site for a dermatose to come to its primary manifestation. This alteration in the terrain is closely related to a reflectorially induced alteration in the terminal vascular system, meaning a slowing down of the blood flow and an increase in the permeability and dependent alterations in the metabolism and functions of the related skin site (8, 15, 18). One might consider that the formation of an appropriate milieu would lead to attraction and localized accumulation of drug-specific memory CD8+ T cells in those skin parts. Activation of these skin-resident T cells by specific drugs would then result in FDE primarily localized within these viscero-cutaneous reflex areas.

Hauser (8, 15) reported a wide spectrum of dermatoses, such as fungal, bacterial and viral infections, inflammatory dermatoses, and skin tumours located in certain Head's zones of the corresponding visceral organ pathology. Herpes zoster was one of the most characteristic examples. The viscero-cutaneous relationship was evident in almost every given case of herpes zoster, known as "reflectory herpes zoster" in the older literature (15). However, there is only one study in the literature reporting a dermatosis, i.e., notalgia paraesthetica, strikingly located on maximal points of Head's zones (19).

There is one single case in the literature of FDE located on the Head's zone of a corresponding visceral pathology, reported by Hauser (8). A 62-year-old man developed FDE lesions on the lower back upon ingestion of pyrazolone derivatives because of abdominal pain. He was then diagnosed to have an active ulcus duodeni. The localization of FDE lesions corresponded to the

duodenal reflection field of Th6–Th10. Although not indicated by the author himself, one of the FDE lesions was located on the Th10-maximal point of the related Head's zone according to Hansen & Schliack (Fig. 1).

A re-evaluation of the literature on previously reported FDE cases might also be informative on this subject. For instance, in a series of 113 patients with FDE, 8 patients were reported to have a solitary lesion over the back below the scapula (1). It would be interesting to know the exact location of these lesions because the described area could have been consistent with certain maximal points of Head's zones.

In conclusion, the primary location of FDE lesions on the maximal points of Head's zones in 3 patients was a striking finding that has not been reported previously. Like herpes zoster and notalgia paraesthetica, FDE might be another optimal model for studying predilection areas in skin diseases.

Conflict of interest: None to declare.

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