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CASE REPORT

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Oralne lezije nalik pemphigusu vulgarisu prouzročene niklom

Nickel - Induced Oral Pemphigus Vulgaris -Like Lesions

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Sažetak
U literaturi je zabilježen samo jedan slučaj oralnog pemfigusa za koji se kao uzrok navodi nikal. U ovom prikazu opisali smo deskvamativni gingivitis kod 49-godišnjeg muškarca. Lezija se nalazila u prednjoj regiji mandibule koja je bila u kontaktu s keramičkim krunicama i mostovima. Osim tog oštećenja pronađene su i opsežne ulceracije u području lijeve i desne obrazne sluznice. Nakon godine dana liječenja lezije se nisu povukle. Uklanjanjem krunica i mostova te jakim topikalnim kortikosteroidima postignut je zadovoljavajući rezultat. Dentalna legura ispitivala se nakon toga metalurgijskim tehnikama. Rezultati su pokazali da je njezin glavni sastojak nikal. Patohistološki test i test imunofluorescencije potvrdili su dijagnozu *pemphigus vulgaris*. To nas je navelo na zaključak da pacijent boluje od lezija nalik na *pemphigus vulgaris* izazvanih niklom.

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Ključne riječi
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Uvod

Pemfigus je rijetko autoimunosno stanje koje zahvaća kožu i sluznicu. Karakterizira ga crvenilo najprije na oralnoj sluznici, a poslije i na koži. U literaturi je navedeno da se pemfigus na početku u 50 posto slučajeva manifestira na oralnoj sluznici prije negoli zahvati kožu (1,2). Etiologija mu je i dalje nejasna. Karakteristično je za pacijente s tom bolešću da imaju autoantitijela koja ciljaju međustanične spojeve epidermisa/epitela te uzrokuju intraepitelna razdvajanja tkiva. To se klinički očituje kao mjehur na koži i oralnoj sluznici. Pemfigus je smrtonosna vezikulobulozna bolest i rano je otkrivanje ključno za uspješno liječenje. U dosadašnjim istraživanjima autori upućuju na činjenicu da određeni lijekovi, kao penicilamin i captopril, mogu izazvati pemfigus (3). Također se pojavljuje kod pacijenata s malignim novotvorinama i to kao paraneoplastični pemfigus (4). U literaturi je opisan samo jedan slučaj za koji autori pretpostavljaju da

Introduction

Pemphigus is a rare autoimmune condition affecting both the skin and mucosa. It is characterized by flare- ups of symptoms that start and persist in the oral cavity prior to presenting in the skin. It has been reported that more than 50% of pemphigus cases initially appear on the oral mucosa prior to the progression of the disease to the skin (1,2). The etiology of majority of pemphigus cases is poorly understood. Characteristically, patients with pemphigus have autoantibodies in the circulation and at the intercellular bridges of the epidermis/epithelium causing the intraepithelial separation leading to blisters on the skin and mucosa. Pemphigus is a fatal vesiculobullous disease and early detection is very important for the effective treatment. Previous reports have shown that pemphigus can be induced by certain medications, for example penicillamine and captopril (3). In addition, pemphigus can occur in patients with malignant neo-

je pemfigus nastao zbog nikla (5). U ovom prikazu opisuje se pacijent čiji metalkeramički fiksno-protetički rad sadržava nikal i imao ga je u ustima više od 15 godina. Predstavili smo rijedak slučaj pojave lezija sličnih pojavi pemfigus vulgaris izazvanih niklom i to uglavnom na oralnoj sluznici

Prikaz slučaja

49-godišnjeg muškarca dermatolog je poslao u Kliniku za oralnu medicinu Stomatološkog fakulteta Sveučilišta Chulalongkorna u Bangkoku u Tajlandu na pregled i obradu bolnih lezija gingive i bukalne sluznice koje su perzistirale u ustima godinu dana. Pacijent je upozorio da ima erozivna oštećenja na lijevoj i desnoj strani bukalne sluznice i na mekom nepcu, zatim generaliziranu eroziju gingive te deskvamaciju gingive donje usne. Osim tih simptoma naveo je i grlobolju koja se pojavila dva mjeseca prije lezija u usnoj šupljini. Pacijent je najprije zatražio pomoć dermatologa u siječnju 2006. godine, uglavnom zbog bolnih oštećenja u usnoj šupljini i disfagije. Na njegovu abdomenu i nogama pronađene su papule, a istodobno su se ljuštili suhi, hiperpigmentirani dijelovi kože. U povijesti bolesti naveo je hemoroide i alergijsku reakciju – osip na lijek Roxithromycin©. Ostale bolesti nema. Rentgenska snimka toraksa pokazala je normalnu kardiovaskularnu strukturu. Nije bilo indikacija za pulmonalne ili pleuralne bolesti.

Histopatologija i imunofluorescencija

Dermatolog je obavio biopsiju bukalne sluznice s desne strane. Mikroskopski nalaz potvrdio je mnoštvo nekrotičnih keratinocita, keratinocita, reaktivnih keratinocita te mnogobrojne neutrofile i fibrin. Nalaz direktne imunofluorescencije bio je pozitivan na IgM i C3 za nekrotične keratinocite, ali negativan za IgG i IgA intercelularno. Patohistološki nalazi i nalazi imunofluorescencije upućivali su na dijagnozu erythema multiforme. Dermatolog je u privatnoj bolnici za terapiju odredio prednisolon, cyclophosphamid, azathioprin, topikalni pimecrolimus, benzidaminsku hidrokloridnu vodicu za ispiranje usta i triamcinolon acetonid 0,1 posto u orabazi. Simptomi grlobolje nestali su nakon tromjesečne terapije, ali oralne lezije samo su djelomice zacijeljele. Na anteriornom dijelu mandibule, u području pričvrstne gingive, lezije su erodirale i pojavila se deskvamacija epitela.

U veljači 2007. godine nastale su egzacerbacije simptoma oralnih lezija te je pacijent poslan u Kliniku za oralnu medicinu Stomatološkog fakulteta Sveučilišta Chulalongkorna. Tamo je pregledom potvrđeno difuzno područje erozija i deskvamacije epitela marginalne i pričvrsne gingive s posebnim naglaskom na labijalne površine anteriornih dijelova mandibule (slika 1.a). Fiksnoprotetički metal-keramički radovi bili su mostovi napravljeni prije 15 godina, a pokrivali su regije 25 – 27, 35 –37 i 33 –46. Bukalna sluznica s desne strane imala je iregularne i duboke ulceracije dimenzija 3,0 x 2,5 centimetara. Bukalna sluznica s lijeve strane te plica bucalis bile su prekrivene erozijama i bijelim naslagama dimenzija 3,5 x 2,0 centimetra (slika 2.a i 2.b). Ponovili smo biopsiju i direktnu imunofluorescenciju s lijeve retromolarne

plasms, so-called paraneoplastic pemphigus (4). There is only one report in the literature which suggests that nickel can induce pemphigus (5). The report discusses a patient who had crowns and bridges in the oral cavity for more than 15 years. Also, the cores of dental alloy mainly contained nickel. We report a very rare case of nickel-induced pemphigus vulgaris-like lesions mainly affecting the oral mucosa.

Case report

A 49-year-old man was referred by his dermatologist to the Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand for evaluation and treatment of painful lesions on his gingiva and buccal mucosa which had been present for a year. The patient reported a history of erosive lesions on the right and left buccal mucosa, soft palate, floor of the mouth, generalized gingival erosion and desquamation on the lower labial mucosa. Additionally, he also experienced a severe sore throat which had begun 2 months prior to oral lesions. The patient initially sought treatment from a dermatologist with a chief complaint of painful lesions and dysphagia in January, 2006. Some dry, scaly, hyperpigmented patches and papules were also present on his abdomen and lower legs. He had a history of hemorrhoids and an allergic rash to Roxithromycin©, but appeared otherwise to be generally healthy. A chest radiograph showed normal heart and vascular structures. There was no evidence of pulmonary or pleural diseases.

Histopathology and immunofluorescence

The referred dermatologist had previously performed a biopsy of the right buccal mucosa and a microscopic examination revealing that the specimen demonstrated both necrotic and non-necrotic keratinocytes and also reactive keratinocytes with numerous neutrophils and fibrin. Direct immunofluorescence was positive for IgM and C3 in necrotic keratinocytes but was negative for IgG and IgA at the intercellular substance. Histopathologic features and direct immunofluorescence results suggested a diagnosis of erythema multiforme. He had been treated by a dermatologist from a private hospital with prednisolone, cyclophosphamide, azathioprine, topical pimecrolimus, benzydamine hydrochloride mouthwash, and triamcinolone acetonide 0.1% in orabase. His symptom of sore throat markedly improved after a three month treatment but oral lesions only partially healed with erosion and desquamative epithelium on the anterior region of the mandibular attached gingiva.

In February, 2007, oral lesions flared up and the patient was referred to the Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University. Oral examination revealed a diffuse area of erosion and desquamative epithelium of the marginal and attached gingiva, particularly on the labial surface of the mandibular anterior region (Fig. 1A). The patient had porcelain fused to metal crowns and bridges on the left permanent maxillary second premolar to the left permanent maxillary second molar (25-27), and the left permanent mandibular second premolar to the left permanent mandibular second molar (35-37), the left permanent mandibular canine to the right permanent mandibular first molar (33-46).

strane zato što je dijagnoza upućivala na pemphigus vulgaris (vremenski slijed progresije bolesti, terapije ljekovima i odgovor na liječenje predstavljeni su na slici 3.).

Analiza dentalnih legura

Nepoznata dentalna legura analizirana je metalurškim tehnikama ispitivanja u koje se ubrajaju radiološka difrakcija, skening elektronska mikroskopija, mikro analiza elektrona i metalografija. Rezultati su pokazali da je sastav legure:

nikal	78,9 wt%	± 3,1 wt%
krom	13,8 wt%	± 2,3 wt%
molibden	5,0 wt%	± 0,5 wt%
aluminij	2,0 wt%	± 0,3 wt%
titan	0,3 wt%	± 0,1 wt%
silikon	u tragovima	

U leguri u ustima uočeno je da je gradijent nikla uz rub gingive bio najniži. Naime, nikal se u tome dijelu s vremenom postupno otpuštao sa slobodnih površina legure.

Izvadili smo sve stare mostove i krunice te liječili lezije jakim topikalnim kortikosteroidom – fluocinolon acetonidom 0,1 posto u otopini (FAS) i clobetasol-propionatom 0,05 posto u orobazi. FAS od 0,1 posto apliciran je na gingivu, a clobetasol-proprionat na bukalnu sluznicu s desne i lijeve strane tri puta na dan. Nakon godine i pol dogodila se kompletna remisija na gingivi (slika 1. b). I za lijevu i desnu bukalnu sluznicu trebalo je isto razdoblje za oporavak, uz liječenje clobetasol-propionatom 0,05 posto do veljače 2010. (slika 2. c i 2. d). U srpnju te godine biopsija je ponovljena na mjestu erozije bukalne sluznice s desne strane.Patohistološki nalaz pokazao je intraepitelno razdvajanje i akantolizu stanica (slika 4. a i 4. b). Direktnom imunofluorescencijom pronađeni su intercelularno depoziti IgG-a. Zato je potvrđena dijagnoza – pemphigus vulgaris. Kako bi se doznalo je li pacijent alergičan na čestice nikla, poslan je na epikutani alergološki test (TRUE). Rezultati su pokazali da je nakon dva dana razvio slabu pozitivnu reakciju na niklov sulfat uz pojavu kutanih eritematoznih papula. Četvrti dan nastala je jaka pozitivna reakcija uz pojavu kutanih eritematoznih papula i vezikula (slika 5.) Na temelju toga možemo zaključi-

He had worn these prosthetic replacements for 15 years. The right buccal mucosa had an irregular and deep ulceration 3.0 x 2.5 cm in size. The left buccal mucosa and mucobuccal fold had an erosive area and mild white patches 3.5 x 2.0 cm in size (Fig.2A, B). We repeated a biopsy and direct immunofluorescence from the left retromolar area. Histopathological features showed many acantholytic cells. Thus, the diagnosis of this case was consistent with pemphigus vulgaris. The time line of the occurrence of the oral lesions, drug administration and the treatment responses is shown in Fig. 3.

Dental Alloy analysis

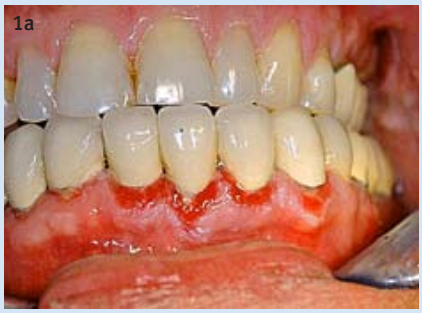
The unknown dental alloy was investigated using metallurgy techniques including X-Ray diffraction (XRD), scanning electron microscopy (SEM), energy dispersive X-Ray spectroscopy (EDS), Electron Probe Micro-analyzer (EPMA) and metallography. The composition of the alloy is shown as follows:

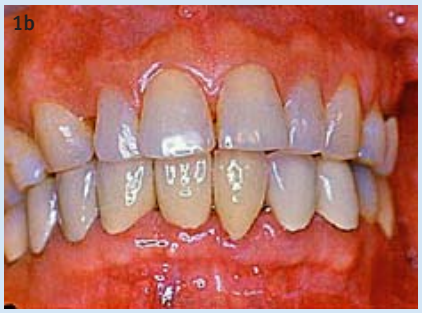
Nickel	78.9 wt%	± 3.1 wt%
Chromium	13.8 wt%	± 2.3 wt%
Molybdenum	5.0 wt%	± 0.5 wt%
Aluminum	2.0 wt%	± 0.3 wt%
Titanium	0.3 wt%	± 0.1 wt%
Silicon	trace	

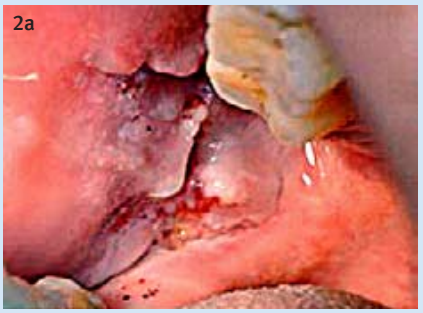
Within the nickel alloy, nickel compositional gradient was noticed, specifically in the area closer to the gingiva. Nickel has been depleted in this region because a significant amount of nickel has been released at the free surface.

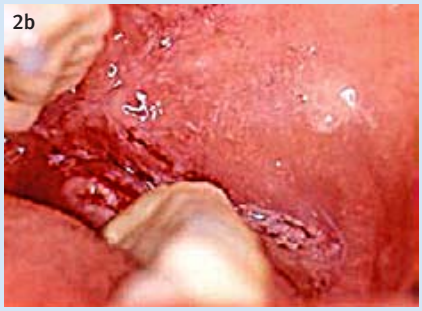
We removed all old porcelain crowns and bridges to porcelain fused to precious metal and treated the lesions with potent topical steroids- fluocinolone acetonide 0.1% in solution (FAS) and clobetasol propionate 0.05% in orabase. FAS 0.1% was applied on the gingiva, whereas clobetasol propionate was applied on the right and the left buccal mucosa three times a day. There was a complete remission on the gingiva one and half years after the treatment (Fig 1B). The right and the left buccal mucosa showed gradual remission one and a half years after the treatment with clobetasol propionate 0.05% until February, 2010 (Fig 2 C, D). In July, 2010, we repeated a biopsy at the erosion of the right buccal mucosa. Again, the histopathologic results exhibited the presence of the intraepithelial separation and acantholytic cells (Fig. 4 A, B). Direct immunofluorescence showed IgG deposited at the intercellular substances. Thus, the diagnosis was then established as pemphigus vulgaris. To investigate whether or not the patient was sensitive to nickel particles, the thin layer rapid use epicutaneous (TRUE) test was performed. The results showed that on day

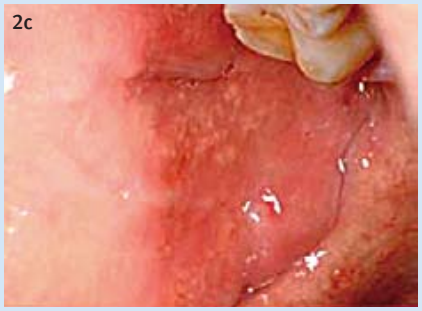
Slika 1.a Erozije gingive i deskvamirani epitel u području mostova i krunica
Figure 1a Gingival erosion and desquamative epithelium at the area of crowns and bridges.
Slika 1.b Nakon uklanjanja fiksnoprotetskih radova od niklove legure i tretmana topikalnim korstikosteroidom – fluocinolon acetonidom 0,1 posto u otopini, tijekom godine i pol gingiva se vratila u normalno stanje
Figure1b After removal of nickel rich-alloy crowns and bridges, treatment with topical steroids-fluocinolone acetonide 0.1% in solution for 1 year and 6 months, the gingiva returned to normal
Slika 2. Lijeva i desna bukalna sluznica (A,B) prije tretmana u veljači 2007; nakon liječenja clobetasol propionatom 0,05 posto, desna i lijeva obrazna sluznica (C, D) vraćene su u normalno stanje u veljači 2010.
Figure 2 The right and the left buccal mucosa (A, B) before treatment in February, 2007. After treatment with clobetasol propionate 0.05%, the right and the left buccal mucosa (C, D) returned to normal in February, 2010

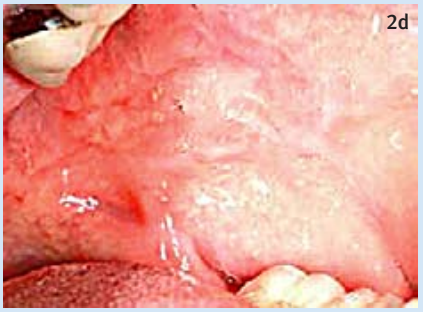


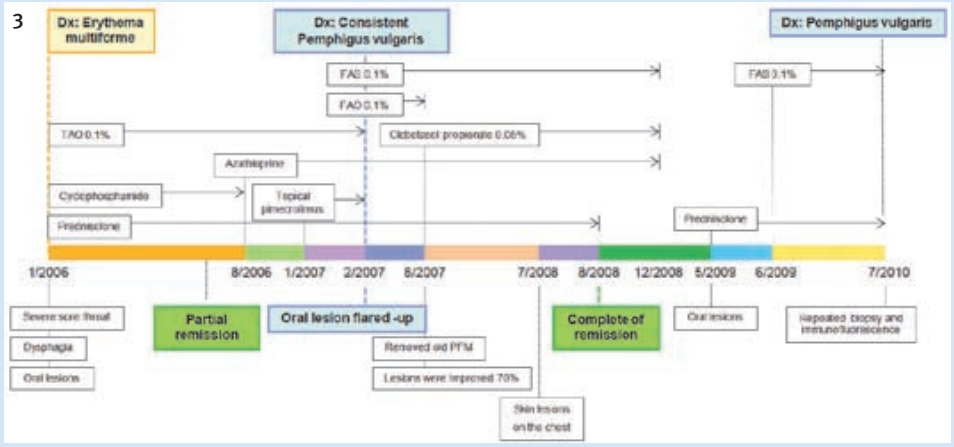


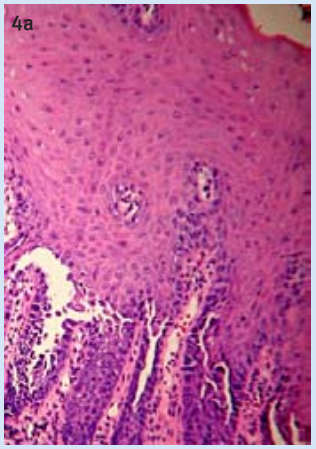


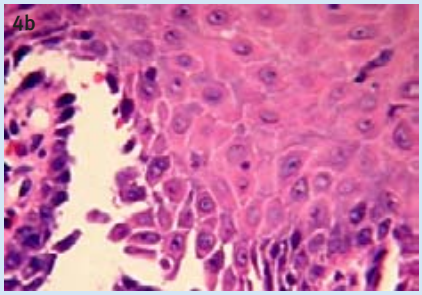


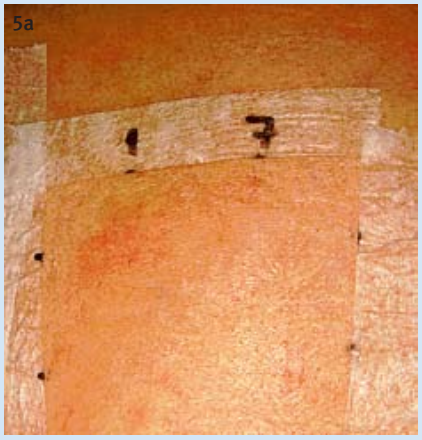


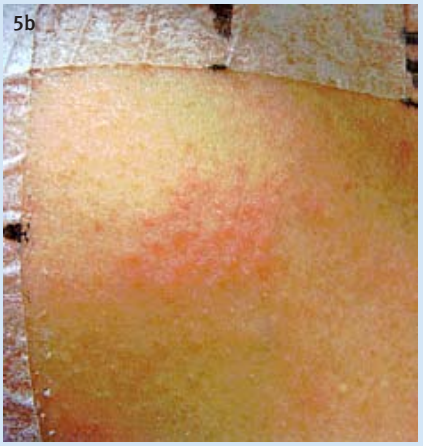












Slika 3. Vremenski slijed progresije bolesti, terapije ljekovima i odgovor na liječenje
PFM = keramika i metal; FAS = fluocinolon acetonid u otopini; FAO = fluocinolon acetonid u orobazi
Figure 3 Time line of the disease activity, drug administration and treatment responses
PFM = Porcelain fuse to metal; FAS = Fluocinolone acetonide in solution; FAO = Fluocinolone acetonide in orabase
Slika 4.ab Histopatološke karakteristike pokazuju tipično intraepitelno razdvajanje (A, H i E bojenje, originalno povećanje 200 x) uz prisutnost akantolitičkih stanica (B, H i E bojenje, originalno povećanje 400 x).
Figure 4ab Histopathological features of this case show a typical intraepithelial separation (A, H & E staining, original magnification 200X) with the presence of acantholytic cells (B, H & E staining, original magnification 400X).
Slika 5.ab Tanki sloj brzoga epikutanog testa (TRUE); drugi dan je test bio pozitivan na niklov sulfat (slaba reakcija – eritematozne papule);četvrti dan test je bio pozitivan na niklov sulfat (jaka reakcija – eritematozne papule i vezikule)
Figure 5ab The thin layer rapid use epicutaneous (TRUE) test was positive for Nickel sulphate (weak reaction - erythematous papule) on day 2, and was positive for Nickel sulphate (strong reaction- erythematous papules and vesicle) on day 4.

ti da se u ovom slučaju radilo o *pemphigus vulgaris* prouzročenim niklom.

Rasprava

Prvi i jedini izvještaj u literaturi u kojem se spominje pemphigus vulgaris prouzročen niklom potječe iz 1998. godine (5). U ovom slučaju demonstrirali smo progresiju bolesti uz patohistološke dokaze, direktnu imunoflorescenciju, analizu dentalnih legura i test TRUE i sve nabrojeno podupire tezu da je kod pacijenta nikal izazvao stanje slično dijagnozi pemfigus vulgaris. Rezultati prve biopsije i direktne imunofluorescencije bili su negativni na prisutnost IgG-a i IgA-a na intercelularnim tkivima, ali je zabilježena velika količina neutrofila. Taj nalaz sugerira da su neutrofili tipične stanice akutne upale koje se skupljaju na mjestu ozljede nakon traume. Smatra se da intercelularne adhezivne molekule epitela (ICAM-1) olakšavaju migraciju neutrofila iz krvnih žila. Neutrofili također proizvode proteaze koje potiču eroziju oralnog epitela. Ako tijekom bolesti nastane epidermalni mjehur, patogeni mehanizam ovisi o aktivaciji komplemenata i migraciji neutrofila na spoj između dermisa i epidermisa (6). Razlog da na prvom testiranju nismo pronašli autoantitijela je dvojak – ili ih nije bilo ili ih bilo jako malo. Nadalje, mehanizam akantolize bez autoantitijela još nije razjašnjen. Imunopatogeneza ovog slučaja slična je onoj pemfigusa prouzročenog lijekovima. Zapravo, ako je pemfigus potaknut lijekovima, nakupljanje antitijela koje rezultira akantolizom isto je kao i kod idiopatskog pemfigusa. Zabilježeno je da neki lijekovi izravno potiču akantolizu bez nakupljanja antitijela (7), no taj molekularni mehanizam još nije razjašnjen. Osim autoantitijela, aktivator plazminogena također je povezan s akantolitičkim lezijama (8). U dosadašnjim studijama istaknuto je da aktivator plazminogena ima važnu ulogu u akantolizi izazvanoj tiolom (9).

Druga biopsija pokazala je prisutnost mnogih akantolitičkih stanica. Njezini rezultati omogućili su različite diferencijalne dijagnoze, kao na primjer Darijerovu bolest i benigni obiteljski pemfigus. Te dvije genodermatoze nasljeđuju se autosomno dominantno, a izazivaju ih mutacije gena ATP2A2 u slučaju Darijerove bolesti te ATP2C1, ako je riječ o benignom obiteljskom pemfigusu (10, 11). No, isključuje ih to što te bolesti nisu navedene u obiteljskoj anamnezi te izostanak klasične kliničke slike keratotičnih papula, odnosno osipa na kožnim pregibima. Groverova bolest bila je također vjerojatna dijagnoza, ali kako se simptomi iznimno rijetko pojavljuju u usnoj šupljini, isključuje je kao mogućnost. Kako smo pronašli intraepitelno razdvajanje s akantolitičkim stanicama, paraneoplastični pemfigus se nametnuo kao jedna od mogućih dijagnoza. Da bi se otkrila eventualna malignost, obavljene su daljnje pretrage, no nisu dale pozitivne rezultate. Direktna imunofluorescencija druge biopsije dala je pozitivne rezultate na IgG intercelularnog tkiva oralnog epitela. Indirektna imunofluorescencija bila je negativna. Ti

2, the patient developed a weak positive reaction to nickel sulphate with the presence of cutaneous erythematous papules. On day 4, the patient developed a strong positive reaction to nickel sulphate, with the presence of cutaneous erythematous papules and vesicles (Fig 5). We have concluded that the present case is “nickel-induced pemphigus pemphigus”.

Discussion

The first and the only short communication report of nickel-induced pemphigus was documented in the literature in 1998 (5). In our case, we have demonstrated the progression of the disease along with the evidence of histopathology, direct immunofluorescence, dental alloy analysis and TRUE test supporting that nickel possibly induced a pemphigus vulgaris-like condition in the patient. At the first biopsy, the finding of direct immunofluorecence was negative for IgG and IgA at the intercellular substances and numerous neutrophils were seen. This finding suggests that neutrophils are recruited to the site of injury following trauma and are the hallmark of acute inflammation. Intercellular adhesion molecule1 (ICAM-1) of the epithelium may facilitate migration of the neutrophils from blood vessels. The neutrophils may also produce protease enzymes that could induce erosion of the oral epithelium. In epidermal blister formation diseases, the pathogenic mechanism was shown to be dependent on complement activation and recruitment of neutrophils to the dermal-epidermal junction (6). The reason why we could not detect the autoantibody in this case was that it was possibly absent or at a very low level. Furthermore, the molecular mechanism of acantholysis in the absence of autoantibody is still unclear. The immunopathogenesis of this case may be similar to drug induced pemphigus. In fact, in case of drug induced pemphigus, some of the drugs induced antibody formation, which resulted in acantholysis via a mechanism identical to that found in idiopathic pemphigus. However, other drugs are postulated to induce acantholysis directly in the absence of antibody formation (7). However, the molecular mechanism of acantholysis in the absence of autoantibody still remains unclear. Besides the autoantibodies, plasminogen activator system has been linked to acantholytic lesions (8). Previous studies showed that the plasminogen activators system also played an important role in thiol-induced acantholysis (9).

The second biopsy showed many acantholytic cells leading to differential diagnosis of various diseases, for example, Darier disease and benign familial pemphigus. These conditions are autosomal, dominantly inherited genodermatoses caused by mutations of ATP2A2 and ATP2C1 genes, respectively (10, 11). However, lack of a familial history and classical clinical signs of keratotic papules in the former and flexural rashes in the later negates the possibility of the conditions. Grover’s disease could be a possible diagnosis but oral mucosal involvement is extremely rare (12). As we found the intraepithelial separation with the presence of acantholytic cells, paraneoplastic pemphigus is one of the possible diagnoses. Further evaluation for malignancies was performed but there was no evidence of any malignant involvement in

rezultati mogu se objasniti činjenicom da je pacijent uzimao sistemske kortikosteroide koji su utjecali na proizvodnju antitijela. Zbog toga su vrijednosti serumskih antitijela bile niske, odnosno testovi ih nisu mogli detektirati.

Keratinociti su prve stanice koje su napadnute kada je oralna sluznica izvrgnuta toksičnim supstancijama. Mikročestice korodiranog metala, na primjer nikla, mogu djelovati kao alergeni te oštetiti keratinocite. Jedno istraživanje in vitro pokazalo je da samo Ni2+, Co2+ i Cr2+ mogu potaknuti veliko otpuštanje TNF-alfa koji test ELISA može detektirati 48 sati nakon stimulacije (13). Nikal je poznat kao kontaktni alergen i često uzrokuje preosjetljivost i promjene u imunosnom sustavu ljudi (14).

Mi smo zaključili da su mikročestice nikla u ovom slučaju djelovale kao alergeni te su potaknule alergijsku preosjetljivost na oralnoj sluznici. Kao odgovor na novi antigen, stvorila su se autoantitjiela pemfigusa zahvaljujući fenomenu širenja epitopa te su kasnije prouzročila akantolizu. Rezultat je intraepitelno razdvajanje koje se kod našeg pacijenta manifestiralo kliničkom slikom oralnog pemfigusa. Također je moguće da je nikal izazvao pemfigus na neki drugačiji način od nastanka akantolize. Imunopatogeneza i akantoliza u ovom slučaju slična je patogenezi kod lijekovima izazvanog pemfigusa u jednom eksperimentalnom istraživanju (15).

Naš prikaz slučaja drugi je u literaturi u kojem se daju dokazi o česticama nikla kao mogućim inicijatorima oralnih lezija sličnih pemfigusu. Osim toga u ovom je opisu istaknuto da primjena visokih doza topikalnih kortikosteroida učinkovito liječi oralni pemfigus. Stomatolozi i dermatolozi trebaju biti svjesni toga rijetkog stanja izazvanog korodiranim metalom fiksnoprotetskih radova.

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this case. The direct immunofluorescence of the second biopsy showed IgG positive to the intercellular substances of the oral epithelium but the indirect immunofluorescence was negative. These findings could be explained by the fact that the patient was on the systemic steroid and the antibody production was suppressed. As a result, the serum levels of autoantibodies were at a very low level or undetectable.

Keratinocytes are the first target cells when oral mucosa is exposed to any toxic substances. Microparticles of the corroded metal such as nickel particles may act as allergens and then damage the keratinocytes. Previously, an *in vitro* study showed that only Ni2+, Co2+ and Cr2+ could induce a significant release of TNF alpha detectable by ELISA after 48 h stimulation (13). Nickel has been known as contact allergen that frequently causes hypersensitivity and alterations of immune responses in humans (14).

We concluded that the nickel microparticles in this case are postulated to act as allergens and induce allergic hypersensitivity in the oral mucosa. The pemphigus autoantibodies to newly-exposed antigens are then developed by the epitope spreading phenomenon resulting in acantholysis later. As a result, the intraepithelial separation formed, leading to severe oral pemphigus in this patient. It is possible that nickel induced pemphigus by activating different mechanisms of acantholysis. The immunopathogenesis and acantholysis process in this case is similar to drug-induced pemphigus in one experimental investigation (15).

Our case report mentions a second case report that showed the evidence of nickel-particles possibly inducing pemphigus-like lesions on the oral mucosa. Moreover, our case report shows that potent topical steroids have been found to be effective in the treatment of oral pemphigus. Dentists and dermatologists should be aware of this rare condition which can develop on the oral mucosa from the corroded metal in crowns and bridges.

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Abstract
So far, only a single case of nickel-induced pemphigus has been reported in the literature. We present a case of a 49-year-old male who had experienced a desquamative gingivitis on the anterior mandibular region which was in contact with porcelain crowns and bridges and severe ulcerations on the right and left buccal mucosa. The lesions did not respond to any medications for a year. After removal of those crowns and bridges with the treatment of potent topical steroids, the lesions responded dramatically. The dental alloy used as the core of crowns and bridges was further investigated using metallurgy techniques. The results showed that the dental alloy mainly contained nickel. Histopathologic and direct immunofluorescence evaluations confirmed a diagnosis of pemphigus vulgaris. We concluded that the patient had experienced nickel-induced pemphigus vulgaris-like lesions on the oral mucosa.

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Key words
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