Fixed Drug Eruption Associated with Nonsteroidal Anti-Inflammatory Drugs for Menstrual Pain: A Case Report

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Abstract

Fixed drug eruption (FDE) is a type of drug reaction in which cutaneous or mucocutaneous lesions recur at the same site due to repeated administration of the causative drug. The most reported FDE-inducing drugs are nonsteroidal anti-inflammatory drugs (NSAIDs). We report a case of FDE associated with the use of NSAIDs for menstrual pain. A 33-year-old woman was referred to our department with blisters and soreness on her lips, tongue, and labial mucosa. The results of blood examination helped rule out herpes simplex virus infection, pemphigus, and pemphigoid. An FDE was suspected because these symptoms coincided with the use of NSAIDs for menstrual pain. Thus, the patient was advised not to use these NSAIDs but to use acetaminophen instead. No recurrence has been observed since the patient began avoiding these NSAIDs.

Introduction

Fixed drug eruption (FDE) is characterized by a well-demarcated erythematous patch, plaque, or bullous lesions that recur at the same site on re-exposure to the causative drug, and it typically heals with hyperpigmentation. The FDE-inducing drugs most commonly
reported are nonsteroidal anti-inflammatory drugs (NSAIDs), followed by antibiotics, antipsychotics, and herbal substances [1–3].

FDE appears approximately 30 min to 8 h after ingestion of the offending drug [3]. The site of the FDE can be any part of the skin or the mucous membranes; lesions on the lips, extremities, and genitalia are frequently described. Oral mucosal FDEs are mainly bullous and erosive lesions that accompany skin or genital FDEs. The most common oral sites involved are the dorsal aspect of the tongue and the hard palate [4, 5].

Clinically diagnosing oral mucosal FDE may be difficult because the differential diagnosis includes entities such as herpes simplex virus (HSV) infection, autoimmune bullous diseases, erythema exudativum multiforme, Behçet’s disease, and erosive lichen planus, whose clinical appearances may be similar [3–5]. We present a case of FDE manifesting on the lips and oral mucosa after oral administration of NSAIDs for menstrual pain.

Case Report

A 33-year-old woman was referred to our department in August 2018 for diagnosis and management of blisters and soreness on her lips, ventral aspect of the tongue, and labial mucosa. According to the patient, in April 2016, she was aware of soreness on her tongue and blisters around her lips that disappeared within a few days. However, blisters on her lips and ventral aspect of her tongue recurred and disappeared regularly for the next 2 years. In March 2018, she received a clinical diagnosis of herpes stomatitis, and acyclovir was prescribed. However, they were not effective, and autoimmune bullous diseases, such as pemphigus or pemphigoid, were clinically suspected. Prednisolone, 20 mg/day orally, was prescribed for the treatment of autoimmune bullous diseases, but the blisters did not resolve; furthermore, the blisters began to appear on the groin and buccal mucosa as well. In August 2018, the patient presented to our department for further examination.

Her health and nutritional status were good, and her family history did not include a similar condition. On clinical examination, the erosions and blisters were observed around the lips with dark red in color and swelling (shown in Fig. 1). Erythematous lesions as large as approximately 15 mm in diameter were found in the right groin. In the oral cavity, blisters were observed on the labial mucosa, the ventral aspect of the tongue, and the buccal mucosa (shown in Fig. 2). Blood examinations for anti-desmoglein 1 or 3 antibodies (for pemphigus), anti-BP180 (for pemphigoid), and immunoglobulins M and G (for HSV) all yielded negative results, and her most recent complete blood cell count was within normal limits.

One week after the initial presentation, the lesions on the lips spontaneously disappeared, and purplish to brown hyperpigmentation was left at these sites (shown in Fig. 3). The blisters in the oral mucosa ruptured, and epithelialization was observed within a week (shown in Fig. 4). In the medical interview at that time, she complained that the appearance

**Fig. 1.** Clinical picture of the lips at initial presentation. The blisters and erosions on the lips with dark red in color and swelling.

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**Fig. 2.** Clinical picture of the oral cavity. Erythematous lesions as large as approximately 15 mm in diameter were found in the oral cavity.

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**Fig. 3.** Clinical picture of the lips after one week. Purplish to brown hyperpigmentation was left at these sites.

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**Fig. 4.** Clinical picture of the oral cavity after one week. Epithelialization was observed within a week.
of these symptoms coincided with the menstrual cycle. Therefore, we suspected contact dermatitis or drug allergies and consulted the dermatologist in our hospital for medical examination. No immunological abnormalities or infectious diseases were found. Because we then suspected FDE, she was asked about the use of medications during menstruation, and she responded that she habitually took 3 types of nonprescription NSAIDs (ibuprofen, acetylsalicylic acid, and loxoprofen) for menstrual pain. She was therefore advised not to use these NSAIDs but to take acetaminophen (paracetamol) instead. She has experienced no recurrence during menstruation ever since. The final diagnosis was FDE in response to NSAIDs suspected.

In October 2018, patch tests were conducted on the rash and nonrash areas in the groin to identify the causative NSAID, but all results were negative. A drug-induced lymphocyte stimulation test (DLST) was conducted in April 2019 and yielded a negative result. The probable

![Fig. 2. Clinical picture of the blisters on the oral mucosa at initial presentation. a The ventral tongue. b The buccal mucosa.](image1)

![Fig. 3. Clinical picture of the lips at 1 week after the initial presentation. The blisters and erosions on the lips spontaneously disappeared, and the hyperpigmentation was left.](image2)

![Fig. 4. Clinical picture at 1 week after the initial presentation showing the blisters on the oral mucosa spontaneously ruptured and epithelialized. a The ventral tongue. b The buccal mucosa.](image3)
causative NSAID has not been identified conclusively; the provocation test by oral administration of the suspected NSAID could not be conducted because the patient did not consent to it.

**Discussion**

FDE is a type IV allergic reaction (a form of classical delayed-type hypersensitivity reaction) to drugs [3]. It is characterized by the recurrence of lesions at the same sites on re-exposure to the causative drug. The number of involved sites may increase, and pre-existing sites may increase in size with repeated ingestion of the causative drug. Furthermore, after discontinuation of the causative drug, the skin lesions spontaneously disappear and leave hyperpigmentation at the site, whereas oral mucosal lesions heal without residual pigmentation [4, 5]. The clinical features of our case were typical of FDE.

A previous report has shown that the lips were most commonly involved in approximately 48% of cases [4]. Another report has shown that in approximately 30% of patients with established FDE, the oral mucosa is involved [4]. The oral sites of onset are diverse; a previous study showed that the lesions frequently occur mainly on the dorsum of the tongue, the hard palate, the labial mucosa, and the buccal mucosa [4]. In our patient, oral lesions accompanied those on her lips, which was consistent with previous reports. However, it was also seen in uncommon sites: the ventral aspect of the tongue and the buccal mucosa.

Oral mucosal FDE often occurs in 1 of 3 major morphological forms: bullous/erosive (77.1% of cases), aphthous (19.7%), or erythematous (3.2%). Particularly, bullous/erosive lesions are located mainly on the labial and buccal mucosa [4]. In our patient, the oral lesions were mainly blisters.

The differential diagnosis includes HSV infection, autoimmune bullous diseases, erythema multiforme, Behçet’s disease, and erosive lichen planus, especially in cases involving the oral mucosa [3]. In this case, menstruation-triggered HSV infection was mainly considered as part of the differential diagnosis. There are many reports of FDE that coincided with menstruation, as in our case. Some patients received a misdiagnosis of menstruation-triggered HSV infection and received long-term treatment with acyclovir [4].

NSAIDs are the drugs that most commonly induce FDE [1]. In our patient, 3 different nonprescription NSAIDs were suspected of being the causative drugs. In Japan, >140 general medicines, including these nonprescription NSAIDs, include allylisopropylacetylurea, an ingredient that causes hypnotic and analgesic effects [6–8]. Allylisopropylacetylurea is the ingredient most reported as a cause of FDE in Japan. Thus, it is possible that allylisopropylacetylurea caused FDE in our patient because it was an ingredient in the 3 NSAIDs that she used. Over-the-counter drugs are easily available and, as in the case of our patient, are often used not as regular medication but as an occasional single dose; consequently, it is difficult to document the medication history accurately.

Topical and systemic provocation tests can be used to identify the causative drug. Topical provocation tests, such as patch tests, application tests, and DLST, are safe diagnostic first steps. Patch tests frequently yield positive results in lesion sites [3]. DLST rarely yields positive results in patients with FDE, in as much as this disease is not associated with many drug-specific T cells in the circulation [9, 10]. The systemic provocation test is the “gold standard” in diagnosing FDE [3]. Because many patients do not consent to undergo the oral provocation test, FDE is diagnosed, and the causative drugs are identified clinically, based on unique characteristics, especially in patients who have taken a single specific drug. In this case, the causative ingredient could not be confirmed because results of the patch test and DLST were negative, and the provocation test was not conducted because the patient did not consent to it.
Identification and discontinuation of the causative drug is the basic treatment for FDE, and topical or systemic administration of steroids should be considered if symptoms are severe. It has been reported that FDE gradually becomes more severe with repeated occurrences [3]. In a retrospective study, 52.6% of patients had the presence of 5–100 lesions, and extensive generalized involvement was seen in 11.3% [3]. In our patient, the symptom sites gradually multiplied, and the recurrences were suspected of exacerbating the symptoms. Hence, it is necessary to identify the causative drug as early as possible because FDE is not always a mild drug reaction.

Conclusion

In our patient, FDE was caused by NSAIDs taken for menstrual pain. For the diagnosis of FDE, it is helpful to understand 3 features: the time when the causative drug was taken, recurrence after re-administration, and site-specific localization of recurrences. Because our patient’s blisters seemed to increase in number with each episode and because recurrences can increase the severity of FDE, as in cases of Stevens-Johnson syndrome, it is important to identify the causative drug promptly and prevent repeated exposure.

Statement of Ethics

In our hospital, we post information that we will use the patient information obtained through medical treatment in anonymity for education and case reports. Therefore, we do not get a direct signature from the patient. The use of opt-out consent for publication of detail of the medical case and any accompanying images was reviewed and approved by the ethical standards of the Ethics Committee Board of the Faculty of Dentistry of Tokyo Medical and Dental University, Approval No. D2015-575. That is the reason why the study is exempt from ethics committee approval. Additionally, ethical approval was not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Shimizu R., main author and the patient’s oral and maxillofacial surgeons and reviewed the literature and contributed to manuscript drafting; Tsushima F., Komiya R., and Yamagata Y., the patient’s oral and maxillofacial surgeons and reviewed the literature and drafted the manuscript. Harada H., test reading and manuscript editing.
Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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