Poganya dijagnoza tuberkuloze usne šupljine kao prekancerozne lezije

Tuberculosis of the Oral Cavity Misdiagnosed as Precancerous Lesion

Introduction

Despite advances in diagnostic and therapeutic opportunities, tuberculosis (TB) still remains one of the leading causes of death around the world. The World Health Organization (WHO) reported the incidence of 9.6 million global cases of TB in 2014, predominantly in South-East Asia and Western Pacific nations. In the last ten years, the prevalence of TB has decreased. The incidence of TB in Croatia is lower than the average incidence in the European region of the WHO (12.4/100 000 in 2013), but it still falls short of...
smanjiti morbidity u razvijenim zemljama (2). Rizični čimbenici za razvoj TB-a uključuju medicinska stanja koja slabe imunosustav domaćina, kao što su dijabetes ili rak, uzimanje imunosupresivnih lijekova, infekcija HIV-om i starija doba (3). TB je kronična zaraza, granulomatozna bolest uzrokovana Mycobacterium tuberculosis i obično je ograničena na pluća, iako može biti zahvaćen bilo koji organ u tijelu (koža, bubrezi, ždrijelo, kosti, gastrointestinalni sustav, središnji čivani sustav i limfni sustav) (4). Obično se pojavljuje u sekundarnom obliku kao rezultat reaktiviranja latentne infekcije. Procjenjuje se da je trećina svjetske populacije po-godena Mycobacterium tuberculosis, a to su većinom asimptomske infekcije (3). Primarni oralni TB rijetko je opisan i taj je oblik obično sekundarna manifestacija plućne tuberkuloze posredstvom kontaminiranog sputuma ili hematogenog širenja. Oralne lezije, kao početna manifestacija tuberkuloze, također su opisane i smatraju se posljedicom aktivnoga plućne TB-a (5). Oralni TB vrlo je rijedak u Hrvatskoj, a može se također vidjeti u većini drugih zemalja, poput Japana (6). Oralne lezije TB-a pojavljuju se u 0,05 do 5 posto zaraženih bolesnika, uglavnom kao bezbolni kronični ulkus (7, 8). Sekundarni oralni TB uglavnom se pojavljuje na jeziku, usnama, sluznici obraz, nepcu, gingivi i jezičnom frenulumu (9 – 11). Protokol liječenja, kad je riječ o odrašćima, sastoji se od dvomješecne intenzivne faze liječenja antituberkulotickima, poput izonizazida, rifampicina, etambutola, pirazinamida, nakon čega slijedi kontinuirana faza liječenja izonizazidom i rifampicinom tijekom četiri mjeseca (12).

Svrha ovog prikaza slučaja bila je pokazati ekstremno rijetku oralnu leziju kao posljedicu primarne plućne tuberkuloze koja je najprije pogrešno dijagnosticirana kao precance pronog oralna lezija.

**Prikaz bolesnika**

Pacijent u dobi od 68 godina upućen je u Zavod za oralnu medicinu Stomatološkog fakulteta Sveučilišta u Zagrebu zbog bolne ulceracije jezika (slika 1.). Tijekom prvog pregleda uzeta je detaljna medicinska anamneza te obavljen klinički pregled sluznice usne šupljine i palpacija regionalnih limfatičkih čvorova. Toluudinski test sumnjive lezije učinjen je tijekom prvog kontrolnog pregleda. Histopatološka analiza prvoga i drugoga biopsijskog uzorka obavljena je u Zavodu za oralnu kirurgiju. Histopatološka analiza prvoga biopsijskog uzorka pokazala je nespecifičnu upalu, a drugoga kazeoznu nekroz bez pozitivnog bojenja prema Ziehl-Neelsen. Treća biopsija učinjena je na Odjelju za kirurgiju glave i vrat Vrinke za tumore Kliničkoga bolničkog centra Sestre milosrdnice. Na konzultaciju trećeg biopsijskog uzorka, histopatološka analiza pokazala je granulomatoznu upalu uvezujuju na sarkoidozu (slika 2.), a pacijent je nakon toga upućen na daljnje pretrage u Zavod za kliničku imunologiju i reumatologiju Kliničkoga bolničkog centra Zagreb, gdje je postavljena sumnja na aktivnu tuberkulozu. Tijekom hospitalizacije u Zavodu za kliničku imunologiju i reumatologiju Kliničkoga bolničkog centra Zagreb, pacijent je bio podvrgnut cjelovitom fizičkom pregledu te laboratorijskoj i radiološkoj dijagnostici. Detaljna medicinska morbidity in developed countries (2). Risk factors for developing TB include medical conditions that reduce host immunity, such as diabetes or cancer, taking immunosuppressive drugs, HIV infection, elderly age (3). TB is a chronic infectious, granulomatous disease caused by Mycobacterium tuberculosis which is usually confined to the lungs, albeit it may affect almost any organ in the body (skin, kidneys, pharynx, bones, gastrointestinal tract, central nervous system and lymphatic system) (4). Tuberculosis usually occurs in its secondary form, as a result reactivation of a latent infection. It is estimated that one third of the world population, or about 2 billion people, have been affected with Mycobacterium tuberculosis, which are mainly asymptomatic infections (3). Primary oral TB has rarely been described and usually oral TB is secondary manifestation of pulmonary TB through contaminated sputum or hematogenous spread. Oral lesions as initial manifestations of TB have also been described and are thought to be consequence of active pulmonary TB (5). Oral TB is very rare in Croatia, as is the case in other countries such as Japan (6). Oral TB lesions are found in 0.05%-5% of infected patients, mostly as chronic painless ulcers (7, 8). Secondary oral TB is usually seen on the tongue, lips, buccal mucosa, palate, gingiva and lingual frenulum (9-11). The preferred regimen for treating adults with TB consists of intensive phase of antituberculosis agents with isoniazid, rifampicin, ethambutol, pyrazinamide during two months followed by a continuous phase with isoniazid and rifampicin during four months (12).

The aim of this case report was to describe an extremely rare oral lesion as a result of primary pulmonary tuberculosis, which was initially misdiagnosed as precancerous oral lesion.

**Case report**

The present case report describes a 68-year-old male patient who was referred to Department of Oral Medicine, School of Dental Medicine, University of Zagreb. He was complaining about painless tongue ulceration (Figure 1). A detailed medical history, clinical examination of the oral mucosa and palpation of regional lymph nodes were performed during the first examination. The toluidine test of suspected lesion was performed at each control examination. The first and second biopsy samples for histopathologic analysis were taken at the Department of Oral Surgery. The analysis of the first biopsy sample for histopathology revealed a non-specific inflammation, the second sample revealed caseous necrosis without positive Ziehl-Neelsen staining. The third biopsy was taken at the Department for Head and neck Surgery, Clinic for Tumors, Clinical Hospital Center “Sisters of Mercy”. After taking the third biopsy sample, histopathology revealed granulomatous inflammation, which was highly suspected to be sarcoidosis (Figure 2), and the patient was further referred to the Department of Clinical Immunology and Rheumatology, Clinical Hospital Centre Zagreb where active TB was suspected.

During hospitalization at the Department of Clinical Immunology and Rheumatology, Clinical Hospital Centre Za-
anamneza pokazala je da je riječ o zdravom pacijentu koji ne uzima nikakve lijekove i dosad nema zabilježene alergijske reakcije, osim što je pušač i konzumira alkohol. Izvijestio je samo o laganom gubitku težine, ali bez općih simptoma poput vrućice, kašlja ili boli u prsima. Klinički pregled sluznice usne šupljine otkrio je ulceraciju na ventrolateralnoj površini jezika promjera oko dva centimetra. Preostala oralna sluznica bila je uredna, bez ikakvih kliničkih promjena i simptoma. Palpacija regionalnih limfnih čvorova nije otkrila povećanje. Toluidinski test sumnjive lezije obavljen je tijekom svakog kontrolnog pregleda, ali uvijek je bio negativan. Fizikalni pregled psrnog koša otkrio je bilateralno prisutne grube krepićnje tijekom hospitalizacije u Zavodu za kliničku imunologiju i reumatologiju Kliničkog bolničkog centra Zagreb, a laboratorijski nalazi kompletnih krivih slika pokazali su normocitnu anemiju kronične bolesti. Radiografija pluća uočili su mali multipli čvorovi bilateralno, a pozitivan direktni sputum potvrdio je dijagnozu aktivnoga primarnog plućnog TB-a (slike 3. i 4.).

Pacijent je liječen četirima standardnim antituberkulotikama kako slijedi – izoniazidom (1x 400 mg), rifampicinom (2x 300 mg), etambutolom (3x 400 mg) i pirazinamidom (3x 500 mg), pa se njegova ulcerozna lezija jezika brzo poboljšala istodobno s plućnim statusom (slika 5.).

greb the patient underwent a complete physical examination, and laboratory and radiological diagnostics. From a detailed medical history of the patient, we found out that he was healthy, was not taking any medication, and had no registered allergy. He was a cigarette smoker and alcohol consumer. He only reported a slight weight loss, but without signs of fever, cough or chest pain. Clinical examination revealed ulceration on his ventro-lateral surface of the tongue, approximately two centimeters in diameter. The remaining oral mucosa was without any clinical changes and symptoms. Palpation of regional lymph nodes has not revealed any enlargements. The toluidine test of the suspected lesion was performed at each control examination but it was always negative. During hospitalization at the Department of Clinical Immunology and Rheumatology, Clinical Hospital Centre Zagreb, physical chest examination revealed a bilaterally coarse crepitation and laboratory findings of his complete blood count revealed normocytic anemia of chronic disease. Radiographic examination of lungs showed multiple small nodules bilaterally and positive direct sputum smear confirmed the diagnosis of active primary lung TB (Figures 3-4).

The patient was treated with four standard antituberculosis agents as following isoniazid (1x 400 mg), rifampicin (2x 300 mg), ethambutol (3x 400 mg) and pyrazinamide (3x 500 mg) and his ulcerated lesion of the tongue rapidly improved along with pulmonary status (Figure 5).
Rasprava

Iako se bilježi porast incidencije ekstrapulmonalnog TB-a, zbog rijetkih kliničkih prikaza ta je bolest i dalje nedovoljno dijagnosticiran klinički entitet (13). Ovaj prikaz slučaja opisuje bezbolan oralni ulkus kao sekundarnu leziju aktivnoga primarnoga TB-a pluća, bez drugih specifičnih plućnih simptoma. Na početku smo mislili da pacijent nije bio svjestan svoje loše navike guranja jezika na preostali zub 33 i/ili na neodgovarajuću protezu, te je u terapiji dobio topikalnu kortikosteroidnu mast (betatematon) u orabizi koju je primjenjivao četiri puta na đan i lezija je zacijelila. Također, lezija je zacijelila nakon dva tjedna liječenja topikalnim kortikosteroidima i ponovno se pojavila nakon jednog mjeseca kada je uzet prvi biopsijski uzorak. Ponovno je ordinirana ista topikalna kortikosteroidna terapija i lezija je zacijelila. Tada se opet pojavila i uzet je drugi biopsijski uzorak. Zanimljivo je istaknuti da je samo u drugom biopsijskom uzorku otkrivena kazeozna nekroza, a bojenje prema Ziehl-Neelenu bilo je negativno i nisu bili identificirani acidorezistentni bacili. Nakon uzimanja trećega biopsijskog uzorka, kada je identificirana granulomatozna upala koja je bila visoko sumnjiva na sarkoidozu, pacijent je upućen na daljnju hospitalizaciju tijekom koje je postavljen na inaktivnu tuberkulozu. Tijekom boravka u bolnici liječenja je kombinacijom četiri standardnih antituberkuloških medicina – izoniazidom, rifampicinom, etambutolom i pirazinamidom. Nakon provedenog liječenja ulceracija jezika brzo se poboljšala, istodobno s plućnim statusom. Nakon provedenog liječenja ulcerozna lezija jezika je pacijent poput jučer i dalje je bezbolan.

Oralni TB rijedak je u kliničkoj praksi i uglavnom se prepoznaje zahvaljujući prikazima slučajeva. Infekcija se širi respiratornim kapljicama. Mehanizam inokulacije u sluznicu je nejasan, istodobno s plućnim statusom. Nakon provedenog liječenja ulcerozna lezija jezika je pacijent poput jučer i dalje je bezbolan.

Ovaj prikaz slučaja upućuje na nužnost da liječnici ostaju svjesni rijetke manifestacije oralne tuberkuloze. Kao što se

Discussion

Although there has been an increase in the incidence of extrapulmonary TB due to rare clinical presentations, it is still an underdiagnosed entity (13). This case report describes a painless oral ulcer as secondary lesion of active primary lung TB without other specific pulmonary symptoms. In the beginning, we thought that patient was unaware of the tongue thrusting either on remaining tooth 33 and/or inadequate denture and he was given a topical steroid (betamethasone) unguent in orbare to be applied four times a day and the lesion subsided. Moreover, the lesion subsided after two weeks of topical steroid treatment, only to reappear again after one month when the first biopsy was taken. The lesion subsided again on the same topical steroid treatment. After that, the lesion reappeared and the second biopsy was taken. It is interesting to mention that caseous necrosis was revealed only in the second biopsy sample, while Ziehl-Neelsen staining was negative and no acid-fast bacilli were identified. After taking the third biopsy of the sample, it was confirmed that a highly suspected granulomatous inflammation was sarcoidosis and the patient was further referred to hospital where active TB was suspected. During hospitalization the patient was treated by a combination of four standard antituberculosis agents: isoniazid, rifampicin, ethambutol and pyrazinamide. After the treatment, his ulcerated lesion of the tongue rapidly improved along with pulmonary status.

Oral TB is rarely seen and mostly recognized through case reports. This infection spreads via respiratory droplets. The mechanism of oral mucosa inoculation with TB is poorly understood (14). Obviously, an intact mucosa together with saliva and its antimicrobial enzymes is known to inhibit many microbial agents such as HIV. Clinically, these changes are non-specific, such as ulcers or nodules, but can also manifest as lesions within the jaw, such as osteomyelitis or radiolucency (15, 16). A biopsy of oral lesion is often insufficient to establish a diagnosis because granulomatous changes may not be present in early stages of the disease and acid-fast bacilli are hard to prove in sample (17). The literature data show that only a small number of histopathological specimens stain have been positive for acid-fast bacilli, hence a negative result should not be exclusive for a diagnosis of TB (17).

Oral TB malignancy was highly suspected due to the chronic nature of non-healing ulcers in a large number of case reports on oral tuberculosis, a finding which was also seen in the present case. Furthermore, oral TB lesions were painful in most of the published case reports. However, in our case, there was no evidence of painful lesions.

Differential diagnosis regarding this case was as follows: oral cancer, traumatic lesion, major recurrent aphthous ulcer, orofacial granulomatosis, Wegener’s granulomatosis, self-inflicted lesions, sarcoidosis, foreign body reaction, tertiary syphilis, deep fungal infections (histoplasmosis), Behçet’s disease, and oral manifestation of Crohn’s disease (18, 19).

This case report highlights the necessity for physicians to remain cognizant of the rare manifestation of oral tuberculosis. As seen also in other case reports on oral TB, refractory ulcerative tongue lesions should be highly suspicious for
Možemo zaključiti da, iako je riječ o rijetkoj manifestaciji tuberkuloze, oralne lezije treba uključiti u diferencijalnu dijagnosticu lezija u usnoj šupljini, posebno u slučaju onih koje ne pokazuju odgovor na konvencionalni antibiotik, protuupalno liječenje ili ciji biopsijski uzorci isključuju zloćudnost. S obzirom na to da uključivanje tuberkuloze kao dio diferencijalne dijagnoze kroničnih oralnih lezija može rezultirati ranijom dijagnozom i liječenjem, time se otvara mogućnost prevencije daljnjeg širenja bolesti.

Conflict of interest

Authors declare that they have no conflict of interest.
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