ABurning IssueonOral MucosalDiseases: CaseSeries

ABSTRACT

Oral Lichenoid Reaction (OLR) is a chronic inflammatory lesion of the oral mucosa that occurs as an allergicresponse to certain dental materials, medications and systemic diseases. The frequency of OLR in the generalpopulation has been documented to be very less. The clinical and histological features of OLR closely resemblethose of Oral Lichen Planus (OLP), making it challenging to distinguish between the two clinically. OLRs mighthave a higher malignant potential than OLP. The diagnosis and treatment of OLR is very crucial as misdiagnosismay result in detrimental effects on the biophysical health of the patient. Here, we present case series of twopatients who presented with amalgam restorations and burning sensation on the buccal mucosa whileconsumption of hot and spicy food. An immunohistopathological evaluation confirmed the diagnosis as OralLichenoid Reaction. Elimination of causative factors remain the mainstay of treatment which markedly reduces thesufferingsof thepatient with acommendableresult.

Keywords:LichenoidReaction,DIF,Burning,Mucousmembrane,Amalgam

1.INTRODUCTION

Theoralmucosaprovides effectivebarrierwhichisofteninconstantcontactwithvariousdeleterioussubstances,acidicor alkalinecompounds,spicyornon-spicyfood,allergenslikechemicalproductsusedintoothpastes,mouthwashes,oral flavoringagents,preservativesanddentalmaterials[1].Orallichenoidreaction(OLR)is characterizedasapersistent inflammatoryconditionaffectingtheoralmucosa,triggeredbyallergicreactionstodentalproducts,specificmedications, individualswithgraft-vs-hostdisease(GVHD)andsystemicconditions[2].Histologically,OLRsmimicorallichenplanus (OLP),thus,clinical interpretationismandatory[3].TheoccurrenceofOLRis acommonphenomenon,manifestingwitha prevalenceof2.4%amongthegeneralpopulace[2].Theselesionsmostcommonlyoccurinmiddle-agedadultswitha slightfemalepredilection[4].Areascommonlyinvolvedarethebuccalmucosa,lateralborderofthetongueandlabial mucosathatareindirectcontactwithmetalrestorationsorotherallergens.Itisgenerallylimitedinsizeandunilateralin distribution.Onthecontrary,OLPlesionsarefrequentlyfoundbilaterallyintheoralmucosawhichserveasthe distinguishingfeature.Clinically,OLPshowsawiderangeofvariations,fromwhiteinterlacingstriationstoulcerations evenblisterformation,andareasymptomatic innature.Patientsmaycomplainofburningsensationalongwithintolerance tospicymeals[2]. Basedonanadmixtureofclinicaldiagnosis,histopathologicalevaluation andimmunofluorescencetest, afinaldiagnosiswas madeandpatientsweresuccessfullytreated.

2.CASEPRESENTATION

CASE1:

A61-year-oldfemalepatientfromasemiurbanareareportedtotheDepartmentofOralandMaxillofacialPathology,Guru NanakInstituteofDentalSciencesandResearch,Kolkatawiththechiefcomplaintofmildburningsensationoverleft buccal mucosa,lowerlabialmucosaandtonguesincelast1-2years,whichwassmallinitiallybutprogressivelyincreased overtimetothepresentsize(measuringabout1.5x1.2cm)beingassociatedwithburningsensationontakinghotand spicyfood.Atthetimeofpresentation,thepatienthadaclassIamalgamrestorationon38thatwasperformed approximately6yearsagowhichwasnowconsideredaspoorordefective.However,theaffectedsitewasfreefrom traumaticocclusionorfromsharpcuspaledgesoftoothordentures.Themedicalhistoryrevealedthatshewas hypertensiveandundermedication.
Intraorally,thepresenceofinflamedanderythematousattachedgingivaandinterdentalpapillawithrespectto31,32,33 and41,42,43toothregion[accordingtoFederationDentaireInternationale(FDI)notation]wasobserved.Gingival recessionwasnotedwrt31,32andpoororalhygieneispresent.Therewasalsopresenceofsmallerythematous ulceratedlesionovergingivobuccalsulcusandbuccalmucosawithrespectto36[FDInotation].Thepatientalsohada fissureddepapillatedtongue[Figure1].Theseledtoaprovisionaldiagnosisoforalmucositis.

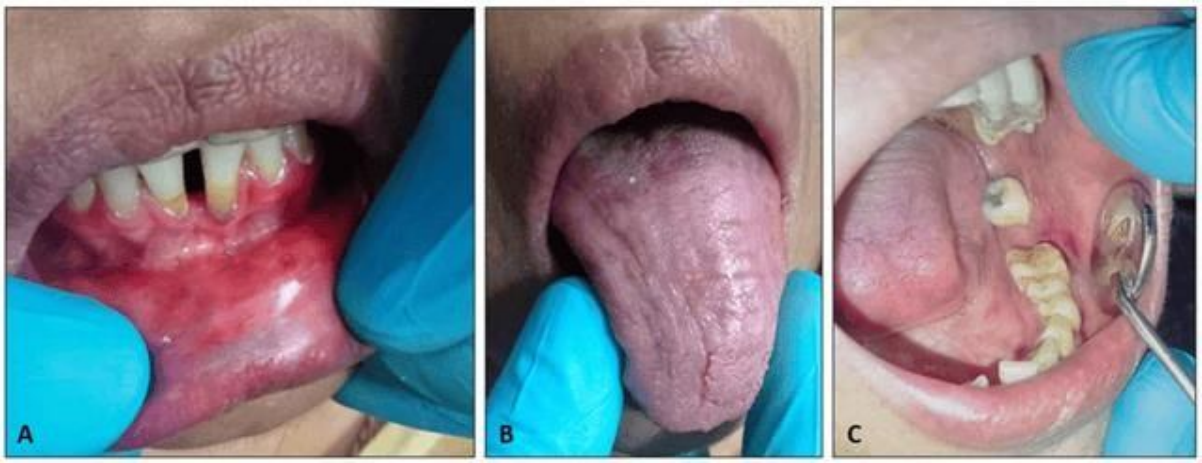

Figure1:Intraoralphotographofthepatientshowing(A)presenceofinflamedanderythematous attachedgingivaandinterdentalpapillawithrespectto 31,32,33and41,42,43toothregion;(B)Fissureddepapillatedtongue;(C)Smallerythematous areaovergingivobuccalsulcus andbuccalmucosawrt edentulousspaceof37.

Thereafter,thepatientwasadvisedfororalprophylaxisalongwithempiricalantibiotictherapyandantibacterial mouthwash.Mostofthelesionsstartedtoregressafter1monthoftherapybutthelesionadjacentto36wasstill persistentandtheincisionalbiopsywasplannedfromthatrepresentativearea.
Thepatientwasthenadvisedtoundergoroutinehematologicalandbiochemicalinvestigationswhichwerewithinnormal limits.
Incisionalbiopsywasperformedunderlocalanesthesiaandsubmittedinbufferedformalinforroutinehistopathological examination.SectionsstainedwithHaematoxylin&Eosinrevealedthepresenceofhyperplasiaofsurfaceepitheliumwith basalcelldegeneration.Spongiosiscanbeencounteredduetopresenceofintercellularedema.Subepithelialstroma showednumerousdiffusechronicinflammatorycellsinfiltrateextendingfromjuxtaepithelialareatodeepintothe connectivetissueaccompaniedbyplasmacellsandhistiocytes.Nocellularatypiawasevident[Figure2].Thelight microscopicfeatureswere suggestiveoflichenoidreaction.

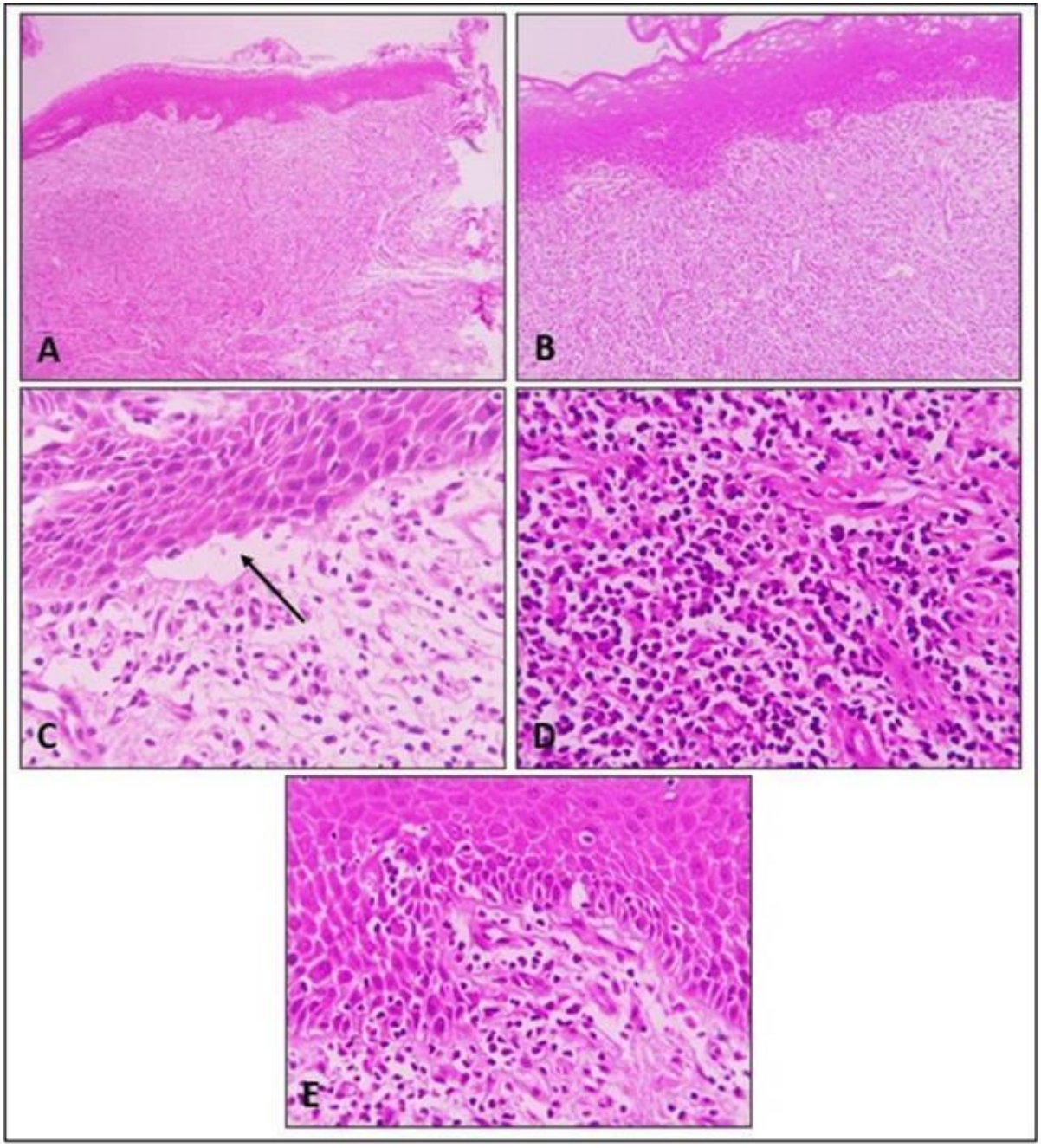

Figure2:(A)Photomicrographshowinghyperplasticstratifiedsquamoussurfaceepitheliumwithunderlyingconnectivetissuestroma(HandE;4X);(B) Spongiosisanddiffusechronic inflammatorycells infiltratedeeperintothelaminapropia(10X);(C,D,E)MaxJosephspaces(arrow)andbasalcell degeneration;numerouschronicinflammatorycellsinfiltratechieflycharacterizedbylymphocytes,histiocytesalongwithplasmacells(40X)

Toconfirmthediagnosis,directimmunofluorescence(DIF)wasadvised.Aperilesionaltissuewastakenandsentforthe DIF testingdirectlyinMichel'smedium,whichrevealednoappreciablestainingdepositsforIgG,IgA,IgMandC3[Figure3].

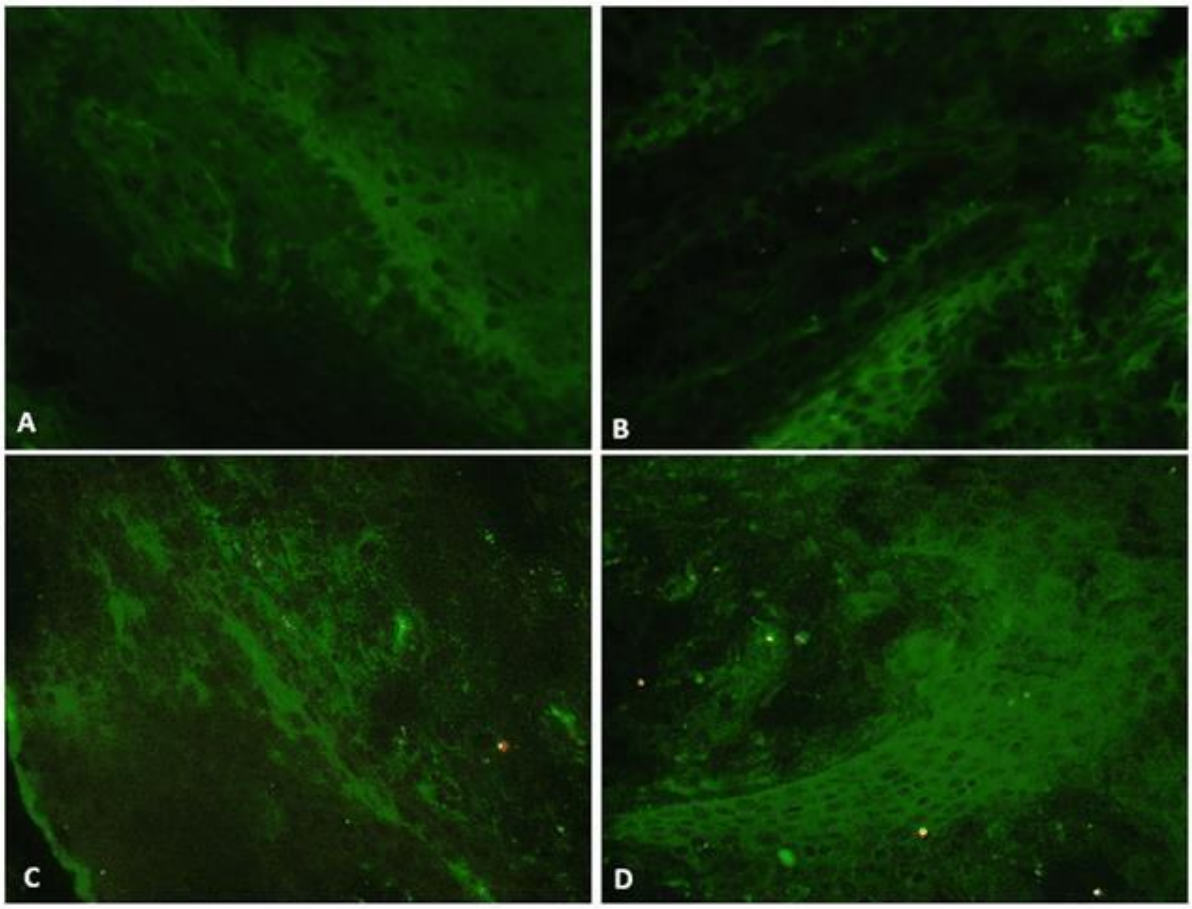

Figure3:DirectImmunofluorescence(DIF)showinganegativestainingdepositsfor (A)IgG(B)IgA(C)IgMand(D)C3

Theoverallclinical,histopathologicalfeaturesandimmunofluorescencestudywereconsistentwithlichenoidinflammation.

The treatmentincludedelimination of the amalgam filling in thelower back tooth region byGlass Ionomer restoration and application of topical clobetasol (0.05% w/w) and miconazole (2% w/w) on the affected areas along with benzydamine (0.15%w/v)mouthwashandfollowedfor2months.Thepatientrespondedwelltotheabove-mentionedtreatmentandnofurther exacerbations werenoticed. [Figure4]

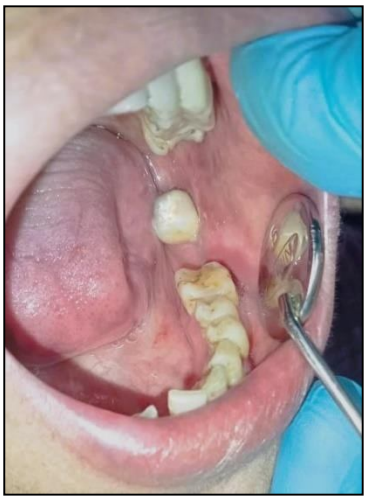

Figure4:Post-treatmentafter2months

CASE 2

A 57-year-old male patient reported to the Department of Oral and Maxillofacial Pathology with a chief complaint of burning sensation in his cheeks while consumption of hot and spicy food for the last 1 year. The patient visited to dental surgeon for similarcomplains 6 months ago and applied steroid ointment as per prescription. Remission of the lesion was observed after1854 monthsof treatment but recurrence wasnoted over a period of 2 months after termination of medication. Medical history186revealedthatthepatientwashypertensiveundermedication.Onintraoralexamination,wenotedthepresenceofwhite187striationswithcentralerythemaonbilateralbuccalmucosa.Amalgamrestorationintheleftmandibularsecondmolarand188rightmandibularthirdmolarwasdoneapproximately3-4yearsago.Therestoftheoralmucosaappearedtobenormal189[Figure5].

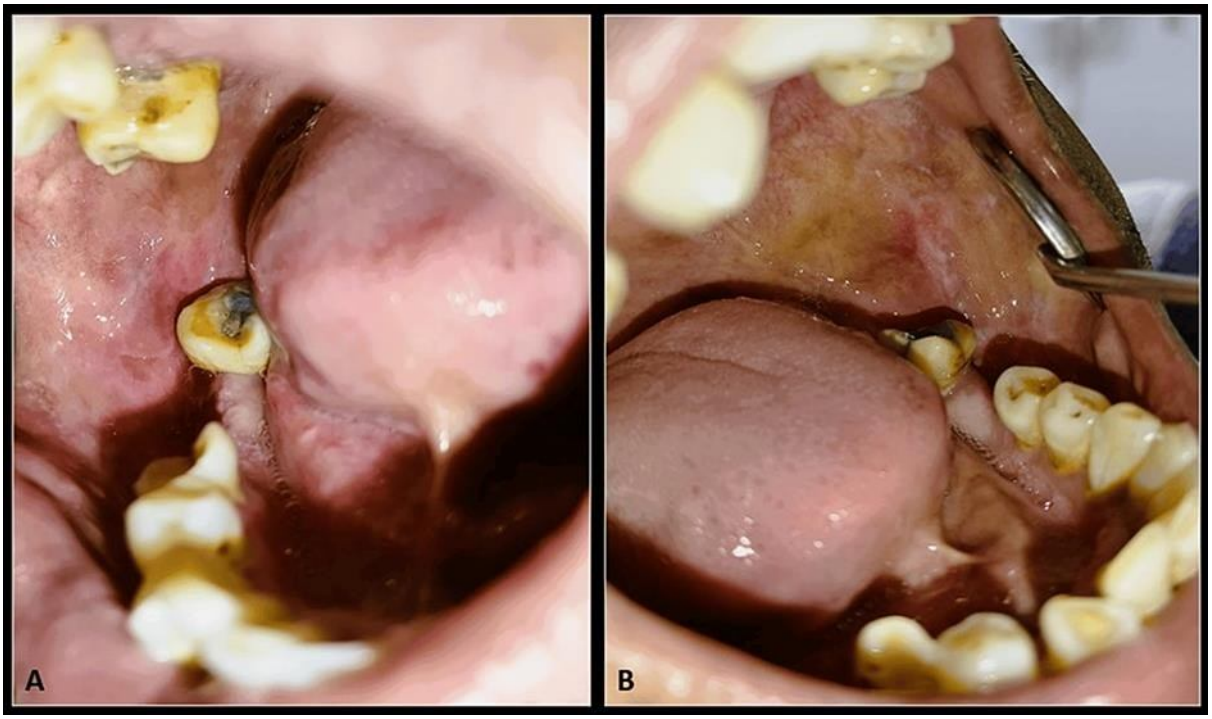

Figure5(A,B):Intraoralexaminationshowingpresenceofwhitestriationswithcentralerythemaonbilateralbuccalmucosaadjacenttoteethwrt37(left mandibularsecondmolar)and 48(right mandibularthirdmolar)filledwithamalgam

A provisionaldiagnosisoforallichenplanuswasmadebasedontheclinicalfindings.Thepatient'shemogramwaswithin normal limits. Incisional biopsy was performed under local anesthesia from the representative site and finally sent for routine195lightmicroscopic histopathologicalevaluationtoconfirmadiagnosis.

Sections stained with H&E revealed the presence of stratified squamous surface epithelium with irregular rete ridges, focal acantholysis and occasional basal cell degeneration. Underlying stroma revealed diffuse chronic inflammatory cell infiltrate extending deeper into the connective tissue layer with engorged blood vessels and large number of eosinophils. No signs of malignancy couldbedetected[Figure6].

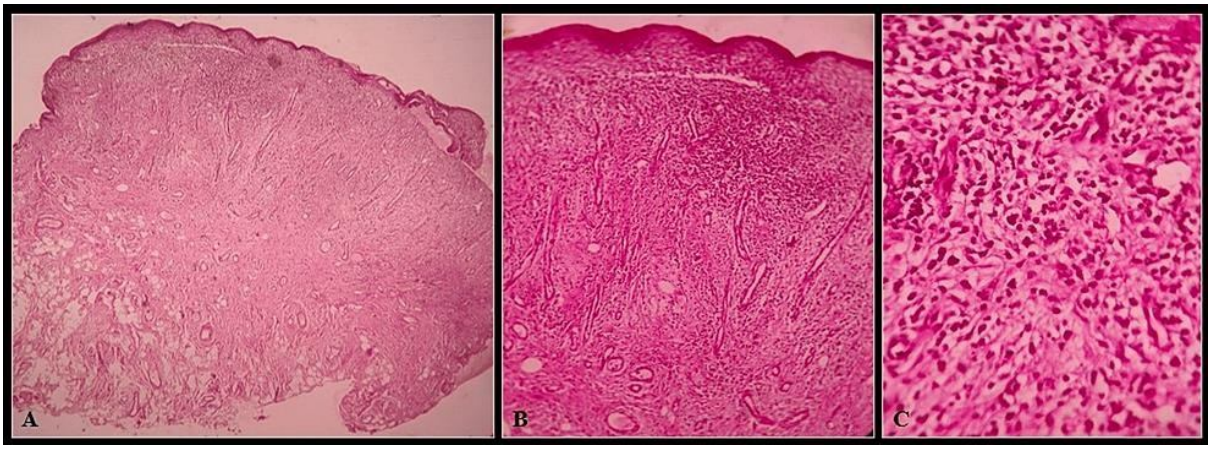

Figure6:(ATOC)Photomicrographshowinghematoxylinandeosin-stainedsections revealingstratifiedsquamousepitheliumwithirregularreteridges (4X);Focalacanthosis,occasionalbasalcelldegenerationandchronicinflammatoryinfiltratedeeperintoconnectivetissuelayer(10X);Inflammatory infiltratealongwithengorgedbloodvesselsandlargenoofeosinophils(40X)

Thus,thediagnosisoforallichenoidreactionwasmadebasedonhistopathologicalevaluation.

The patient was then advised to replace the amalgam restorations with a tooth-colored restorative material and composite resin restoration was done. His symptoms regressed and complete healing was noted after 2.5 months. There has been no evidenceofrecurrenceordiscomfort overaperiodof1year.ThecomparativeanalysisofboththepatientsgiveninTable1.

DISCUSSION

Pinkusfirstintroducedtheterm"OralLichenoidTissueReaction"in1973todescribethehistologicalpatternindicating damage to keratinocytes along with the infiltration of inflammatory cells in the connective tissue that may also extend into the epithelium[1].OralLichenoidTissueReactionhasalsobeentermedasOralLichenoidLesions(OLL),OralLichenoid Reaction (OLR),lichenoidcontact stomatitis, orlichen-planus-like lesionsdueto theclinical and histological similarities between OLR and Oral Lichen Planus [2]. OLRs can manifest either as a distinct pathological condition or as an exacerbation ofpre-existingorallichenplanus.AccordingtoVanderWaal(2009)OLRscanbecategorizedintofourtypes:Amalgam restoration topographically associatedlesions, Drug-associatedlichenoidlesions, Lichenoid lesions in individuals having chronic graft versus host disease and lesions that have a lichen planus like aspect but that lack one or more characteristic clinical aspects[1].

LichenoidreactionshavebeenattributedtoseveraldrugssuchasBetaBlockers,NonsteroidalAnti-InflammatoryDrugs (NSAIDs), Dapsone, Oral Hypoglycemics, Penicillamine, Sulfonylureas, and Anti-Psychotic like Phenothiazines, Vasodilators. They have also been associated with dental materials including amalgam, dental acrylics etc. [4,5]. Association of systemic diseasessuchasChronicHepatitisCandpatientsvaccinatedagainstHepatitisBhavebeenobservedinnumerous cases[6].Inourcase,oneofthepatientshadtheamalgamrestorationon38(classI)whiletheotherhadon38and48respectively.

The pathogenesis of OLRs is still largely unknown. It is postulated that various pathways of antigen presentation could serve as a fundamental determinant. At the time of restoration, OLRs are barely encountered due to insolubility of amalgam into the saliva and its washing mechanism [7]. The response initiates when haptens (incomplete antigens, combine with proteins/counterparts to create full antigens) interact with the oral mucosa. Following the first encounter, an initial local immune and inflammatory response takes place and the antigen internalized by macrophages and monocytes is subsequently displayed to T cells leading to their sensitization and activation of CD4+ T cells. Upon subsequent exposure to the identical allergen, these cells secrete cytokines and chemokines that have the potential to incite an immune reaction against epithelial antigens, thereby instigating the formation of OLR and this seems to manifest as a T-cell mediated delayed hypersensitivity reaction (Type IV) upon contact with either the mercury or another constituent of amalgam. This response could be delayed for a minimum 48 hours and the manifestation of symptoms may vary based on the severity of the reactions which can manifest as either be acute or chronic [8,9,10,11]. Previous studies demonstrated that the expression of nuclear

factorkβ-dependentcytokinesinserum,oralkeratinocytesandtissue-infiltratedmononuclearcellsincludingTNF-α,IL-1and IL-6was increasedinindividualswithOLR[5].

The prevalenceof LRhasbeenreportedtobeapproximately2.4%in thegeneralpopulationand middle-aged individualsare commonlyaffected [2].Inourcaseseries,ourpatientsalsobelongedtothementionedagegroup.

Clinical presentations may vary depending on the type of reaction, allergen location and duration of contact. The asymmetry240ofthelesionisnotable;however,itcanbepresentbilaterallyiftherearealgamrestorationsonbothsides.Thebuccal241 mucosa is the most frequently affected site followed by border of tongue [5]. Acute lesions may present with symptoms such242asburningsensationandredness.Vesiclesarenotcommonlyobserved,butifpresent,theytendtoruptureshortlyafter243 forming, leading to the presence of erythematous areas. Chronic lesions typically manifest as regions of erythema, oedema,244 desquamation and occasionally ulceration [11]. Both the patients had a lesion over the buccal mucosa which was consistent245 withtheclinical presentation documentedin theexistingliterature. In the 2ndcase, the patienthad white striationswith246erythema in certainareas ofbuccalmucosa whichwasclinicallycorroborativewith thefeatures ofOLP.

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Histopathologically,thereisthepresenceofhyperkeratosisofsurfaceepitheliumalongwithspongiosis,liquefactive248degenerationofthe basalcelllayeranddiffuseinflammatoryinfiltrateextendingdeeperintothelaminapropriaunlikeOLP249 where chronic inflammatory cells are restricted to the juxta-epithelial connective tissue in a band like fashion. This infiltrate250 comprises of plasma cells and eosinophils in addition to lymphocytes and increased numbers of colloid or civatte bodies in251 case of OLR. Perivascular chronic inflammatory cell infiltrate may be seen in drug related lichenoid lesions [12]. Our cases252showedsimilarhistologicpresentations.Since,inboththecases,thereispresenceofchronicinflammatorycellinfiltrate253extend ing deeperintotheconnectivetissuelayerandlargenumberof eosinophils,the possibilityofOLPisexcluded.

254 Clinicallyandimmunohistopathologically,differentialdiagnosisofOLRsinclude:Vesiculo-BullousDiseasessuchas255PemphigusVulgaris,Leukoplakia,Lupuserythematosus(LE)etc.[11].Histopathologicalevaluationofbullou sdiseases256 revealsintraepithelial,subepithelial andsuprabasilarsplit.We can alsoexclude Leukoplakia from OLRas Leukoplakia257clinicallyappearsasgreyish-whitewithcrackedmudappearanceandshowsdysplasticepithelium[12].Allthesefeatures258weremissinginour cases.

Direct Immunofluorescence (DIF) was used to examine the fluorescence patterns in oral lichenoid reactions and to compare260thedegreeofintensityoftheirfluorescence[13].Itwasobservedthattheimmunofluorescencepatternof OLPismore261ragged andfibrillarywhereasitismoreuniformandlessintenseinOLR.However,fibrinogendepositionatthebasement262membrane zonewasabsentin29.2%ofOLR[3].No appreciablestaining was alsonotedinourcase.

IncaseofLupus,DIFoflesionaltissuetypicallyrevealsthepresenceofoneormoreimmunoreactants(usuallyIgM,IgG,or C3)forming ashaggyorgranularband atthebasementmembranezone[14]whichwasnegativeinourcases.

The confirmation of pemphigus vulgaris diagnosis necessitates the direct immunofluorescence evaluation of the perilesional266 tissue,demonstratingthepresenceof antibodies (usuallyIgGor IgM) and complement components(usuallyC3)inthe267 intercellular spaces between the epithelial cells, characterized by a pattern resembling a fish net or chicken wire which is not268presentinourcaseseries.[15].

Inthepresentcaseseries,wepinnedourconfirmatorydiagnosisasOrallichenoidreactionbasedonclinicalfindings, histopathologicalfeaturesanddiagnosisofexclusion.

RemissionofOLRinvolvesthesubstitutionofcausativerestorationswithnon-allergicmaterial.Replacingamalgam272 restorationshasresultedinsignificantenhancementsin93%ofhypersensitivity lesionsassociatedwithamalgam273 contact [16]. In both the cases, the amalgam restoration was replaced by a tooth-coloured restorative material like composite274 resin. The patient started experiencing relief around 2.5-3 months and complete healing was seen in subsequent follow-up.275 There has been some controversy about the malignant potential of lichenoid reactions (2.43%) which is usually thought to be276extremelyrare [1,17].Ioccaetal.(2020)statedthatthetruepotentialofthemalignanttransformationofOLLsishigh277(3.8%) [18].However,thepatientsshould beregularlymonitoreduntilthecompleteremission ofthelesionisnoted[1].

TABLE1:Comparativeanalysisofbothcaseswithfollowingcriteria

FEATURES	CASE 1	CASE 2
Age&sex	61-year-oldfemalepatient	57-year-oldmalepatient
Typeofreaction	Delayed	Delayed
Allergenlocation	Amalgamrestorationon38	Amalgamrestorationon38 and 48 respectively.
Durationofcontact	6years	3-4years
Burningsensation	Present	Present
Erythema	Present	Present
Whitestriations	Absent	Present
Site	Buccalmucosavicinitytoamalgam restoration	Buccalmucosa onbothsidesvicinityto amalgamrestoration
Histologicalfeatures	Diffuse inflammatory infiltrateextending deeper into the laminapropria; basal cell degeneration;numerouschronicinflammatorycellsinfiltrate chiefly characterized bylymphocytes, histiocytes along withplasmacells	Diffuseinflammatoryinfiltrateextendingdeeperintothe laminapropria. Occasional basal cell degeneration andchronicinflammatoryinfiltratealongwithengorged blood vessels and large no ofeosinophils
DIF	Noappreciablestainingdepositsfor IgG,IgA,IgMand C3	Notperformed
Treatment	Amalgamrestorationwasreplacedby a tooth-coloured restorativemateriallikecompositeresin.	Amalgamrestorationwasreplacedbyatooth-coloured restorative material likecompositeresin.
Follow-up	Startedexperiencingreliefafter3monthsoftherapy	Started experiencing relief around 2.5monthsandcompletehealingwasnoticed insubsequentfollow-up

4.CONCLUSION

Dentalamalgamcontinuestobethemostpreferredandaffordablerestorativematerialinthefieldofrestorativedentistry beforeadecadedespitetheavailabilityofnewsyntheticnon-metallicalternatives,predominantlyduetoitssuperior strengthaswellas minimaltechniquesensitivity. Butitmight resultinorallichenoid reactionin susceptible patients.When thelesionappearsintheccloseproximitytoamalgamrestoration,replacementofsuchrestorationcanbeeliminatedby substitutionwithalternativetoothcoloredrestorativemateriallikeGlassionomerorcompositeresinsarerecommended. AlthoughtheclinicopathologicalcharacteristicsofOLParesimilar,OLRandOLPmustbedistinguishedfromoneanother

duetodifferencesinetiology,diagnosisandprognosis,failuretodosomayresultindetrimentaleffectstothepatient. OLRsexhibitahighsusceptibility toundergomalignanttransformation.So,early diagnosis andperiodic follow-up representcrucialmeasures inimpedingtheprogressionofthecondition.

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COMPETINGINTERESTS

Authorshavedeclaredthatnocompeting interestsexist.

AUTHORS'CONTRIBUTIONS

'**DURBAROYCHOWDHURY**'designedthestudy,performedthestatisticalanalysis,wrotetheprotocol,andwrotethefirst draftofthe manuscript.'**RUDRAPRASADCHATTERJEE',''SK.ABDULMAHMUD**'**AND'SUDESHNABAGCHI'** managedtheanalysesofthestudy.'**ARUNITCHATTERJEE**'managedtheliteraturesearches**.**Allauthorsreadand approvedthefinalmanuscript.

CONSENT

Asperinternationalstandardsoruniversitystandards,writteninformedconsenthasbeenobtainedfromthepatient(or otherapprovedparties) andpreservedbytheauthorforpublicationofthiscasereportandaccompanyingimages**.**

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