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CASE REPORT

Ursodeoxycholic acid induced generalized fixed drug eruption

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Abstract

Fixed drug eruption (FDE) is a rare form of drug allergies that recur at the same cutaneous or mucosal site in every usage of drug. Single or multiple round, sharply demarcated and dusky red plaques appear soon after drug exposure. Ursodeoxycholic acid (UDCA: 3 α ,7 β -dihydroxy-5 β -cholanolic acid) is used for the treatment of cholestatic liver diseases. Some side effects may be observed, such as diarrhea, dyspepsia, pruritus and headaches. We encountered only three cases of lichenoid reaction regarding the use of UDCA among previous studies. In this article, we reported a generalized FDE case related to UDCA intake in a 59-year-old male patient with cholestasis for the first time in the literature.

Keywords

Bile acids, generalized fixed drug eruption, ursodeoxycholic acid

History

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Introduction

Fixed drug eruption (FDE) is the occurrence of a reddish-brown swelling in a same site after every intake of drug. The mechanism for this remarkable phenomenon is obscure. The most affected areas are the face, backs of the hands, genitalia, limbs or mouth. Generalized FDE is rarely seen. It mostly occurs depending on usage of single drug, however, emergence of this disorder is also known to form after combined intake of several drugs. The most common causative agents are antibacterial substances, barbiturates and other tranquilizers, non-steroid anti-inflammatory drugs, phenolphthalein and related compounds¹. Ursodeoxycholic acid (UDCA) is used for the treatment of various cholestatic disorders. It is normally present in human bile at a low concentration of almost 3% of total bile acids².

In this paper we present fixed drug eruption caused by UDCA for the first time in the literature.

Case

A 59-year-old male was admitted to our clinic with complaints of erythematous lesions on his body. He received UDCA for cholestasis, and lesions developed on his body after five days exposure to drug. Primary diagnosis of our patient was cholelithiasis. He was taken UDCA due to gallstones. The patient had no history of non-steroidal anti-inflammatory drugs intake before. There were neither similar complaints before nor any history of other drug use. As a drug, the patient has used only pantoprasole for five years

because of stomach pain. However, he said that, he hadn't a similar complaint before. Patient had a negative history of skin reactions until that time. This was the first episode of FDE. A dermatological examination revealed multiple round, sharply demarcated, dusky red plaques on the trunk and abdomen. Lesion sizes ranged from 1 to 10 cm (Figure 1). The systemic examination was normal. Laboratory results showed no abnormalities. A histopathological examination revealed exocytosis of lymphocytes and rare necrotic keratinocytes, vacuolar degeneration and destruction of the basal layer. Pigmentary incontinence and numerous melanophages in the upper dermis, perivascular and interstitial inflammatory were also found. Infiltrations of lymphocytes were observed in the dermis and these infiltrations were predominantly of mixed type (Figure 2). Biopsy taken from the lesion was determined as FDE. Systemic treatment with levocetirizine HCl in a dose of 5 mg/day was given to patient and topical treatment with mometasone furoate ointment was launched twice daily. At the end of the first week, the lesions regressed and left brown pigmentation.

Discussion

FDE is a clinical condition in which round, sharp edged erythematous and edematous plaque is visible. Patches of blackish or purplish color may sometimes appear as well. Although they can occur anywhere on the body, generally they settle on the face, lips, hands and genital areas³. FDE is generally represented with only one or very few lesions whereas a rare form of FDE that is known as generalized FDE is observed with many lesions. Whenever the causative drug is taken, the illness relapses generally in the same area⁴. Late type cellular sensitivity is considered to play a vital role in etiology of disorder (Type 4c). Familial cases were also

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Figure 1. Close-up view of the violet multiple, round, erythematous lesions on trunk.

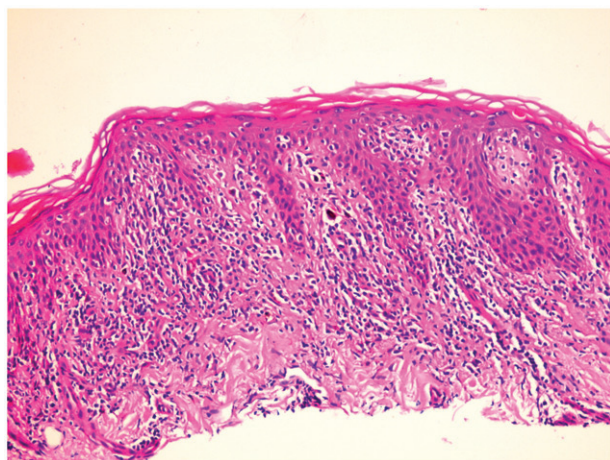


Figure 2. Dyskeratotic cell in epidermis, vacuolar degeneration of the basal layer, incontinence of pigment, melanophages and perivascular lymphocytic infiltration (Hematoxylin-Eosin stain X200).

informed and this status was thought to be associated with genetic tendency. The relationship between FDE with HLA-B22, HLA-A30 and HLA-CW6 antigens has been documented in recent studies⁵. Generalized FDE can occur depending on either a single or sometimes multiple drugs. In FDE, lesions develop 1–2 weeks after intake of the drug³. In present report, lesions developed one week after usage of UDCA in our patient.

Erythematous plaque continues during intake of the drug and disappears a few days or weeks after cessation of drug. Hyper-pigmentation in a grayish tone may remain despite the loss of disease activation. In the last examination of our subject, brown pigmentation was observed in the regions in which lesions originally formed.

Many drugs are known to cause FDE. Among them especially analgesics, sulphonamides and tetracyclines were reported to be causative agents¹. Co-trimoxazole has been informed as the drug, which is most frequently responsible for allergic reactions in many studies⁶. UDCA is used to alleviate a cholestatic condition for liver disease, gallstones and cholestasis related to parenteral nutrition. So far, studies have revealed three cases with lichenoid reactions related to UDCA⁷. However, no cases with generalized FDE have been reported due to UDCA.

UDCA is used in cholesterol gall stone dissolution and primary biliary cirrhosis. It is cytotoxic, immunosuppressive, anti-proliferative, inhibits cellular regeneration and p53. It inhibits DNA repair, co-enzyme A, cyclic AMP, p53, phagocytosis and induction of nitric oxide synthetase. Fever, aggravation of condition, ascites, hepatic function abnormality, increased blood bilirubin, hypotension, diarrhea are common side effects of UDCA. Unexpected reactions of UDCA are hepatitis, pruritus, cholangitis, severe watery diarrhea, pneumonia, dysuria, immunosuppression and mutagenic effects. Other adverse drug reactions of UDCA are convulsions, nausea, vomiting, sleep disturbance, diabetes and cancer breast⁸. Skin side effects of UDCA are pruritus, lichenoid drug eruption, morbiliform eruption and leukocytoclastic vasculitis^{6,9,10}. The cytotoxic effect of UDCA may have given rise to fixed drug reaction.

An intense lichenoid inflammation with increased infiltration of lymphocytes at the epidermal – dermal junction is observed in histopathological examinations of acute lesions. Frequently, hydropic degeneration of the basal cells is seen with necrosis. Intensive edema is also observed with subepidermal blister. Basal layer hyperpigmentation and macrophages loaded with melanin are often detected¹¹. In our patient, skin biopsy specimens of erythematous lesions were in consistent with FDE.

Generalized FDE can be confused with lichenoid eruption, erythema multiform and Stevens–Johnson syndrome. Furthermore, ashy dermatose, lichen planus pigmentosus, urticaria pigmentosa must be considered in differential diagnosis during the hyperpigmentation phase¹².

The causative agent can be confirmed by oral challenge. Although oral challenge test seems to be the safest method to identify the causative agents, it always cannot be performed because of risky situations. Development of generalized bullous eruption was detected depending on this test, therefore, some authors do not recommend this test. Topical and intradermal tests have been used as an alternative to foregoing test^{13,14}. We did not apply oral provocation test to our case due to his generalized involvement. Patch test of UDCA was performed but result was negative. Negative test results do not exclude FDE¹³.

Conclusion

There is little data in literature concerning skin reaction associated with UDCA. It is known as an innocent drug. Previously a few lichenoid drug eruptions have been reported related to UDCA. However, this is the first study in the literature reporting FDE caused by UDCA.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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