Probable etoricoxib-induced fixed drug eruption involving the oral mucosa: A case report

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Fixed drug eruption (FDE) is a cutaneous adverse drug reaction characterized by recurrence of lesions at the same sites each time a specific drug is taken. Oral mucosal involvement is rare. Nonsteroidal anti-inflammatory drugs are one of the most common offending drug groups in FDE; however, selective cyclooxygenase-2 inhibitors, such as etoricoxib, are rarely implicated. We present a case of oral mucosal and cutaneous FDE induced by etoricoxib that, to the best of our knowledge, is the first reported case of this nature. We describe the diagnostic challenges and review the pertinent literature. The value of drug provocation testing and patch testing in FDE is also discussed. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e100–e107)

Fixed drug eruption (FDE) is a relatively common cutaneous adverse drug reaction (CADR), with reported incidence rates varying from 2.5% to 22% of CADRs.[1,2] It is characterized by the recurrence of cutaneous and/or mucosal lesions in the same site or sites each time the causative drug is administered. The reaction usually develops within 30 minutes to 8 hours after intake of the drug and typically appears as well-demarcated round or oval erythematous plaques/macules, occasionally associated with bullae and erosions.[2-5] These lesions may be asymptomatic or cause pruritus and/or burning. Residual postinflammatory hyperpigmentation generally persists at the site after the lesions resolve. Various drugs are implicated in FDE, with some of the most common offending groups including nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, tetracycline antibiotics, sulfonamide antibiotics, and antifungals.[2,6,7]

The pathogenesis of FDE is suspected to be related to resident $CD8^+$ T cells with an effector memory phenotype located within the epidermis of resting FDE lesions. When activated upon intake of the drug, the $CD8^+$ T cells release cytokines such as interferon-γ, which contribute to keratinocyte apoptosis. In fully evolved lesions, the damage is caused in conjunction with $CD4^+$ T cells that are recruited later. T-regulatory cells are eventually recruited to the site to suppress the immune response. A proportion of the $CD8^+$ T cells will escape apoptosis, leading to resident effector memory $CD8^+$ T cells, resulting in lesions in the same locations upon re-exposure of the drug. In addition to their destructive immune response, evidence shows these type of T cells also have a protective function, which may explain why FDE lesions can appear at previous sites of trauma or infection, including herpes simplex virus recurrences.[5,8]

Oral mucosal involvement in FDE is relatively rare. A review of the literature revealed a total of 183 cases of oral mucosal FDE in 43 papers. If oral lesions occur, they typically accompany the more common cutaneous reaction; however, cases of isolated oral mucosal involvement were also reported.[9] Özkaya[9] observed 3 morphologic forms of oral mucosal FDE: bullous/erosive, aphthous, and erythematous, with bullous/erosive the most common. Alongside antibiotics, NSAIDs are one of the most common reported triggers for oral mucosal FDE.[9]

NSAIDs are widely used drugs with analgesic and anti-inflammatory properties. They function by competitively inhibiting the cyclooxygenase (COX) enzymes, COX-1 and COX-2, preventing conversion of arachidonic acid to prostaglandins and thromboxanes.[10] COX-1 is constitutively expressed throughout the body and possesses several "housekeeping" functions, including protecting the gastric mucosa by reducing gastric acid secretions. By contrast, COX-2 expression is absent in healthy tissues and only induced by activated inflammatory cells. COX-2 inhibition therefore provides the therapeutic anti-inflammatory effects of NSAIDs, whereas COX-1 inhibition usually accounts for adverse side effects, particularly

Statement of Clinical Relevance

This case report brings awareness to the diagnosis of oral mucosal fixed drug eruption, its clinical and histopathological presentation, differential diagnoses and management. It highlights that selective COX-2 inhibitors are rarely implicated although reports at cutaneous sites are increasing.

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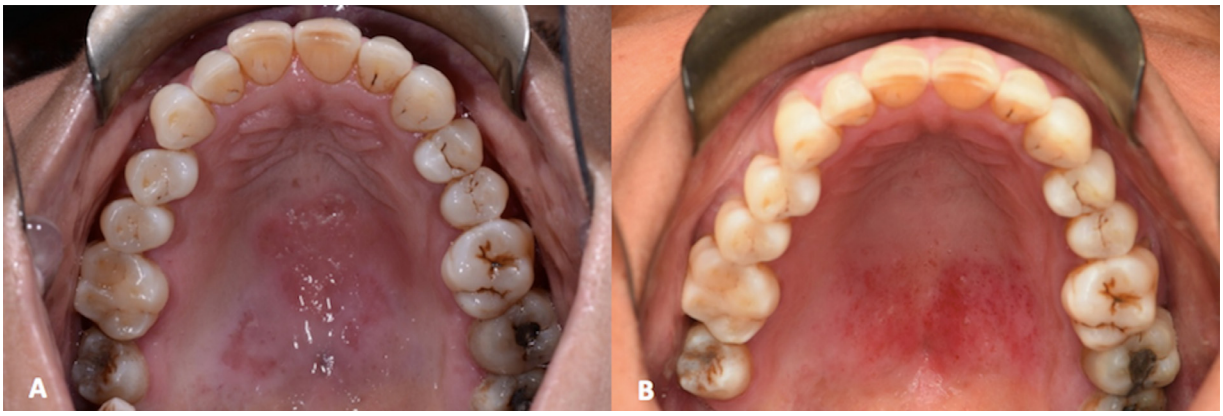

Fig. 1. Atrophic/erosive lesion in the midline of the hard palate: (A) second fixed drug eruption episode and (B) third fixed drug eruption episode.

gastrointestinal related.[10,11] Therefore, selective COX-2 inhibitors were developed to reduce the risk of side effects of traditional NSAIDs.[10,12,13] Celecoxib was the first of these drugs to be approved, in 1999, followed by the development of several others; however, because adverse cardiovascular effects, many have since been removed from the market.[10] Etoricoxib is 1 of only 3 currently licensed selective COX-2 inhibitors alongside celecoxib and parecoxib. It was approved in 2002 and is indicated for treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout.[14]

Selective COX-2 inhibitors are implicated in FDE much less frequently than traditional NSAIDs.[12,15] A review of the literature revealed a total of 47 cases of etoricoxib-induced FDE. Twenty-four of these cases are from the same 2015 review by Heng et al.,[16] whose findings contrast with those of most other studies, which do not show any significant association between FDE and etoricoxib or other selective COX-2 inhibitors.[4,6,9,12,17-19] Though traditional NSAIDS are implicated in oral mucosal FDE, to the best of our knowledge there are no reports of oral mucosal FDE induced by selective COX-2 inhibitors. Furthermore, of the 47 cases of etoricoxib-induced FDE, none reported oral mucosal involvement.

We present a novel case of oral mucosal and cutaneous FDE induced by etoricoxib presenting in an oral medicine setting and review the relevant literature.

CASE REPORT

A 57-year-old female presented to the Oral Medicine Department in Birmingham Dental Hospital with 3 episodes of bilateral palatal blistering and ulceration over a 3-year period. These episodes occurred approximately 18 months apart and were always accompanied by pruritic skin lesions in 3 uniform locations: right forehead, right philtrum, and left neck. Both oral and cutaneous symptoms self-resolved within 10 to 14 days. The patient did not report any prodromal or systemic symptoms and initially could not identify any clear trigger. She did have a preexisting diagnosis of reticular oral lichen planus; however, this was mild, stable, and asymptomatic. Her only other relevant medical history was hypothyroidism, and she took levothyroxine daily for 9 years. She also took occasional NSAIDs as required. She was a nonsmoker.

On examination during her second episode, there was evidence of postinflammatory hyperpigmentation on the right side of the philtrum and left side of the neck. Intraoral examination revealed mild reticular lichen planus bilaterally in the buccal mucosae. There was also an atrophic oval lesion in the midline of the hard palate, with superficial erosions and sloughing (Figure 1A). During her third episode, 20 months later, she had oval erythematous macules on the right side of her forehead, right side of her philtrum, and left side of her neck (Figure 2). These were approximately 10 to 15 mm in diameter. Again, there was an atrophic lesion crossing the midline of the hard palate; however, this was slightly milder in appearance, with no erosions present (Figure 1B). Neither cutaneous nor palatal lesions were typical of lichen planus.

At this stage, the differential diagnoses included herpes zoster, lichen planus, and lupus erythematosus; however, the clinical presentation was not typical for these conditions. Routine hematological, biochemical, and immunologic blood tests were performed. These were normal except for marginally elevated eosinophils 0.6 (normal range 0.04-0.4). antinuclear antibodies (ANA), double-stranded DNA (dsDNA), and epidermal antibodies (indirect immunofluorescence) were negative. No microorganisms were cultured from swabs taken from either palatal or neck lesions.

An incisional biopsy was taken from the palatal lesion. Microscopic assessment revealed inflamed

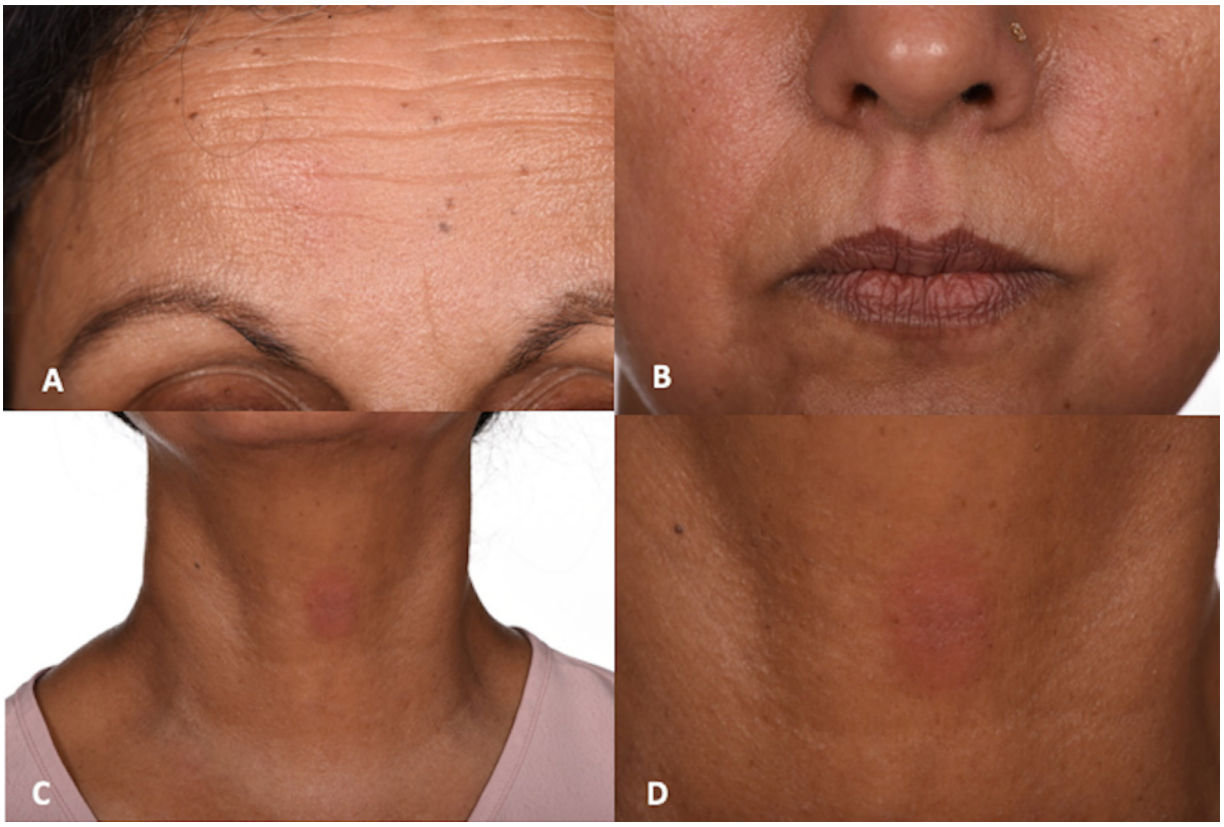

Fig. 2. Oval erythematous macules during second fixed drug eruption episode: (A) forehead, (B) philtrum, and (C), (D) neck.

squamous mucosa with marked epithelial spongiosis (Figure 3A). Variably sized spongiotic vesicles containing eosinophils were seen; eosinophils were accompanied by macrophages, lymphocytes, and neutrophils (Figure 3B). Immunohistochemistry for viral infection (herpes simplex virus and cytomegalovirus) was negative. The features included eosinophilic spongiosis, an unusual reactive pattern with a broad differential diagnosis including precursor vesiculobullous disorders (Table I). Further biopsy for direct immunofluorescence studies was suggested to exclude the possibility of a precursor vesiculobullous disorder, such as mucous membrane pemphigoid.

The patient was prescribed benzydamine hydrochloride 0.15% mouthwash for symptomatic relief and was referred for dermatology opinion. Based on clinical and histopathologic findings, dermatology proposed that the most likely diagnosis was FDE. The patient was advised to keep a diary noting all medications she took except her daily levothyroxine. From this, the patient noted that she had taken ibuprofen multiple times without event but did recall that 30 to 60 minutes before her most recent episode she had taken a different NSAID, Arcoxia (etoricoxib), for joint pain. Because of the length of time since the previous 2 episodes, she could not recall whether any prior medications were taken on these occasions.

Based on patient history and clinical and histopathologic findings, a diagnosis of probable FDE induced by etoricoxib was made. Because the patient was very content to avoid future use of etoricoxib, drug provocation testing was not deemed necessary in this case. She was also advised to avoid other selective COX-2 inhibitors, in addition to etoricoxib, because the risk of cross-sensitivity. Since avoidance she has not had any further episodes in 20 months.

DISCUSSION

Clinical presentation and differential diagnosis

This patient had the hallmark characteristics of FDE: recurrence of cutaneous and/or mucosal lesions in the same sites, developing within 30 to 60 minutes after intake of etoricoxib. Her cutaneous lesions had the typical presentation of pruritic, well-demarcated oval erythematous macules, resolving to leave hyperpigmentation. Her oral mucosal lesions presented in the bullous/erosive form, which is the most common presentation for oral mucosal FDE (77.1% of cases).[9] Since avoiding the offending drug, she has not experienced any further eruptions. Clinical differential diagnoses for this patient include herpes simplex, lichen

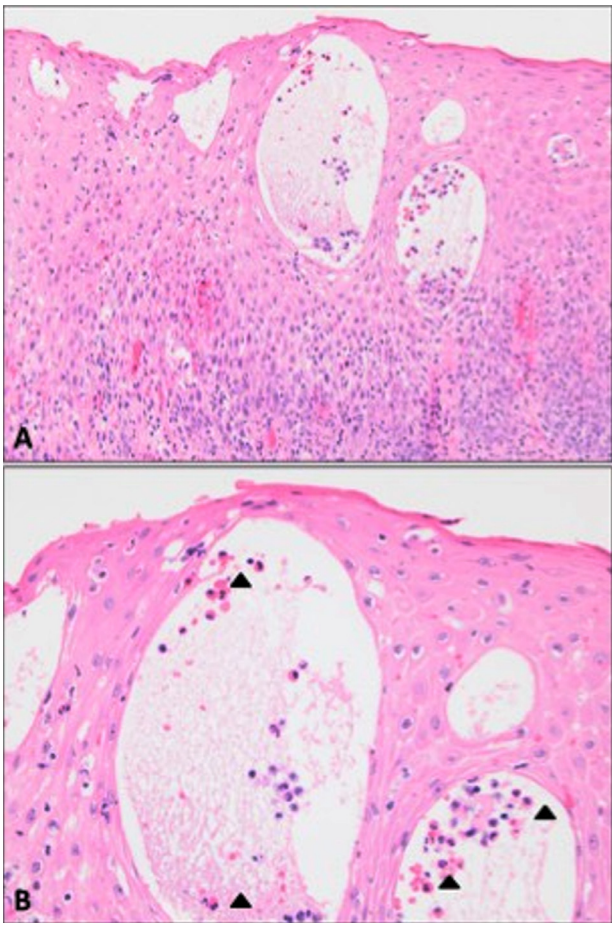

Fig. 3. Histopathological features of the palatal mucosal lesion. **(A)** This hematoxylin and eosin−stained section from palatal biopsy shows inflamed squamous mucosa. The squamous epithelium is spongiotic with intercellular oedema and elongate intercellular bridges. There are several variably sized spongiotic vesicles (× 200 original magnification). **(B)** The spongiotic vesicles contain prominent eosinophils (examples are highlighted by arrowheads), with smaller numbers of macrophages, lymphocytes, and neutrophils (× 400 original magnification).

planus, and lupus erythematosus, although the presentation would be atypical for these conditions. The available literature highlights that diagnosis of oral FDE is challenging; Özkaya[9] found that 44.3% of patients with oral FDE were referred with a prior clinical diagnosis, including Behçet's disease, herpes simplex, pemphigus vulgaris, erythema multiforme, erosive lichen planus, candidosis, and food allergy.[9]

In addition to the clinical history, the histopathology from the palatal lesion revealed eosinophilic spongiosis (ES), which is in keeping with FDE. This finding was not consistent with the aforementioned clinical differential diagnoses. Table I summarizes the pathologic differential diagnoses for ES. From the cutaneous differential diagnoses the pathologist in this case

Table I. Summary of the clinical conditions characterized by eosinophilic spongiosis on diagnostic biopsy*

Conditions characterised by eosinophilic spongiosis
Pyostomatitis vegetans
Pemphigus: precursor lesions, pemphigus vegetans; herpetiform pemphigus
Pemphigoid: bullous, mucous membrane (cicatricial)
Herpes gestationis
Idiopathic eosinophilic spongiosis
Eosinophilic polymorphic and pruritic eruption
Allergic contact dermatitis
Atopic dermatitis
Arthropod bites
Incontinentia pigmenti
Drug reactions
'Id' reactions
Still's disease
Wells' syndrome

*Adapted from Patterson.[48]

suggested that allergic/atopic dermatitis, insect bite, incontinentia pigmenti, and Wells syndrome were ruled out because these are not reported to have oral mucosal involvement. Incontinentia pigmenti is, however, associated with dental abnormalities such as hypodontia and delayed tooth eruption.[20] Wells syndrome, or eosinophilic cellulitis, is a rare inflammatory dermatitis characterized by raised, warm, erythematous skin lesions that persist for 4 to 8 weeks.[21] Although these lesions can recur, their duration, common sites, and appearance are not consistent with our patient's cutaneous lesions. Precursor pemphigus and pemphigoid were also mentioned; however, the clinical suspicion of a vesiculobullous disorder was very low, the lesions had resolved after etoricoxib avoidance, and histopathologic examination from the palatal mucosa did not reveal intra- or subepithelial clefting. Furthermore, indirect immunofluorescence studies were negative, which, although not excluding mucous membrane pemphigoid, would exclude pemphigus vulgaris and bullous pemphigoid. Therefore, a clinical decision was made jointly between oral medicine and dermatology not to perform repeat biopsy for direct immunofluorescence studies.

The preexisting diagnosis of oral lichen planus in this patient appears to be unrelated to FDE; the literature does not describe any known relationship between the 2 diagnoses. The clinical appearance of both oral and cutaneous FDE may mimic lichen planus[9,22]; however, the patient's oral lichen planus was confined to the buccal mucosa, a more common mucosal subsite for oral lichen planus than the palate. Furthermore, the histopathologic features of lichenoid interface mucositis are distinct from eosinophilic spongiosis.[23] Although some lymphocyte exocytosis accompanied

the ES in our case, the histopathologic features were not typical of either oral lichen planus or a lichenoid drug eruption (Figure 3).

Rationale for diagnosis of probable FDE

Systemic or oral drug provocation testing (DPT) is the controlled administration of a drug under close medical supervision and is considered the gold standard diagnostic method for FDE.[9,18,24,25] However, DPT is a potentially dangerous procedure and requires serious ethical, practical, and safety considerations, including a full risk-benefit assessment.[3,9,24,25] In addition, there are no validated protocols or guidelines.[3,24] A position paper on DPT by Aberer et al. advised "DPT should be performed only if other, less dangerous test methods do not allow relevant conclusions"[p. 855] and "with drugs of limited future necessity for the individual patient, DPT should be avoided."[p. 855,24] In our case, the patient had no future necessity to use etoricoxib or other selective COX-2 inhibitors; she was content to use ibuprofen, which she had confirmed did not induce a drug reaction. It could be argued that because this patient's reaction was relatively mild, DPT in this case would not pose any risk. However, FDE lesions can become more numerous and more severe with repeated exposure.[1,8] Therefore, mirroring the conclusions of Aberer et al.,[24] although DPT may be gold standard for diagnosis, in clinical practice it was safer and more pragmatic to simply avoid the highly suspected causative drug and use a safe alternative.

Patch testing is a safer and simpler diagnostic method than systemic DPT; however, it is also not without its limitations and its reliability in FDE is not confirmed.[25,26] It is widely discussed in the literature that the main limitation of patch testing in FDE is lack of sensitivity.[2-4,16,18,25] False negatives occur for several reasons, including insufficient dose or ineffective skin infiltration, and can vary depending on drug type.[2,3,18,25] To reduce the risk of false negatives in FDE, it is essential for patch testing to be performed on lesional skin with nonlesional skin as a control. In a 20-year retrospective review, Andrade et al.[4] showed that nonlesional skin gave a negative patch test result in 98% of patients with FDE.[4] This is thought to be related to the fact that resident memory $CD8^+$ T lymphocytes are located within the lesional epidermis.[3,4,8,25]

Overall, the value of both DPT and patch testing in FDE is still yet to be confirmed, and there are many issues surrounding safety, practicality, and necessity. Furthermore, much of the literature supports that a diagnosis of FDE is most often readily available from clinical history and examination and that provocation tests are helpful diagnostic adjuncts as opposed to crucial for diagnosis.[18,23] Indeed, an observational study of FDE by Heng et al.[16] used the World Health Organization-Uppsala Monitoring Centre causality assessment criteria to classify patients as probable FDE if they had characteristic FDE lesions with identifiable drug cause based on history.[16]

Oral mucosal involvement and drugs implicated in FDE

A literature search performed on July 7, 2020, using PubMed and Web of Science databases using the search terms "fixed drug eruption" AND "oral" OR "mucosal" in addition to hand-searching reference lists revealed a total of 43 papers with 183 cases of oral mucosal FDE. The lips are a common site for FDE; Mahboob and Haroon[17] found that this was the most common site (48%), and other studies have shown similar findings.[1,16] Therefore, it is important to state that in this literature review, lip involvement was excluded unless it clearly specified the labial mucosa. Seven of the 43 papers were observational studies and the others were case reports. Of the observational studies, only one specifically aimed to evaluate the characteristics of oral mucosal FDE; in 2013 Özkaya[9] identified 61 patients with oral mucosal FDE between January 1996 and May 2011. Most of these patients had orogenital FDE lesions (68.8%), whereas 16.4% had oral and skin lesions only, highlighting the rarity of our case.

In 1998, Mahboob and Haroon[17] evaluated 450 patients with FDE to determine the causative drugs and found that 30 patients had oral mucosal involvement (6.67%). In this study, co-trimoxazole was found to be the most common cause of FDE, implicated in 73% of patients.[17] In 2014, Cho et al.[27] studied features of generalized bullous FDE (GBFDE) and found that 9 of 23 patients had oral mucosal involvement (39.1%), which is significantly higher than the findings of Mahboob and Haroon.[17] This may be because this study focused on bullous FDE alone and Özkaya[9] found that the clear majority of oral FDE lesions (77.1%) take on the bullous/erosive form. Cho et al.[27] aimed to differentiate GBFDE from Stevens-Johnson syndrome and toxic epidermal necrolysis. They found that the most important distinction was the lower expression of granulysin in patients with GBFDE.[27] In this study, the most commonly implicated drugs were antibiotics, followed by NSAIDs (30.4%).[27] In 2012, Lee et al.[28] also aimed to identify differences between GBFDE and Stevens-Johnson syndrome/toxic epidermal necrolysis. They found that 12 of 39 patients had oral/lip mucosal involvement (30.8%); however, this was much higher in GBFDE compared to non-GBFDE (44.4% and 26.7%, respectively).[28] Again, this concurs with Özkaya's findings regarding bullous oral FDE.[9] NSAIDs were the most common causative drug group (12.8%) in the Lee et al. study, followed by antibiotics.[28] In 2015, Kavoussi et al.[19] observed 30 patients

with generalized FDE over a period of 9 years and found that 8 patients had oral mucosal involvement (26.7%). Co-trimoxazole was again found to be the most commonly implicated drug (26.1%), followed by metronidazole (17.4%). NSAIDs were implicated in 30.4% cases.[19] It is particularly relevant to note that of the 47 oral mucosal FDE cases induced by NSAIDs, none were selective COX-2 inhibitors, strengthening the rarity of our cases.

Selective COX-2 inhibitors and FDE

Selective COX-2 inhibitors were first introduced in 1999 and are deemed to have lower risk of adverse side effects than traditional NSAIDs.[10,12] Atzori et al.[12] conducted a surveillance program to reassess the incidence of CADRs to selective COX-2 inhibitors. Over a 4-year period, only 17 of 380 CADRs were related to selective COX-2 inhibitors (4.5%), and there was only 1 case of FDE, which was induced by celecoxib.[12] Etoricoxib was only indicated in 1 CADR, which was leukocytoclastic vasculitis.[12] Etoricoxib itself was approved for medical use in 2002; therefore it could be because of its relative infancy compared to traditional NSAIDs that FDEs are far less commonly reported with etoricoxib. All except 1 of the case reports of etoricoxib-induced FDE were published from 2011 onwards, showing an increase in reported cases as it becomes a more established drug. Furthermore, it is only in the more recent studies (2015 and 2018) that etoricoxib is strongly associated with FDE.[1,16]

In 2015, Heng et al.[16] evaluated 62 patients in Singapore with definite or probable FDE. Although they described that the mucosal lips were involved in 21 patients (33.9%), we were unable to confirm with the authors whether this equated to the labial mucosa; therefore, we do not include them as oral mucosal FDE. In 50% of the patients, NSAIDs were the offending drug and, in stark contrast to the other studies, etoricoxib was the most common NSAID, accounting for 38.7% of all FDEs (24 cases).[16] This finding is particularly intriguing because we performed a separate literature search of the same databases using the search terms “fixed drug eruption” AND “etoricoxib” that revealed only 23 additional cases of etoricoxib-induced FDE, making a total of 47 cases (Supplemental Table S1; available at [URL/link]). In 2018, Jhaj et al.[1] reviewed 50 cases of FDE and found that 5 were induced by etoricoxib (10%). Extremities and lips were the most commonly affected sites and no oral mucosal involvement was reported.[1] In 2011, Andrade and Goncalo[15] reported 2 cases of etoricoxib-induced FDE affecting the skin only. The other 16 cases are described in individual case reports and, other than Augustine et al.,[29] all were reported in the past decade.[4,15,30-44] None of the 47 cases described oral mucosal involvement; meaning that to the best of our knowledge, we have reported the first case of oral mucosal FDE induced by etoricoxib.

Eosinophilic spongiosis

ES is a cutaneous reactive pattern characterized by spongiosis (intercellular edema with elongation of intercellular bridges) and intraepidermal eosinophilic infiltrates.[45-47] Initially described as a characteristic of pemphigus foliaceus and pemphigus vulgaris, it is now a recognized as a feature of various dermatologic conditions (Table I).[45-48] In 1994, Ruiz et al.[46] published a retrospective study of 144 dermatologic ES cases that showed that 81 patients had a diagnosis of dermatitis (56%), 34 patients had an autoimmune vesiculobullous disorder (24%), and 8 patients had a drug-induced reaction (5.6%).[46] Weyers and Metze[23] found spongiotic dermatitis in at least 62 of 300 drug eruption biopsy specimens (21%). Thirty-eight of 300 displayed severe vacuolar interface dermatitis with presence of numerous eosinophils and/or neutrophils (13%), with 13 of these FDE.[23]

ES is rarely seen in oral mucosa (Karwan Moutasim, written communication, October 2020). In the oral cavity, ES is classically associated with pyostomatitis vegetans,[49] a rare disorder clinically characterized by miliary pustules and ulcers on an erythematous base, most commonly affecting the labial gingivae. It is strongly associated with inflammatory bowel disease,[49,50] which was not a factor in our case. Given the broad differential diagnosis for ES at cutaneous sites (Table I), the biopsy pathology did not provide a definitive diagnosis. There was no clinical rationale to perform repeat biopsy for direct immunofluorescence in this case for the reasons previously discussed. Although the possibility of drug reaction was raised among the differentials, further clinical workup was critical to establishing the diagnosis of probable FDE in our case.

Management

The 2 main considerations in treatment of FDE are recognition and avoidance of the causative drug. Depending on the intended purpose of the causative drug, the patient may then require a safe alternative. Therefore, consideration needs to be given to the possibility of cross-sensitivity with other chemically related drugs.[3] Cross-sensitivity is defined as “sensitivity to one substance that renders an individual sensitive to other substances of similar chemical structure.”[51] Etoricoxib is pharmacologically similar to its fellow selective COX-2 inhibitor, celecoxib, but its chemical structure is different.[43] Despite this, cross-sensitivity was confirmed to occur between etoricoxib and celecoxib in 1 FDE case[34]; however, most of the literature reports tolerance

to celecoxib in these patients.[15,31,35-40,43] Drugs from a separate class of NSAIDs could be considered as alternatives for joint pain; our patient found ibuprofen, which is a propionic acid derivative, to be sufficient.[14]

Withdrawal of the causative drug alone is often sufficient for resolution of the lesions; however, topical corticosteroids, antihistamines, or possibly even systemic corticosteroids may be required depending on the severity of the lesions.[3] For this patient, benzydamine hydrochloride 0.15% mouthwash provided adequate symptomatic relief, and discontinuation of etoricoxib resulted in resolution of both oral and cutaneous lesions.

CONCLUSION

Oral mucosal FDE is rare. It provides a diagnostic challenge because it mimics other conditions in both its clinical and histopathologic presentation. This case highlights the importance of a multidisciplinary approach, as collaboration with dermatology and histopathology was critical to establishing the diagnosis. To the best of our knowledge, this is the first reported case of oral mucosal FDE induced by etoricoxib. Although FDEs induced by selective COX-2 inhibitors are rare, the number of reports at cutaneous sites are increasing. Therefore, despite being regarded as having fewer side effects than traditional NSAIDs, the occurrence of CADRs when using these drugs should be taking into consideration.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.oooo.2020.12.019.

REFERENCES

1. Jhaj R, Chaudhary D, Asati D, Sadasivam B. Fixed-drug eruptions: what can we learn from a case series? *Indian J Dermatol*. 2018;63:332-337.
2. Aquino MR, Sher J, Fonacier L. Patch testing for drugs. *Dermatitis*. 2013;24:205-214.
3. Lee A-Y. Fixed drug eruptions. Incidence, recognition, and avoidance. *Am J Clin Dermatol*. 2000;1:277-285.
4. Andrade P, Brinca A, Goncalo M. Patch testing in fixed drug eruptions—a 20-year review. *Contact Dermatitis*. 2011;65:195-201.
5. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. *Curr Opin Allergy Clin Immunol*. 2009;9:316-321.
6. Fadhel NB, Chaabane A, Ammar H, et al. Clinical features, culprit drugs, and allergology workup in 41 cases of fixed drug eruption. *Contact Dermatitis*. 2019;81:336-340.
7. Sehgal VN, Srivastava G. Fixed drug eruption (FDE): changing scenario of incriminating drugs. *Int J Dermatol*. 2006;45:897-908.
8. Mizukawa Y, Shiohara T. Fixed drug eruption: a prototypic disorder mediated by effector memory T cells. *Curr Allergy Asthma Rep*. 2009;9:71-77.
9. Özkaya E. Oral mucosal fixed drug eruption: characteristics and differential diagnosis. *J Am Acad Dermatol*. 2013;69:e51-e58.
10. Zarghi A, Arfaei S. Selective COX-2 inhibitors: a review of their structure-activity relationships. *Iran J Pharm Res*. 2011;10:655-683.
11. Rang HP, Dale MM, Ritter JM, Moore PK. *Pharmacology*. 5th ed. Edinburgh, UK: Churchill Livingstone; 2003.
12. Atzori L, Pinna AL, Pau M, et al. Adverse cutaneous reactions to selective cyclooxygenase 2 inhibitors: experience of an Italian drug-surveillance center. *J Cutan Med Surg*. 2006;10:31-35.
13. Flower RJ. The development of COX2 inhibitors. *Nat Rev Drug Discov*. 2003;2:179-191.
14. Joint Formulary Committee. *British National Formulary*. 79th ed. London, UK: BMJ Group and Pharmaceutical Press; 2020.
15. Andrade P, Goncalo M. Fixed drug eruption caused by etoricoxib—2 cases confirmed by patch testing. *Contact Dermatitis*. 2011;64:118-120.
16. Heng YK, Yew YW, Lim DSY, Lim YL. An update of fixed drug eruptions in Singapore. *J Eur Acad Dermatol Venereol*. 2015;29:1539-1544.
17. Mahboob A, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. *Int J Dermatol*. 1998;37:833-838.
18. Jung J-W, Cho S-H, Kim K-H, et al. Clinical features of fixed drug eruption at a tertiary hospital in Korea. *Allergy Asthma Immunol Res*. 2014;6:415-420.
19. Kavoussi H, Rezaei M, Derakhshandeh K, et al. Clinical features and drug characteristics of patients with generalized fixed drug eruption in the west of Iran (2005-2014). *Dermatol Res Pract*. 2015;1:1-4.
20. Chen AY-L, Chen K. Dental treatment considerations for a pediatric patient with incontinentia pigmenti (Bloch-Sulzberger syndrome). *Eur J Dent*. 2017;11:264-267.
21. Sinno HS, Lacroix J-P, Lee J, et al. Diagnosis and management of eosinophilic cellulitis (Wells' syndrome): a case series and literature review. *Can J Plast Surg*. 2012;20:91-97.
22. Malkarnekar SB, Naveen L. Fixed drug eruption due to clarithromycin. *J Res Pharm Pract*. 2013;2:169-171.
23. Weyers W, Metze D. Histopathology of drug eruptions—general criteria, common patterns, and differential diagnosis. *Dermatol Pract Concept*. 2011;1:33-47.
24. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy*. 2003;58:854-863.
25. Patel S, John AM, Handler MZ, Schwartz RA. Fixed drug eruptions: an update, emphasizing the potentially lethal generalized bullous fixed drug eruption. *Am J Clin Dermatol*. 2020;21:393-399.
26. Kalogirou E-M, Tosios KI. Fixed drug eruption on the tongue associated with piroxicam: report of two cases and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;127:393-398.
27. Cho Y-T, Lin J-W, Chen Y-C, et al. Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. *J Am Acad Dermatol*. 2014;70:539-548.
28. Lee C-H, Chen Y-C, Cho Y-T, et al. Fixed-drug eruption: a retrospective study in a single referral center in northern Taiwan. *Dermatologica Sinica*. 2012;30:11-15.
29. Augustine M, Sharma P, Stephen J, Jayaseelan E. Fixed drug eruption and generalised erythema following etoricoxib. *Indian J Dermatol Venereol Leprol*. 2006;72:307-309.
30. Antunes J, Prates S, Leiria-Pinto P. Fixed drug eruption due to etoricoxibe—a case report. *Allergol Immunopathol (Madr)*. 2014;42:623-624.
31. Miroux-Catarino A, Silva L, Amaro C, et al. Bullous fixed drug eruption induced by etoricoxib, confirmed by patch testing, with tolerance to celecoxib. *Contact Dermatitis*. 2019;81:388-389.

32. Calistru AM, Cunha AP, Nogueria A, Azevedo F. Etoricoxib-induced fixed drug eruption with positive lesional patch tests. *Cutan Ocul Toxicol*. 2011;30:154-156.
33. Cantero Macedo AM, Palmerín-Donoso A, Tejero-Mas M. Fixed drug eruption induced by etoricoxib. *Aten Primaria*. 2019;51: 518-520.
34. Carneiro-Leão L, Rodrigues Cernadas J. Bullous fixed drug eruption caused by etoricoxib confirmed by patch testing. *J Allergy Clin Immunol Pract*. 2019;7:1629-1630.
35. Ponce V, Muñoz-Bellido F, Moreno E, et al. Fixed drug eruption caused by etoricoxib with tolerance to celecoxib and parecoxib. *Contact Dermatitis*. 2012;66:107-108.
36. de Sousa AS, Gouveia MP, Teixeira VB, et al. Fixed drug eruption by etoricoxib confirmed by patch test. *An Bras Dermatol*. 2016;91:652-654.
37. Botia Martinez-Artero B, Cabeza Rodriguez NC, de Luque Piñana V, Guardia Martínez P. Fixed drug eruption by etoricoxib with good tolerance to celecoxib. *Allergy*. 2016;71: 525-526.
38. Pacheco Coronel MV, Arevalos Prette JD, Martí Garrido J, et al. Fixed drug eruption to etoricoxib. *Allergy*. 2015;70:333-334.
39. Corrales-Vargas SI, Pérez-Calderón R, Gonzalo-Garijo MA, et al. Bullous fixed drug eruption by etoricoxib. *Allergy*. 2014;69:350-351.
40. Rojas Hijazo B, Compes García E, Pérez Camo I, San Juan de la Parra S. Fixed drug eruption caused by etoricoxib with tolerance to celecoxib. *Allergy*. 2012;67:398-399.
41. Prucha H, Müller T, Zirbs M, Leon-Suarez I. Etoricoxib-induced multilocular fixed drug eruption mimicking recurrent herpes simplex virus infection. *Allergy*. 2013;68:394.
42. Giurcaneanu C, Petrutescu B, Popa L, et al. Fixed drug eruption induced by etoricoxib in an elderley patient. *Allergy*. 2012;67:399-400.
43. Gómez de la Fuente E, Pampín Franco A, Caro Gutiérrez D, López Estebaranz J. Fixed drug eruption due to etoricoxib in a patient with tolerance to celecoxib: the value of patch testing. *Actas Dermosifiliogr*. 2014;105:314-315.
44. Movsisyan M, Fiandor A, González-Muñoz M, et al. The lymphocyte transformation test is useful in the diagnosis of fixed drug eruption induced by etoricoxib. *J Investig Allergol Clin Immunol*. 2019;29:307-309.
45. Morais KL, Miyamoto D, Wakisaka Maruta C, Aoki V. Diagnostic approach of eosinophilic spongiosis. *An Bras Dermatol*. 2019;94:724-728.
46. Ruiz E, Deng J-S, Abell EA. Eosinophilic spongiosis: a clinical, histologic, and immunopathologic study. *J Am Acad Dermatol*. 1994;30:973-976.
47. Crotty C, Pittelkow M, Muller SA. Eosinophilic spongiosis: a clinicopathologic review of seventy-one cases. *J Am Acad Dermatol*. 1983;8:337-343.
48. Patterson JW. *Weedon's Skin Pathology*. 4th ed. London, UK: Churchill Livingstone Elsevier; 2016.
49. Regezi JA, Sciubba JJ, Jordan RCK. *Oral Pathology—Clinical Pathologic Correlations*. 6th ed. Missouri: Elsevier Saunders; 2012.
50. Hegarty AM, Barrett AW, Scully C. Pyostomatitis vegetans. *Clin Exp Dermatol*. 2004;29:1-7.
51. Anovadiya AP, Barvaliya MJ, Patel TK, Tripathi CB. Cross sensitivity between ciprofloxacin and levofloxacin for an immediate hypersensitivity reaction. *J Pharmacol Pharmacother*. 2011;2:187-188.

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