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Mucosal fixed drug eruption in a patient treated with ornidazole

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Abstract

Background: Therapeutic drugs have been observed to cause a wide spectrum of adverse oral effects such as dry mouth, gingival enlargement, taste disturbance, oral mucosal ulceration, halitosis, etc.

Observations: A rare case of intra-oral fixed drug eruption (FDE) induced by ornidazole presenting on the hard palate, an extremely rare site for FDE, in a 40-year-old male is reported.

Conclusions: Ornidazole is a relatively newer 5-nitroimidazole derivative commonly prescribed for Amoebic dysentery in developing countries. FDE is a rare adverse drug effect characterized by onset of round/oval, erythematous macules on the skin or mucosa that can be associated with itching and burning sensation. The exact mechanism causing FDE is unknown. (*J Dermatol Case Rep*. 2012; 6(1): 21-24)

Introduction

Therapeutic drugs are known to cause a wide spectrum of adverse oral effects such as dry mouth, gingival enlargement, taste disturbance, oral mucosal ulceration, halitosis and swelling.[1] Fixed drug eruption (FDE) is a rare adverse drug effect. The term FDE was the first introduced by Brocq in 1894.[2] 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 though studies strongly suggest involvement of immune system.[2]

FDE has been associated with the usage of pseudo ephedrine, trimethoprim, tetracycline, barbiturates, salicylates, phenolphthalein, ibuprofen and oxyphenbutazone.[3] Other miscellaneous drugs like acyclovir, griesofulvin, magnesium trisilicate, tranexemic acid and colchicines have also been demonstrated to cause FDE.[3] FDE with skin reactions has been documented in three previously published cases involving ornidazole, a relatively newer 5-nitroimidazole derivative.[4-6] We report a rare case of intra-oral FDE induced by ornidazole affecting hard palate, an extremely rare site for FDE, in a 40-year-old male.

Case Report

40-year-old male in general good health presented to the department of oral medicine at the dental school complaining of burning sensation in mouth for the last two days. Medical history revealed that the patient suffered from gastroenteritis for the last 4-5 days and was currently taking ornidazole 400 mg/day twice a day orally for the last 2 days. The patient was not taking any other medication. Patient informed that he was suffering from the third episode of gastroenteritis in last one year.

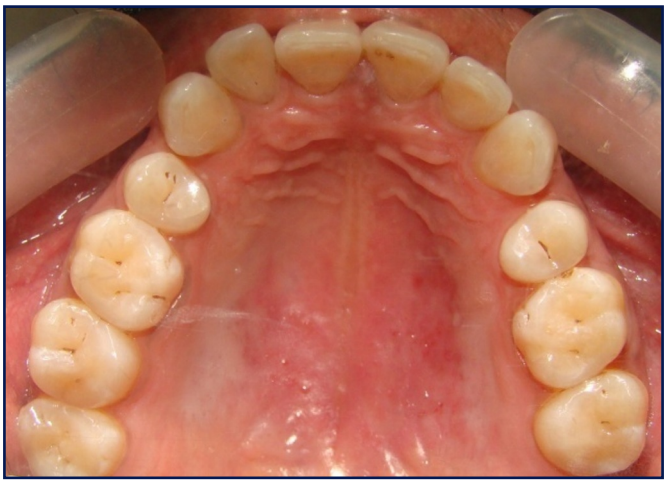

Figure 1

On intraoral examination a 3 × 3 cm well defined erythematous macule was observed in hard palate. There was no evidence of blistering, ulceration in lips and skin.

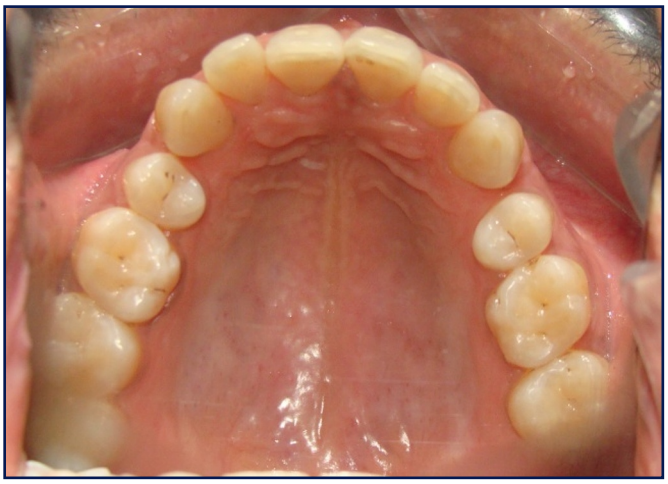

Figure 2

One week follow-up after cessation of drug; complete healing with no scar formation and complete absence of previously noted erythematous macule.

The previous episode of gastroenteritis, about six months ago was also treated with ornidazole and patient informed that he recalled burning sensation in mouth associated with previous episode. Patient had noticed a red lesion on palate and had considered it to be insignificant. He did not complete the seven days course of ornidazole as he had recovered completely from gastroenteritis. Patient informed that the burning sensation had subsided with discontinuing the medication. Patient also informed that he recalled a similar episode of intra-oral burning sensation to the drug tinidazole. The patient did not have a history of tobacco usage. On extra-oral examination, patient did not report any itching and skin examination did not reveal any significant findings. Intraoral examination revealed a 3 × 3 cm well defined erythematous macule with ill-defined margins in hard palate (Fig. 1). A Sony DSC-H50 digital cyber shot camera (9.1 Megapixels) having a maximum optical zoom of 15X with a 2.7-4.5/5.2-7.8 Carl-Zeiss lens was used to image the lesion using occlusal photographic mirror. There was no evidence of blistering in lips and skin. There was no ulceration intraorally. Based on patient's history and no further significant findings, a provisional diagnosis of FDE due to ornidazole was achieved. Ornidazole was withdrawn immediately and patient was prescribed topical triamcinolone acetonide 2 times/day to relieve burning sensation. The follow-up examination one week later revealed complete healing with no scar and complete absence of previously noted erythematous macule (Fig. 2). On the follow-up visit after obtaining appropriate consent an oral challenge test was conducted with 50 mg of ornidazole. The drug in tablet form was taken orally and after 2 hours the patient felt burning sensation in mouth and a small erythematous macule was observed on the hard palate. The patient was informed of the fixed drug reaction observed with ornidazole; a drug belonging to the nitroimidazole group. This information was also conveyed to the patient's physician.

Discussion

FDE is a form of classic delayed type hypersensitivity mediated by CD8+ T cells. The drug is postulated to be acting as a hapten that binds to basal keratinocytes and resulting in the release of lymphokines and antibodies that in turn damage the basal cell layer.[4] On drug intake CD8+ are reactivated to release IFN and cytotoxic granules into the local microenvironment. Mast cells are also believed to contribute to activation of intraepidermal CD8+ cells through the induction of cell adhesion molecules.[7]

All ages are vulnerable to FDE. It has been reported even in infancy. Most of cases usually involve ages 30-40 years. A slight male predilection has been observed in FDE. Most of FDE lesions tend to occur with oral route of administration rather than other routes (like intravenous, parenteral). FDE occurs more commonly in patients who intermittently receive the causative agent rather than continuous administration. FDE lesions tend to be occurring upon the administration of related drugs similar in structure to offending drug (Cross-sensitivity).[3]

The common morphologic presentation is a single erythematous pigmented macule, evolving into an edematous plaque or rarely bullous form. These lesions typically recur at exactly the same site with each frequency of offending drug, but upon the discontinuation of the drug resolves spontaneously, leaving hyperpigmentation. It may be asymptomatic or accompanied by burning or itching sensation. These lesions become more relentless with frequent exposures and new lesions also develop on the previously uninvolved areas. Systemic symptoms such as fever and malaise are generally absent.

Some lesions may evolve into bullous and generalized eruptions which may be potentially life threatening. A rare non-pigmenting variety of FDE consisting of large plaques associated with systemic symptoms has also been documented.[8]

Some cases of recurrent FDE have been attributed to non pharmacological causes like pregnancy, menstrual abnormalities, UV irradiation and food (often referred as Fixed food eruption).[9]

The diagnosis of FDE is generally thought to be straightforward, but due to varied clinical manifestations, it is often can be misdiagnosed as Erythema multiforme,[10] Stevens-Johnson syndrome, Lichen planus and parapsoriasis en plaques,[11] Herpes labialis[12] and Discoid lupus ertyhematosus.[13] The residual hyperpigmentation after the lesions have subsidized is hallmark of FDE. Careful history taking about drug intake and a previous history of recurrent lesions in the same sites are essential for the diagnosis of FDE.

Oral challenge test and topical provocation test are useful in the confirmatory diagnosis of FDE. Oral challenge test is generally done with one-tenth the therapeutic dose of the offending drug.[7] If the reaction is not perceived at the site of FDE, a gradual increase (e.g. 1/8, 1/4, 1/2) is undertaken until the full therapeutic dose is achieved. The appearance of erythema, edema, vesicles and bullae, accompanied by burning sensation, is indicative of positive test. A positive topical provocation test confined to previously involved site is suggestive of FDE. However a negative test does not excludes FDE. Topical provocation test has however got certain limitations, like sensitivity of the patient to metabolite but not to the drug and low concentrations of drug used in patch testing may yield false negative tests. False negative tests may also be caused by the limited penetrability of the drug.[7] In summary, oral challenge test remains the more reliable method for diagnosing FDE. FDE is the only condition in which oral provocation test is ethically admissible.[14]

The erythematous macule found in palate in our case could also have been misdiagnosed with allergic stomatitis. Contact allergic stomatitis tends to involve the entire oral mucosa and a history of contact of an allergen with oral mucosa should be there. There was no history of any usage of mouthwashes, dentrifices or intake of any altered dietary or beverage intake that could have implicated the diagnosis of contact allergic stomatitis. However, the recurrence at same site on taking same medication raised a greater possibility of FDE. The diagnosis of FDE in our case was confirmed by oral challenge test that showed the presence of similar erythematous area in palate using subtherapeutic dose of ornidazole. Oral challenge test remains so far the only reliable method of confirmatory diagnosis of FDE.[15] Histopathological examination was not conducted as patient had reported an improvement in symptoms after withdrawal of the drug and was not willing for biopsy procedure.

The involvement of FDE is generally restricted to mucous membranes and skin, with most commonly involved sites being lips,palms, soles, glans penis and groin area. The most common sites according to Sharma VK, 1996 are trunk and limbs (24%), lips alone (20.8%) and genitalia (20.8%).[16] In intraoral involvement of FDE, the involvement has been restricted to lips and tongue.

Nitroimidazoles are commonly the first line drugs used in treatment of intestinal amoebiasisis. Due to high incidence of intestitinal amoebiasis in developing countries in the south-east Asia, patients are frequently prescribed nitroimidazoles. All the nitroimidazoles; metronidazole, tinidazole, satranidazole, ornidazole and secnidazole, have a similar nitroimidazole group but different side chains.[4] Only metronidazole and tinidazole have been known to cause FDE and have been included in the list of drugs causing FDE.[1] On eliciting medical history patient revealed that he used to get a similar condition due to tinidazole but not to metronidazole. Thus our patient had cross-sensitivity to ornidazole and tinidazole but not to metronidazole. This is different from the previously reported cases where the patients had cross-sensitivity to ornidazole and secnidazole but not to other nitroimidazoles.[1]

Intraoral involvement (excluding lips) of FDE is extremely rare. To the best of our knowledge we could find only six cases of intraoral involvement of FDE in English literature (Table 1).[17-22] Hard Palate is a rare site of FDE. Only one case of FDE has been reported to occur in palate due to fluconazole.[21] The commonest differential diagnosis for FDE in palate is allergic stomatitis and erythematous candidiasis. FDE due to ornidazole in previously documented three cases had involved lips, chest and antero-lateral aspect of thigh.[4-6] Our case described here is unique as it involved the intra-oral site of hard palate, a site never associated with FDE, resulting due to use of ornidazole.

Table 1

List of documented cases of intraoral fixed drug eruption (excluding lips).

Authors	Drug implicated	Intra oral site
Tagami H [17]	Aminopyrine	Tongue
Murray [18]	Tetracycline	Buccal mucosa
Dhar S [19]	Amoxicillin	Tongue
Wersterhof [20]	Heroin Pyrolysate, Methaquaton vapour	Tongue
Mahendra A [21]	Fluconazole	Palate
Mehta V [22]	Azithromycin	Buccal mucosa
Present case	Ornidazole	Palate

Conclusion

FDE is a potential rare side effect that can be observed in patients taking nitroimidazoles for amoebic dysentery. An increased awareness among dental and medical practitioners about FDE will prepare the health care providers to better diagnose and manage FDE. Recent localised skin or oral mucosal lesion should not be neglected and possibility of FDE should be considered in patient who have ties or have recently visited developing countries with high incidence of dysentery. If FDE is suspected then the offending drug should immediately be withdrawn and supportive treatment with topical steroids should be instituted and nutritional supplements should only be given "if needed".

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