Case Report

Fixed drug eruptions with intraoral presentation

Rahul Srivastava, Manorama Bihari¹, Jyoti Bhuvan², Ahmed Saad³

Department of Oral Medicine and Radiology, Rama Dental College Hospital and Research Centre, Kanpur. ¹Department of Oral Pathology, Dental College, Azamgarh, Uttar Pradesh. ²Department of Physiology, CM Medical College, Durg, Chattisgarh. ³Department of Dental Surgery, Ranchi Institute of Neuro-Psychiatry and Allied Sciences, Ranchi, Jharkhand, India

Abstract

Fixed-drug eruption (FDE) is an unusual and rare adverse drug reaction. This type of reaction is actually a delayed type of hypersensitivity reaction that occurs as lesions recurring at the same skin site due to repeated intake of an offending drug. Here is a case report of a 58-year-old male patient who developed intraoral FDEs after ingestion of the first dose of ornidazole.

Key words: Allergy, fixed drug eruption, hypersensitivity, drug reaction

INTRODUCTION

According to the World Health Organization, an adverse drug reaction (ADR) may be defined as “A response to a drug which is noxious and unintended, and which occurs at doses normally used or tested in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.”[1] Drug hypersensitivity reactions account for about one-sixth of all ADRs. They comprise allergic and so-called pseudoallergic reactions. The latter is characterized by features of an allergic reaction without detectable reactions of the adaptive immune system.[2] It has been estimated that medical in-patients receive a total of 90 million courses of drug therapy per year and that the frequency of ADRs is about 5%. By limiting the use of the term allergic to those reactions that are immunologically mediated or can reasonably be presumed to be, estimates are that drug allergy may account for 6–10% of these adverse reactions. Recognizing the magnitude of this problem, the National Institute of Allergy and Infectious Diseases noted that if knowledge gained from research findings in drug allergy could be widely used, it should be possible not only to improve diagnosis and treatment but also to prevent allergic drug reactions.[3]

Drug allergy is one type of unpredictable ADR that encompasses a spectrum of immunologically mediated hypersensitivity reactions with varying mechanisms and clinical presentations. It accounts for approximately 5–10% of all ADRs.[4] A wide spectrum of drugs can sometimes give rise to numerous adverse oral manifestations, particularly dry mouth, taste disturbances, oral mucosal ulceration and/or swelling.[5] Fixed drug eruption (FDE) is a rare adverse drug effect. The term FDE was first introduced by Brocq in 1894. FDE is characterized by onset of round/oval, erythematous well-defined macules on the skin and/or mucosa associated with itching and burning sensation. The exact mechanism causing FDE is unknown, although studies strongly suggest involvement of the immune system.[6] The oral cavity may be the target organ for a number of diverse abnormalities that develop from the side-effects of medications.[7] 5-Nitroimidazole derivatives have been used in the treatment of various intestinal protozoal infections for many years. Among these agents, metronidazole is a common anti/protozoal agent that is used worldwide, while ornidazole is a relatively new derivative that is used in some countries in treating particular protozoal infections and that has higher patient compliance because of its longer half-life.[8] Ornidazole is typically employed in the treatment of infections throughout the organism, especially in the case of intestinal infections or vaginal/urinary tract infections, as it has been proven to have a
strong effect against invasive amoeba and anaerobic bacteria. In many cases, ornidazole is also indicated as a prophylactic agent in order to prevent infections from occurring as a result of surgical procedures.[9]

**CASE REPORT**

A 58-year-old male patient reported to the outpatient department (OPD) of the Ranchi Institute of Neuro-Psychiatry and Allied Sciences, Kanke, Ranchi, Jharkhand, India with the chief complaint of dirty teeth. He also wanted to replace his missing teeth. The patient gave a history of dirty teeth since 10 years and he got his teeth extracted (31, 32, 33, 34, 35, 36, 41, 44, 46, 47) 15 years back because of mobility. The patient had history of chewing pan masala with tobacco (three to four pouches per day) since 23 years. There was no relevant family history. The patient used to clean his teeth with commercially available dried tooth powder. On examination, the patient was moderately built and nourished and his vital signs were within normal limits. Intraoral examination revealed a generalized edema of gingiva with bleeding on probing and deposits of stains and calculus. Cervical abrasion was present in 11, 13, 14, 15, 16, 24, 25, 27 and 43 and root stumps of 12, 21, 22, 23 and 43 were also present. The patient was advised complete oral prophylaxis, extraction of root stumps (12, 21, 22, 23 and 43), restoration of cervically abraded teeth and fabrication of prosthesis for replacement of missing teeth. Oral prophylaxis was performed under aseptic conditions and ornidazole 500 mg was prescribed to the patient in the form of tablet with a dose of one tablet twice daily and the patient was recalled after 3 days. The next day, the patient again came to the outpatient department with a complaint of ulcers in the mouth with burning sensation. The patient gave a history of intake of tablet ornidazole and, 6–4 h after ingestion of the tablet, he noticed a burning sensation in the oral cavity along with painful ulcers. Intraoral examination revealed a well-defined erythematous macule in the hard palate approximately 4 cm × 4 cm in size that was located on the mid portion of the hard palate having ill-defined margins associated with some grayish white lesions over the erythematous base. He recalled that 10 years back he had similar lesions on the same locations on taking some anti-diarrheal; on the initial history taking, he had missed on divulging this information. On palpation, all findings were confirmed and the lesion was 4 cm × 3.5 cm in size, shallow, tender on palpation [Figure 1].

Another pseudomembranous lesion was present with erythematous base over the labial vestibule. The lesion was approximately 6 cm × 3 cm in size extending from the right upper buccal vestibule to attached gingiva of 16, 15, 14, 13, 12 and 11, extending mesially across the mid line and extending over the upper left buccal vestibule to attached gingiva of 21, 22, 23, 24, 25 and 26. The lesion was tender on palpation and revealed an erythematous area on gentle rubbing [Figure 2]. Based on history and clinical examination, a provisional diagnosis of mucosal FDE due to ornidazole was given.

The patient was advised to stop intake of ornidazole and he was prescribed prednisolone 10 mg PO thrice daily for 3 days followed by one tablet twice daily for 3 days, followed by one tablet once daily for 3 days along with levocetrizine 5 mg once daily for 7 days. The patient was recalled after 7 days and satisfactory healing was seen [Figure 3].

**DISCUSSION**

Drug hypersensitivity reactions can manifest in a great variety of clinical symptoms and diseases, some of which are quite severe and even fatal.[2] In the clinical setting, ADRs are a common and important public health problem, and they always need to be included in the differential diagnosis of patients under treatment with drugs. There are different classifications of ADRs. The most commonly used classification, proposed by Rawlins and Thompson, differentiates these reactions into two major subtypes:

- **Type A reactions** that are due to a pharmacological propriety of the causative drug and are thus predictable
- **Type B reactions** that occur only in predisposed individuals and are thus hard to predict.[10]

Gell and Coombs classified immune-mediated allergic reactions to drugs, which describes the predominant immune mechanisms involved in these reactions. This classification system includes:

- **Type I** - Immediate-type reactions mediated by immunoglobulin E (IgE) antibodies
- **Type II** - Cytotoxic reactions mediated by immunoglobulin G (IgG) or immunoglobulin M (IgM) antibodies
- **Type III** - Immune-complex reactions
- **Type IV** - Delayed-type hypersensitivity reactions mediated by cellular immune mechanisms, such as the recruitment and activation of T cells.[2,4]

FDE has been reported in male patients after history of sexual contact with their spouses, who were found to be receiving the same medication to which the male partners were hypersensitive.[11]
high doses or frequent doses are more likely to lead to hypersensitivity reactions than a large single dose.\(^4\)

FDE is a type of allergic reaction to drugs. It characteristically recurs in the same sites each time a particular drug is taken. FDE is usually solitary in the initial attack, but with each subsequent exposure, the number of involved sites may increase and preexisting sites may increase in size. The lesions usually develop within 30 min to 8 h of taking a drug. The eruption may initially be morbilliform, scarlatiniform or erythema multiforme like. However, urticarial, nodular or eczematous lesions are uncommon.\(^{11,12}\)

The exact pathogenesis of FDE is unknown, although antibodies, antibody-dependent cell-mediated cytotoxicity and serum factors have been implicated. CD8+ T cells seem to play a major role in initiating epidermal injury by producing interferon \(\gamma\) and interacting with other inflammatory cells. Even if a drug is responsible for activation of CD8+ T cells, it does not seem to be the antigen recognized by CD8+ T cells. The reason for recurrence of lesions at the same site may be explained by the persistence in situ of CD8+ memory T cells. The involvement of CD8+ T cells may suggest a role for cell-mediated hypersensitivity in the pathogenesis of FDE.\(^{13,14}\)

FDE represents a unique CDR pattern characterized by skin lesion(s) that recur at the same anatomic site(s) upon repeated exposures to an offending agent. Most commonly, the skin lesion is a dusky erythematous macule and is usually found on the extremities, lips, genitalia and perianal areas, although any skin or mucosal surface may be involved. The skin lesions may be associated with a burning sensation and may be present in multiple numbers or progress to the development of central vesicles and bullae, particularly after the repeated use of an agent.\(^{13}\)

The most characteristic feature of FDE is reactivation of the inflammatory process in the previously involved site(s) with each subsequent exposure. The classic morphology of FDE lesion is dusky red painful patch(es) that leave long-lasting or permanent deep postinflammatory hyperpigmentation. Other, nonclassic lesions of FDE are occasionally seen, including erythema multiforme, Steven Johnson syndrome, cheilitis, psoriasis, lichen planus-like, hand eczema, melasma, discoid lupus erythematosus, pemphigus vulgaris or hypermelanosis of the vulva and peri-anal area.\(^{11}\)

Intraoral involvement of FDE is rare. To the best of our knowledge, we could find only seven cases of intraoral involvement of FDE in the English literature (Table 1).\(^{15-20}\)
Table 1: Cases of intraoral involvement of FDE

| Authors           | Drug implicated     | Intraoral site       |
|-------------------|---------------------|----------------------|
| Tagami H          | Aminopyrine         | Tongue               |
| Murray            | Tetracycline        | Buccal mucosa        |
| Dhar S            | Amoxicillin         | Tongue               |
| Wersterhof        | Heroin, pyrolysate, methaquaton vapor | Tongue |
| Mahendra A        | Fluconazole         | Palate               |
| Mehta V           | Azithromycin        | Buccal mucosa        |
| Marya C M         | Ornidazole          | Palate               |

FDE: Fixed-drug eruption

The case described here is unique as it involved the intra-oral site of the hard palate, labial mucosa (a site rarely associated with FDE), resulting due to the use of ornidazole.

CONCLUSION

Although allergic reactions to antibiotics account for only a small proportion of reported ADRs, they are associated with substantial morbidity and mortality and increased health care costs. Awareness among dental and medical practitioners about FDE can lead to correct diagnosis and treatment in order to prevent unnecessary morbidity and the potential risk of death from these severe reactions, and to provide proper medical advice on future drug use.

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How to cite this article: Srivastava R, Bihari M, Bhuvan J, Saad A. Fixed drug eruptions with intraoral presentation. Indian J Dent 2015;6:103-6.

Source of Support: Nil. Conflict of Interest: None declared.