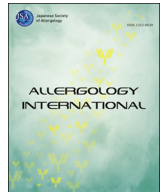




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Letter to the Editor

A case of fixed drug eruption caused by loxoprofen sodium hydrate

Dear Editor

Fixed drug eruption (FDE) is a cutaneous adverse drug eruption characterized by skin lesions which recur in the same sites upon re-exposure to the drug.^{1,2} It may occur as single or multiple lesions affecting any part of the body, with predilection for the genitalia, hands and lips.¹ Loxoprofen sodium hydrate³ (LX-P) (Loxonin; Daiichi Sankyo Co., Ltd, Tokyo, Japan) is a nonsteroidal anti-inflammatory drug (NSAID) that was approved in Japan in 1986. Amoxicillin hydrate⁴ (AMPC) (Sawacillin; Astellas Pharma Inc., Tokyo, Japan) is an antibiotic that was approved in Japan in 1974. Here, we report a case of a 38-year-old man diagnosed with FDE caused by LX-P.

A 38-year-old man visited the emergency department in our hospital for diagnosis and treatment of erosions on the lip and intraoral mucosa that had been present for 3 days. Two weeks before his first visit to the emergency department, he had taken azithromycin hydrate for 1 day, oseltamivir phosphate for 3 days, and LX-P for 5 days to suppress the symptoms of common cold. On the following day, he noticed an erosion on the left side of lower lip. The erosion was healed spontaneously in 3 days. Three days later, he started taking LX-P for 5 days and AMPC for 1 day because he still had the symptoms of common cold. During this period, he noticed a fever over 37 °C and severe erosions on the lip and intraoral mucosa. Therefore, he stopped all drugs and visited the emergency department (on day 3 after the onset of second eruption). The emergency room doctor suspected herpes simplex virus (HSV) infection and prescribed valacyclovir hydrochloride 1000 mg/day for 5 days. Two days later (on day 5 after the onset of second eruption), he visited our department.

Deep erosions were present on the left side of lower lip (Fig. 1a), intraoral mucosa, and glans penis (Fig. 1b) with normal body temperature (36.5 °C). There were no clinical ocular symptoms or erythematous skin lesions. He complained of difficulty in mouth opening because of the severe intraoral pain. He stated that he noticed new erosions on the glans penis this morning. Laboratory tests were within normal limits, including liver and kidney functions. The white blood cell count (8800/μl; normal range, 3400–7300/μl), including neutrophils (6590/μl; normal range, 1214–5110/μl), and serum levels of C-reactive protein (0.79 mg/dl; normal range, 0–0.2 mg/dl) were slightly elevated. The eosinophil percentage (0.2%; normal 0–8%) was within normal limits. The negative serological tests for syphilis and human immunodeficiency virus were seen. No fungal infection on the glans penis was identified by a potassium hydroxide test. On the basis of his

history and these rapid test results, herpesvirus infections, autoimmune blistering diseases such as pemphigus vulgaris and cicatricial pemphigoid, and FDE or Stevens–Johnson syndrome (SJS) caused by LX-P, AMPC, azithromycin hydrate, or oseltamivir phosphate were considered. We recommended him to start treatment with oral steroids in case of SJS, but he refused the treatment. After 3 days (on day 8 after the onset of second eruption), the difficulty in mouth opening as well as the erosions on the lip (Fig. 1c) and glans penis (Fig. 1d) tended to improve spontaneously. HSV type 1- and 2-specific antigens were not confirmed in smears on a prepared slide from the scrapings of the erosion of the lip. HSV and varicella zoster virus showed serological past-infection patterns. The serum autoantibodies against desmoglein 1 and 3, and bullous pemphigoid antigen 180 were all negative. Therefore, we excluded herpesvirus infections and autoimmune blistering diseases. Lymphocyte transformation tests (LTTs) to azithromycin hydrate (stimulation index [SI], 1.4; normal <1.8) and oseltamivir phosphate (SI, 1.3) were negative (a negative control, 174 counts per minute [cpm]; a positive control, 102232 cpm), but the positive LTTs with LX-P (SI, 2.9) and AMPC (SI, 1.9) were obtained using blood samples taken 9 days after the onset of second eruption (a negative control, 116 cpm; a positive control, 82788 cpm). Based on these LTT results, we diagnosed this case as FDE due to LX-P. On day 13 after the onset of second eruption, all mucous membrane eruptions healed completely (Fig. 1e,f).

This patient had no fever and the lesions resolved spontaneously in a relatively short period of time. Therefore, SJS was excluded. Patch tests and drug provocation tests were not performed because the patient refused the examination. There have been some reports of FDE caused by AMPC.^{5,6} While there have been no reports of FDE caused by LX-P in the English language literature. There have been a few reports of FDE caused by LX-P in the Japanese language literature.^{7,8} In Mizuno et al.⁷ the patch test with LX-P was negative. However, the positive LTT (SI, 5.6) and positive oral provocation test with LX-P were confirmed. In Tanaka et al.⁸ the patch test with LX-P was positive. The oral provocation test with LX-P was not performed. There was no description of LTT with LX-P.

The problem of false positivity in the LTT has been suggested.⁹ Penicillins like amoxicillin are typical haptens. They modify proteins and these might be stimulatory for some T cells of nonsensitized donors and elicit a slightly enhanced proliferation in exposed but not sensitized individuals.¹⁰ Pichler and Tilch¹⁰ proposed an SI >3 to be judged as positive for beta-lactam reactions. Some NSAIDs also slightly enhance the proliferation, which is normally explained by their ability to inhibit prostaglandin E2 synthesis.¹⁰ However, this effect is not seen consistently.¹⁰ In the present case, LTT was positive for both LX-P and AMPC, at a relatively higher level of SI

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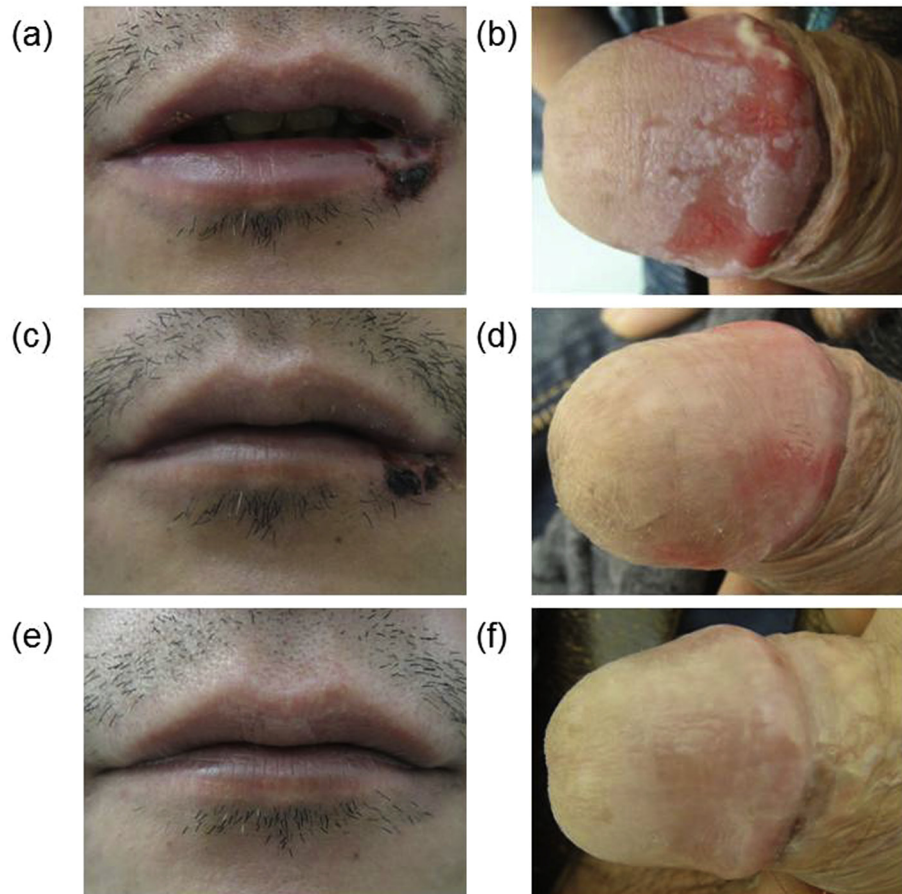


Fig. 1. Clinical photographs (a–f). (a, lip; b, glans penis) At first visit (on day 5 after the onset of second eruption). (c, lip; d, glans penis) On day 8 after the onset of second eruption. (e, lip; f, glans penis) On day 26 after the onset of second eruption.

for LX-P. Therefore, LX-P was considered at least as the causative drug. LTT might be low usability for the diagnosis of FDE. It was reported to be rarely positive in patients with FDE.¹⁰ However, LTT is still considered useful in case the patients with FDE refuse patch tests and drug provocation tests. This case illustrates the importance of medical practitioners being aware of LX-P as potential causes of FDE.

Conflict of interest

The authors have no conflict of interest to declare.

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