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Case Report

Pharmacovigilance through Clinical Observation: Case Series of Drug-Related Oral Lesions and Reactions

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Abstract

The Pharmacovigilance Program of India (PvPI) includes a sensitization program focused on the adverse effects of not only medications but also materials used in medical and dental diagnosis and therapeutics under the Materiovigilance Program of India (MvPI). The oral cavity could be significantly affected by the adverse effects of both medicines and dental materials. Consequently, dental professionals are more involved in reporting and studying the adverse effects that occur in the oral cavity. Since many lesions caused by these adverse effects can mimic other oral conditions, it was essential to report these cases and closely monitor de-challenges and re-challenges to draw accurate conclusions. This series highlighted 15 cases of oral lesions resulting from adverse drug and material reactions that were documented at the Department of Oral Medicine. These cases were duly reported under both the PvPI and MvPI.

Keywords: Amalgam, Adverse effects, dental materials, Dentistry, Pharmacovigilance.

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Introduction

In the late 1960s, similar to developments in other parts of the world, many medical scientists began focusing on the rational use of medicine and monitoring adverse drug reactions (ADRs). Eminent pharmacologists in India also joined this effort to study ADRs and grasped the concept of pharmacovigilance. It became evident that not all approved medications are safe and that they might cause adverse reactions even at therapeutic doses. [1] The same pattern was noticed in dental practices, and in 1971, *Almeyda* and *Levantine* first reported drug interactions that cause oral lesions similar to oral lichen planus (OLP). [2] The use of anti-malarials like quinacrine and metacrine during World War II sparked reports of lichenoid reactions. As dental restorative materials, particularly gold, gained popularity, cases of oral lichenoid lesions also increased. [3] The oral cavity, encompassing the lips, faces constant exposure to a diverse array of potentially irritating and sensitizing substances. During routine dental treatments, approximately 10 to 15 different metals, alongside topical treatments, disinfectants, and various other dental materials, can significantly impact the delicate buccal mucosa. Understanding of this intricate interplay underscores the importance of careful consideration in dental care practices.[4] Hypersensitivity reactions in the oral mucosa are emerging as significant clinical challenges that profoundly impact the lives of countless patients. These conditions manifest in a variety of distressing symptoms, such as fiery redness, painful ulcers, and a persistent burning sensation, all of which can severely diminish a patient's quality of life. The complexity of these reactions is further intensified by the myriad potential allergens, including metals, dental materials, and flavouring agents, each capable of triggering discomfort. Consequently, achieving an accurate diagnosis and implementing effective treatment strategies becomes not just important, but essential for restoring well-being and improving the everyday experiences of those affected. [5]

This paper, based on a case series, highlights the diverse presentations of confirmed cases of oral manifestations resulting from hypersensitivities to dental materials and medications. These patients visited the Department of Oral Medicine between *January 2023* and *September 2025*, all presenting similar complaints. As a part of the Pharmacovigilance Programme of India (PvPI) and Materiovigilance Programme of India (MvPI), all cases reported to the Adverse Drug Reactions Monitoring Centre (AMC) and Regional Training Centre (RTC) of the Jawaharlal Nehru Medical College, Aligarh Muslim University under the Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India.

Case Series -

A total of **15 adverse events** were documented between *January 2023* and *September 2025* in a dental practice. All patients were verbally informed, and written consent was acquired for record-keeping, tracking the healing process, and publication. The case series was under the guidelines of the *Declaration of Helsinki and CARE.*

The majority of affected individuals were middle-aged females, reflecting a higher susceptibility among women to mucocutaneous adverse drug reactions. The total number of cases was n=15, 9 females (60%), 6 males (40%); age 20–70 with a mean age of ~39.9 years. Female: Male ~60:40; exact binomial test shows no significant departure from 50:50 ($p>0.05$)

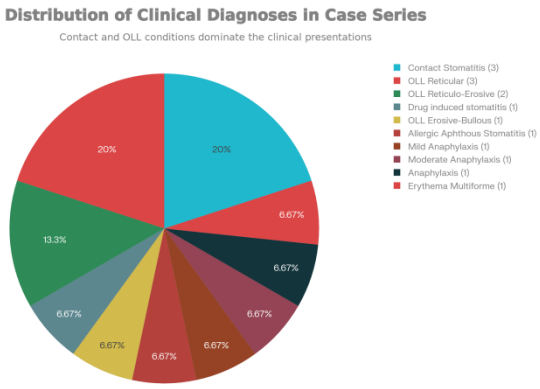


FIGURE 1- Pie Chart: Distribution of Clinical Diagnoses (n=15 cases)

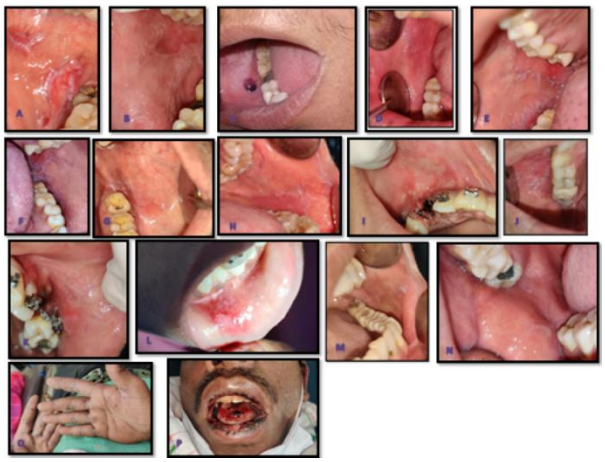
The cases comprised 9 females (60%) and 6 males (40%), with an age range of 20–70 years (mean age ≈ 39.9 years). Using WHO–UMC causality assessment scale, cases were classified 12 cases (80%) as probable and 3 cases (20%) as possible, demonstrating strong causality associations. Notably, all cases exhibited a positive de-challenge, with full or marked resolution of lesions following withdrawal of the suspected offending agent, confirming the diagnostic significance of pharmacovigilance in clinical dental practice.

TABLE 1 – Demographic details of patient with casualty assessment as per WHO-UMC casualty assessment scale.

S. No	Age	Gender	Casualty Assessment
1	40	F	Probable
2	58	F	Probable
3	39	F	Probable
4	24	F	Probable
5	30	M	Probable
6	42	F	Possible
7	22	M	Probable
8	20	F	Probable
9	42	M	Probable
10	62	F	Possible
11	30	M	Probable
12	70	M	Probable
13	32	F	Probable

14	30	F	Probable
15	40	M	Probable

Among the 15 patients, 60% (9 cases) presented with oral lichenoid or contact lesions, 20% (3 cases) showed systemic hypersensitivity or anaphylaxis, and 1 case (6.6%) each manifested *erythema multiforme*, drug-induced stomatitis, or allergic aphthous stomatitis. All lesions and reactions resolved following withdrawal or replacement of the offending agent, confirming pharmacologic causality.



FIGURES 2- A: OLL due to Areca Nut; B: Drug Induced Stomatitis by Betadine® mouth wash; C & D: OLL erosive- bullous type and OLL erosive- reticular type with Nimesulide 100 mg; E & F: Right & Left buccal mucosa showing sulfasalazine induced OLL; G& H: Tooth Powder causing OLL and Contact Stomatitis; I, K & L: Ni-Ti induced allergic apthous stomatitis; J & M: OLL due to PFM crown and GIC restoration in close proximity with lesion; N: Amalgam induced Contact Stomatitis; O- P: Acetaminophen triggered Erythema Multiforme.

Overall, probable causality dominated (80%), indicating strong temporal correlation and positive de-challenge response, while possible cases (20%) involved confounding factors such as mixed exposures.

TABLE 2- Table showing features with suspected agents.

S. No	Patient Complain	Clinical Presenting Feature(S)	Diagnosis	Suspected Agent	De-challenging
1	Non- scrapable Red and white patches with burning sensation in right side of buccal mucosa in lower right back tooth region	Non- scrapable Red and white irregular shaped patch with periphery of lesion had white *Wickham's* like striae not crisscrossing each other.	OLL Reticulo-Erosive pattern	Areca Nuts	Positive
2	Burning sensation in mouth and erosion of oral mucosa	Reddish mucosa with sloughing of epithelium.	Drug induced stomatitis	Betadine® mouth wash	Positive
3	Burning sensation and Multiple ulcers and	Blood tinged fluid containing Bullous formations with	OLL mixed type (Erosive-	Neamuslide 100 mg	Positive

	vesicles in mucosa	surrounding erosion of mucosa	Bullous type)		
4	Burning sensation and Multiple ulcers in mucosa	Reticulo-Erosive lesions with surrounding area showing erythema	OLL Reticulo-Erosive pattern	Neamuslide 100mg	Positive
5	Red and white patches with burning sensation in whole mouth	Reticular lesions with surrounding area showing erythema. The periphery of lesion had white *Wickham's* like striae not crisscrossing each other	Oral lichenoid Reaction ~ *Reticular* type	Sulfasalazine 500 m	Positive
6	Non- scrapable Red and white patches with burning sensation in both side of buccal mucosa	Reticular lesions with surrounding area showing erythema. The periphery of lesion had white *Wickham's* like striae not crisscrossing each other	Oral lichenoid Reaction ~ *Reticular* type	Tooth powder	Positive
7	Generalized redness of oral mucosa with small ulcers on buccal mucosa	Generalized erythema of oral mucosa with 2-3 small ulcers ~ 0.5 mm on buccal mucosa and dorsum of tongue.	Contact Stomatitis	Tooth Powder	Positive
8	Multiple ulcers in mouth	Multiple apthae like ulcers with characteristic red halo around size ranging 0.5-0.6 cm	Allergic aphthous Stomatitis	Ni-Ti Wire	Positive
9	Burning sensation and ulcer on buccal mucosa of right upper back tooth region.	Erythematous area with sloughing of epithelium around the opening of Stenson's duct of right side	Contact Stomatitis	PFM Crown	Positive
10	Burning sensation with redness in left side buccal mucosa of lower back tooth region	Reticular lesions with surrounding area showing erythema with sloughing of epithelium.	Oral Lichenoid Lesion-Reticular type	GIC	Positive
11	Burning sensation with redness in left side buccal mucosa of lower back tooth region	Reticular lesions with surrounding area showing erythema with sloughing of epithelium	Contact Stomatitis	Amalgam	Positive
12	Swelling and redness of face	Swollen face with redness all over, breathing is not affected	Mild Anaphylaxis	Betadiene 5%	Positive
13	Swelling on whole body and shortness of breath	Anasarca and Dyspnea	Moderate Anaphylaxis	Thiocholchicoside 40 mg	Positive
14	Dizziness , Palpitations, unconsciousness, Skin	Low BP, Urticaria, Tachycardia	Anaphylaxis	Carbamazepine 400 mg	Positive

	allergy				
15	Bleeding from Lips and Tongue, redness in eyes and redness on hand	Bloody crustations on lips and bleeding gums, target lesions on hands.	Erythema Multiforme	Acetaminophen 500 mg	Positive

Morphologically, reticular and erosive lesions predominated, mirroring typical hypersensitivity-mediated lichenoid pathology. The histopathology examination was duly performed for them. **[FIGURE 3]** The most frequently implicated agents were *Nemuslide*, *tooth powder*, and *areca nut*, collectively accounting for 40% of all reactions.

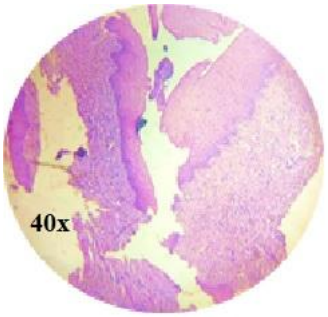


FIGURE 3- Histopathology image of most suspected OLL pertaining to cause by PFM crown.

The suspected PFM crown was sent to the University Sophisticated Instrument Facility to determine the composition of the crown via Scanning Electron Microscopy(SEM) and replace it with a hypoallergenic material, i.e. zirconia crown, at the Department of Prosthodontics.

FIGURE 4- Removed PFM crown and SEM images of composition of PFM crown done at USIF.

Management And Clinical Significance

Oral Lichen Planus (OLP) was identified as the leading differential diagnosis for Oral Lichenoid Lesions (OLL). All suspected patients received a similar empirical treatment, including Topical Triamcinolone 0.1% before meals and immediate de-challenging, resulting in healing within six weeks.

For Contact Stomatitis, patients were treated with de-challenging and given Benzydamine Hydrochloride Mouthwash 0.15% for immediate relief from burning pain. Follow-ups confirmed that all patients healed satisfactorily within two weeks.

In the case of Allergic Aphthous Stomatitis due to Ni-Ti wire, healing took nearly two months. The wire was first covered with wax, and once the lesion shrank, it was replaced with a ceramic wire. Patients also received Benzydamine Hydrochloride Mouthwash 0.15% for relief and Topical Triamcinolone 0.1% before meals.

Anaphylaxis patients received prompt treatment at the hospital's triage with oral methylprednisolone 10 mg daily for three weeks and IV antihistamines (Avil 2 ml stat).

Currently, all patients have ongoing biannual follow-ups and have experienced smooth healing.

Discussion

Adverse drug reactions (ADRs) pose a serious threat to patient well-being, leading to illness, hospitalizations, and, in some cases, tragic fatalities. It is imperative to recognize these reactions promptly and to determine the causal relationship between the medication and the adverse event. To ensure clarity and precision, ADRs should be evaluated objectively and presented through a widely accepted *"Probability Scale."*[6] The causality assessment systems developed by the World Health Organization Collaborating Centre for International Drug Monitoring, known as *the Uppsala Monitoring Centre (WHO–UMC*) was widely recognized and accepted methods for evaluating causality in clinical practice. [7] In case series on study the same casualty assessment scale was used.

In addition to dental materials, several topical substances, such as phytotherapy products, oral cosmetics, various food items, beverages, and additives, can trigger adverse reactions in the oral mucosa. These substances may cause not only non-specific contact stomatitis and cheilitis but can also lead to lichenoid manifestations. [8] Similarly this case series had wide arena of variation related to OLL including Areca Nuts, Tooth Powder, and GIC etc.

The diagnosis of oral lichenoid changes relies on a detailed patient history, clinical examination, and histopathological identification. The most common form is reticular lesions, with other variations including plaque-like, papular, atrophic, bullous, and erosive forms. [9] This case series shows concurrence with these. Histopathological examination of these suspected lesions are mandatory to exclude other mucosal lesions like OLP, SLE etc. as well as to rule out possible dysplastic changes. [10, 11] Similarly duly biopsy were done for suspected cases.

From 1997 to 2004, the Surgery Anaphylactic Reaction Study and Research Group reported an immediate hypersensitivity reaction to Betadine® in 3 out of 786 cases. While this frequency is minimal, it is similar to findings in this series.[12]

Activation of T- Cell is the most documented cause of hypersensitivity caused by drugs including Anti-epileptics and Carbamazepine metabolites can trigger the same pathway. [13] On the contrary NSAIDs and Muscle relaxants showed Ig-E mediated hypersensitivity reaction. [14] In both the reported cases of anaphylaxis to carbamazepine and muscle relaxant patient was given emergency medical care in triage without delay to avoid impairment or long hospital stay.

Romanian authors in 2016 concluded that the corrosion products of Amalgam are responsible for the development of Oral lichenoid reaction.[15] In our series the case with OLL having positive de-challenging with amalgam had no other restorations in oral cavity nor on any medications.

Reports by Sarkar [16] Cordeiro[17] and Kumaran[18], have documented oral mucosal lesions associated with Nimesulide, with bullous lesions being among the rarest manifestations. In line with these findings, the present case series describes one of the rarest oral adverse effects induced by Nimesulide. Drug-induced erythema multiforme (DI-EM) presents diagnostic challenges, as it can closely resemble several other mucocutaneous disorders. Drug-induced oral erythema multiforme (DI-OEM) is characterized by lesions confined to the oral cavity, typically occurring without any associated skin involvement. [16]This case series had one case with Acetaminophen which showed DI-OEM with cutaneous manifestations. The same case had negative HSV antibody titer making the diagnosis definite.

In 1968 ten countries participated in pioneering WHO-led initiative, establishing a spontaneous reporting framework for the systematic documentation and monitoring of adverse drug reactions at the international level. *Ohuju-obodo et al*. [19] conducted a survey among resident doctors of Nigeria about ADRs reporting

in which they concluded that majority of respondents (78.1%) possessed inadequate knowledge about pharmacovigilance, with 71.2% unaware of NAFDAC's yellow reporting forms for adverse drug reactions. Although 92.4% had encountered ADRs during their professional experience, only 25.5% reported these cases, and merely 7.3% submitted reports to National Agency for Food and Drug Administration and Control (NAFDAC). Case series of this nature serve as valuable educational resources, offering insights into clinical presentations and diagnostic considerations that might otherwise be overlooked in routine practice.

Awodele O et al. [20] conducted a study in Nigerian population evaluation patterns of adverse drug reaction signals in NAFDAC pharmacovigilance activities from January to June 2015. They documented higher number of ADR reports in females (65.5%) and highest percentages of reports were from the age range of 21-40 years (45.6%). In our study, we also noticed that the reaction predominantly were more common in females which could possibly due to hormonal and immunological factors.

Conclusion

This series underscores the pivotal role of pharmacovigilance in dental settings prompt recognition, reporting, and management of drug and material induced oral and systemic adverse events are essential to ensuring patient safety and informed dental therapeutics. The importance of diagnosis, reporting and management of these adverse events was quintessential to maintain national wide PvPI and MvPI data. Large amount of record maintenance and laboratory data was required for better understanding of these effects and decisions for policy makers. Thus, this case series brought the rarest of findings like that of Acetaminophen and PFM.

Future Perspectives

There is an urgent need to establish laboratory-based testing facilities for suspected drugs and materials, including assays such as MELISA. As India continues to develop, strengthening the healthcare sector is essential to make such diagnostic tests affordable and accessible to individuals from lower socio-economic groups. Furthermore, advancements in pharmacogenetics are expected to play a pivotal role in achieving this goal by enabling personalized and cost-effective therapeutic approaches.

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