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CASE REPORT

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Pagetova bolest kostiju: prikaz slučaja

Paget's Disease of the Bone: a Clinical Report

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Sažetak
Pagetova bolest kostiju (PBK) kronični je poremećaj remodeliranja kostiju s povećanom resorpcijom posredstvom osteoklasta te stvaranjem nove kosti, što rezultira neorganiziranim mozaikom „divlje" i lamelarne kosti na pogođenim područjima kostura. Ta se bolest obično klinički ne zapaža prije dobi od 40 godina. Kliničke manifestacije mogu biti u rasponu od asimptomatičnih do bolnih deformiteta više od jedne kosti. Od PBK najčešće obolijevaju bijelci europskog podrijetla, ali i crnci, no vrlo rijetko žuta rasa. Mnogi se simptomi mogu liječiti antiosteoklastnom terapijom, poput kalcitonina i bifosfanata. Nažalost gotovo da i nema dokumentiranih dugoročnih rezultata. U ovom radu izvještavamo o kliničkom slučaju Pagetove bolesti kostiju i dajemo kratak pregled literature.

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Uvod

Pagetova bolest kostiju (PDB) kronični je poremećaj s povećanim i deformiranim kostima u jednom ili više područja kostura. Prvi ju je put 1877. godine opisao Sir James Paget (1). Ne zna se kada počinje, no čini se u starijoj dobi i da češće obolijevaju Europljani (2). Premda je etiologija bolesti nepoznata, istraživanja upućuju na virusne i nasljedne uzroke. Kod pogođenih osteoklasta stručnjaci su zahvaljujući mnogobrojnim metodama otkrili virusne antigene. Pozitivna obiteljska anamneza ustanovljena je kod četrdesetak posto pacijenata s Pagetovom bolešću (3). Klinička slika varira od asimptomatskih kod onih kojima je slučajno dijagnosticira, pa sve do bolnih deformiteta jedne ili više kostiju. Simptomi i znakovi uglavnom se pojavljuju kod bolesnika s više pogođenih mjesta negoli kod jednostavnih poremećaja skeleta (4). Mogu nastati različite deformacije kostura te sekvele i mnoge druge komplikacije.

U ovom radu izvještavamo o slučaju PBK, te dajemo kratak pregled etioloških čimbenika, kliničkih slučajeva, terapije i istraživanja.

Introduction

Paget's disease of bone (PDB) is a chronic disorder which typically results in enlarged and deformed bones in one or more regions of the skeleton. This was first reported by Sir James Paget in 1877 (1). The onset of Paget's disease is insidious, generally occurs later in life and more commonly in Europeans (2). Although the etiology of Paget's disease is unknown, studies have provided some support for both viral and hereditary causes. Viral antigens have been detected in affected osteoclasts by numerous methods and research teams. A positive family history is reported in as many as 40 percent of patients with Paget's disease (3). The clinical presentation of Paget's disease can range from no symptoms in patients who are diagnosed accidentally to painful deformities of one or more bones in symptomatic patients. Symptoms and signs are more likely to occur in patients with polyostotic involvement than in those with monostotic involvement of the skeleton (4). A variety of bone deformities may occur and as sequelae to this many other complications occur. We report here a case of PDB, with a brief review of the etiological factors, clinical presentation, investigations and management.

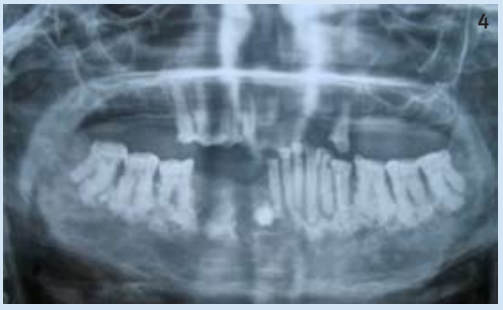
Prikaz slučaja

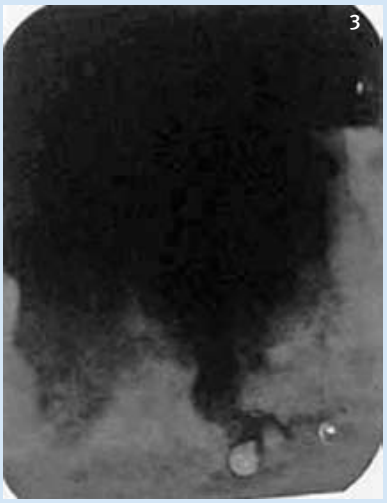
Žena u kolicima, u dobi od 70 godina, došla je u Zavod za oralnu medicinu i radiologiju i potužila se da već godinu dana ima nezacijeljene postekstrakcijske rane u području donjih prednjih zuba. Upozorila je i na stalne tupe bolove. U povijesti bolesti navela je da je prije godinu dana imala traumatsku ekstrakciju 2. zuba. Medicinska anamneza sadržavala je podatak da joj je prije 10 godina bila dijagnosticirana Pagetova bolest, a imala i hipertenziju te je primala odgovarajuću terapiju. Prije 10 godina, a nakon što joj je bila dijagnosticirana Pagetova bolest, izgubila je sposobnost hodanja zbog bolesti obiju nogu. Bolest se pogoršala te joj se zakrivila desna noga i od tada je u invalidskim kolicima (slika 1.). Nakon toga je odlazila na terapiju. Pacijentica nije imala neurološke simptome, poput gubitka sluha. Dobivala je subkutano Biocalcin (Calcitonin, United Biotech) 100 jedinica jedanput na dan tjedan dana, a zatim 50 jedinica tri puta na tjedan sljedeća četiri tjedna. Nakon toga je prestala uzimati lijek misleći da je na adekvatnoj dozi. Kliničkim pregledom otkrivene su nezacijeljene postekstrakcijske rane u području donjega desnog središnjeg i lateralnog sjekutića (slika 2). Okolna sluznica bila je blijedo ružičasta i osjetljiva na palpaciju. Ustanovljeno je obostrano proširenje kortikalne kosti u odnosu prema ostalom dijelu donjega zubnog grebena. Intraoralni periapikalni radiogram (IOPAR), panoramski radiogram i latero-lateralni kefalogram snimljeni su kako bi procijenile koštane promjene. IOPAR-om s otkrivene nezacijeljene ek-

Case report

A 70-year-old woman came to the department of Oral Medicine and Radiology in a wheel chair with the complaint of unhealed extraction sockets in lower anterior teeth region for one year. She also complained of a dull persistent pain in that area. She revealed history of traumatic extraction of 2 teeth a year ago. Medical history revealed that she had been a known case of Paget's disease for the past 10 years and also had a controlled hypertension. 10 years ago, the patient developed inability to walk due to pain in both legs after which she was diagnosed with Paget's disease of bone. Progress of the disease led to disfigurement of the right leg, confining her to a wheel chair (Figure 1). After that, she was treated for that condition. The patient had no neurological symptoms such as hearing loss. The patient reported that she had taken subcutaneous injections of Biocalcin (calcitonin by United Biotech) 100 units once a day for one week followed by 50 units three times a week for the following 4 weeks. The patient stopped taking the medication after this although she was advised to be on maintenance dose.

Clinical intraoral examination revealed unhealed extraction sockets in mandibular right central incisor region and lateral incisor region (Figure 2). The mucosa surrounding that area was pale pink in color and was tender on palpation. Bi-cortical expansion was found with respect to lower ridge. Intraoral periapical radiographs (IOPAR), panoramic radiograph and lateral skull radiographic views were taken to as-





Slika 1. Deformitet desne strane desne noge
Figure 1 Disfigurement of the right of right leg.
Slika 2. Klinička slika koja pokazuje nezacijeljene ekstrakcijske rane i bikortikalno proširenje mandibularne čeljusne kosti
Figure 2 Clinical picture showing unhealed extraction sockets and bicortical expansion of mandibular jaw.
Slika3. IOPAR područja 41 i 42 s vidljivim nezacijeljenim ekstrakcijskim ranama, nepravilnim rubovima i promijenjenom trabekularnom građom kostiju
Figure 3 IOPAR in the region of 41, 42 showing unhealed extraction sockets having irregular outlines and altered trabecular pattern of bone.
Slika 4. Ortopantomogram na kojem se vidi paučinast izgled mandibule, generalizirana hipercementoza i manje naznačena lamina dura oko mandibularnih zuba
Figure 4 Cropped panoramic radiograph showing cotton-wool appearance of the mandible, generalized hypercementosis and less evident lamina dura of mandibular teeth.

strakcijske rane s nepravilnim rubovima (slika 3). Okolna kost imala je promijenjene trabekule s radioopacitetnim džepovima. Na panoramskom radiogramu vidjela se paučinasta kost mandibule, generalizirana hipercementoza mandibularnih zuba i manje uočljiva lamina dura (slika 4). Na lateralnom kefalogramu nije bilo odstupanja od normale.

Područje je kiretirano, inducirano je svježe krvarenje i rane su zašivene. Postoperativne upute uključivale su Hexidine (0,2-postotni Chlorhexidine Gluconate, ICPA) za ispiranje usta dva puta na dan tijekom deset dana te terapiju Novamoxom (Amoxicillin od Cipla) – 500 miligrama tri puta na dan oralno tijekom pet dana, Metrogyl (Mertronidazole, JB Chemicals) – 400 miligrama oralno dva puta na dan tijekom pet dana, te Dicloran (Diclofenac sodium, JB Chemicals) – 50 miligrama oralno dva puta na dan tijekom pet dana. Šavovi su izvađeni nakon sedam dana, a simptomi su se smirili.

Rasprava

Pagetova bolest (PBK) fokalni je poremećaj kostura i može pogoditi jednu ili više kostiju. Obolijevaju kako žene tako i muškarci, s blagom predominacijom muškaraca (2). Trenutačna stajališta poduprta dokazima pokazuju uključenost genetskih okolišnih čimbenika u klasičnom PBK-u. U SAD-u je kod takvih bolesnika najčešće bio otkriven virus rubeole (5–7). Pretpostavlja se da su pojedinci s genetskom predispozicijom prema PBK-u podložniji tom poremećaju nakon što su preboljeli tu viralnu infekciju. Mutacije gena *SQSTM1,* koje su opisane kao povremene, nađene su kod nekih bolesnika s PBK-om (8).

Bolest ima tri faze. U ranoj, nazvanoj „osteolitičkom", dominantna je razgradnja kostiju te su one tada jače prokrvljene. Pretjeranu razgradnju tzv. Pagetove kosti obično slijedi stvaranje nove. Tijekom te druge faze bolesti – „osteoblastične faze", stvara se nova strukturalno abnormalna kost, najvjerojatnije zbog neprirodno brzog postupka remodeliranja. Nova tek izlučena vlakna kolagena neorganizirana su i ne slijede linearni raspored te tako stvaraju „divlju kost". S vremenom se povećani stanični sadržaj nove kosti smanjuje te nastaje sklerotična, manje prokrvljena mozaična Pagetova kost, bez znakova aktivnog područja koštanog pregrađivanja. To je treća faza nazvana i „sklerotičnom" ili „izagorjelom" fazom Pagetove bolesti. U svim trima fazama karakteristično je da se kod istog pacijenta mogu istodobno vidjeti samo na različitim mjestima (9).

Pacijenti bez simptoma obično se slučajno otkriju kada odu na radiografska snimanja ili su im potrebne laboratorijske pretrage. Pacijenti s bolovima prouzročenima Pagetovom bolešću obično ističu da su neprekidni i pojačavaju se tijekom noći. Mogu nastati i različita izobličenja, uključujući kifozu, skraćene ili zakrivljene udove, lavlje lice, izbočenje čela, abnormalnosti zuba poput prostora između njih što može završiti malokluzijom i gubitkom zuba, a u teškim slučajevima tu je i povećani kranium uz poteškoće u održavanju položaja glave (10). S PBK-om glave i kralježnice mogu se povezati različite tegobe i neurološki simptomi zbog povećane kosti i pritiska na mozak, leđnu moždinu ili živce (11). Protok krvi

sess the bony changes. IOPAR revealed unhealed extraction sockets with irregular outlines (Figure 3). The surrounding bone revealed altered trabeculae with radiopaque patches of abnormal bone. Panoramic radiograph revealed cotton-wool appearance of the mandible, generalized hypercementosis of mandibular teeth and less evident lamina dura (Figure 4). Lateral skull radiograph showed no abnormality.

Curettage was performed in that area and fresh bleeding was induced and wound sockets were sutured. Postoperative instructions included the use of Hexidine (0.2 percent Chlorhexidine Gluconate by ICPA) mouthrinse twice a day for 10 days and the treatment with oral Novamox (Amoxicillin by Cipla) 500 mg three times a day for 5 days, oral Metrogyl (Mertronidazole by JB Chemicals) 400 mg twice a day for 5 days and oral Dicloran (Diclofenac sodium by JB Chemicals) 50 mg two times a day for 5 days. Sutures were removed after seven days and the patient's symptoms were reduced.

Discussion

Paget's disease of bone is a focal disorder of the skeleton that can affect one or more bones. It affects both males and females, with a slight predominance in males (2). Current evidence suggests that both environmental and genetic factors are involved in classic PDB. In the United States, the measles virus antigen is most commonly detected in patients with Paget's disease (5-7). Individuals with a genetic predisposition to PDB may be more susceptible to develop the disorder after exposure to a viral infection. Mutations in the *SQSTM1* gene have been described in sporadic and familial PDB patients (8).

The disease has three major phases. In the early phase, termed "osteolytic phase", bone resorption predominates and there is a concomitant increased vascularity of involved bones. Commonly, the excessive resorption of pagetic bone by osteoclasts is followed closely by formation of new bone. During this second phase of the disease ("osteoblastic phase"), the new bone that is made is structurally abnormal, presumably because of the accelerated nature of the remodeling process. Newly deposited collagen fibers are laid down in a disorganized rather than a linear manner, creating the so called "woven bone". With time, the hypercellularity at the affected bone may diminish leading to development of a sclerotic, less vascular Pagetic mosaic bone without any evidence of active bone turnover. This is the so-called "sclerotic" or "burned-out" phase of PDB. Typically, all these three phases of the disease can be seen at the same time at different sites in a single pagetic patient (9).

Asymptomatic patients are usually diagnosed accidentally on radiographs and during laboratory investigations. Patients with bone pain caused by Paget's disease usually describe the pain as continuous which increases with rest, and at night. A variety of deformities may occur, including kyphosis; shortened or bowed limbs, leonine facies; frontal bossing of the forehead; dental abnormalities such as spacing between teeth leading to malocclusion and the loss of teeth; and in severe cases, an enlarged cranium that may be difficult to hold erect (10).

se u ekstremitetima pogođenima tom bolešću može znatno povećati, što ponekad može rezultirati zastojem srca zbog povećanog opterećenja. Postoje i izvještaji o kalcificiranju aorte ili zalistaka (12). Kod polistotičkih slučajeva rijetko se javlja neoplastična degeneracija (13). Obično su tako nastali tumori vrlo agresivni maligni osteosarkomi, fibrosarkomi ili nediferencirani sarkomi vretenastih stanica (10).

Serumska koštano-specifična alkalna fosfataza smatra se najosjetljivijim biljegom stvaranja kosti. Povećana razina utječe na veću aktivnost osteoblasta u sklerotičnim lezijama ljudi oboljelih od Pagetove bolesti te neposredno korelira s opsegom zahvaćenog skeleta (14). Drugi biokemijski biljeg Pagetove bolesti jest urinarni pirinidolin (15). Oba mogu biti u dopuštenim granicama kod pacijenata s monostitičnom Pagetovom bolešću.

Scintigrafija kostiju obvezatna je pretraga ako se želi procijeniti koliko je zahvaćena kost. Radiografske snimke visoko su specifične zbog svoje klasične prirode. Kada se dijagnosticira Pagetova bolest, potrebno je ponavljati radiograme zato da bi se pratila degeneracija nosećih zglobova. Kompjutorizirana tomografija i magnetska rezonancija nisu potrebne (10). PBK radiološki ima tri faze – ranu radiolucentnu resorptivnu; te gustu i više radioopacitetnu kasnu fazu. Trabekule se mijenjaju kako prema broju tako i prema obliku. U ranoj fazi broj im se smanjuje, a kasnije se mogu organizirati u zaobljene, radioopakne otekline abnormalne kosti, stvarajući paučinasti izgled. Pogođena kost uvijek je povećana te tako u povećanim čeljustima vanjski kortikalis može biti stanjen, ali ostaje intaktan. Maksila je češće zahvaćena od mandibule u omjeru većem od 2 prema 1. Zubi se mogu razmaknuti ili pomicati kako se čeljust povećava (16). Često se razvija hipercementoza na nekoliko zuba ili kod većine u pogođenoj čeljusti te može biti opsežna i nepravilna, što je sve svojstvo PBK (17).

Primarna svrha terapije u slučaju PBK jest vratiti normalnu kontrolu koštane pregradnje kako bi se smirili simptomi kao što je bol u kostima te spriječiti komplikacije nekontroliranog rasta kostiju koje mogu potaknuti abnormalne resorpcije. Kod oboljelih od Pagetove bolesti s ortopedskim komplikacijama indicirani su selektivni kirurški zahvati pogođenih koštanih područja. Kod starijih pacijenata s uznapredovalom bolešću, terapija se određuje kako bi se tretirala hiperkalcijemija. Trenutačno su svi lijekovi koji se određuju za Pagetovu bolest antiresorptivni, te uključuju kalcitonin i bifosfonate (9). Iako antiresorptivna terapija može smanjiti bol, kod nekih je bolesnika potrebna simptomatska terapija s nesteroidnim protuupalnim lijekovima kako bi im se dodatno ublažila bol u kostima zbog osteoartritisa ili kompresije živaca. U tim okolnostima pacijent može povoljno reagirati i na opoidne analgetike, akupunkturu, električnu stimulaciju živaca ili se može koristiti pomagalima za hodanje (18). Kalcitonin je bio prvi antiresorptivni lijek koji se ordinirao u slučaju PBK, a i danas je sastavni dio terapije. Bolesnici obično primijete smanjenu razinu boli četiri tjedna nakon početka terapije, a ako poboljšanje ne osjete ni za tri mjeseca, tada ih Pagetova bolest vjerojatno ne uzrokuje. U tom slučaju terapiju treba prekinuti i istražiti druge moguće uzroke, a krivac može biti i oseoartritis. Bolesnika koji reagira na terapiju

A variety of disturbances and neurological syndromes can be associated with PDB of the skull and spinal column as a result of pressure on the brain, spinal cord or nerves by enlarged pagetic bones (11). Blood flow may be markedly increased in extremities involved with PDB, leading in some cases to high-output heart failure. There are also reports suggesting an increased incidence of calcific aortic disease or other valve calcifications (12). Neoplastic degeneration can rarely occur in polyostotic cases (13). Usually, these tumors are highly malignant osteosarcomas, fibrosarcomas, or undifferentiated spindle cell sarcomas (10).

The serum bone-specific alkaline phosphatase is considered the most sensitive marker of bone formation. Elevations of alkaline phosphatase level reflect an increased activity of osteoblasts in the sclerotic lesions of a patient with Paget's disease and correlates directly with the extent of skeletal involvement (14). The other biochemical marker of Paget's disease is urinary pyridinoline (15). These markers may be normal in patients with the monostotic form of Paget's disease.

Bone scintigraphy is a mandatory investigation to evaluate the extent of involvement of bone. Radiographs in PDB often have a high specificity because of their classic nature, but a low sensitivity. Once a diagnosis of Paget's disease is confirmed, repeated radiographs are required only to monitor degeneration around the weight-bearing joints. Computed tomography and magnetic resonance imaging are not necessary (10). PDB has three radiographic stages: an early radiolucent resorptive stage; a granular stage; and a denser, more radiopaque late stage. The trabeculae are altered in number and shape. In early stages they decrease in number. In later stages the trabeculae may be organized into rounded, radiopaque patches of abnormal bone, creating a cotton-wool appearance. The affected bone is always enlarged and in enlarged jaws the outer cortex may be thinned but remains intact. The maxilla is more frequently involved than the mandible in the ratio of more than 2:1. The teeth may become spaced or displaced in the enlarging jaw (16). Often hypercementosis develops on a few or most of the teeth in the involved jaw. The hypercementosis may be exuberant and irregular, which is characteristic of PDB (17).

The primary goal of PDB treatment is to restore normal bone turnover in order to relieve symptoms such as bone pain and to prevent complications that result from the abnormal resorption and overgrowth of pagetic bone. The treatment can be also indicated for PDB patients with orthopedic complications, undergoing elective surgery at affected bone sites. In elderly polyostotic patients with advanced disease, treatment is also indicated for management of immobilization hypercalcemia. Currently, all agents used to treat PDB are antiresorptive in nature, and include calcitonin and bisphosphonates (9). Even though antiresorptive therapy may reduce bone pain, symptomatic treatment with nonsteroidal anti-inflammatory compounds could be required in some patients to further reduce bone pain due to osteoarthritis or nerve compression. Under these circumstances, patients may also respond to opioid analgesics, acupuncture, electrical nerve stimulation or the use of walking aids (18). Calcitonin was the first antiresorptive agent to be used for

obično ponovno pogode isti simptomi i to vrlo brzo nakon prestanka terapije te je zbog toga terapija doživotna. Oni kojima se bolest vrati iako su pod terapijom jedne vrste kalcitonina, mogu dobro reagirati na drugu vrstu (19). Uobičajena početna doza je 100 i.u. subkutano, na početku na dnevnoj bazi. Simptomi se ublažavaju nakon nekoliko tjedana, a biokemijski nalazi (50 posto smanjena razina serumske alkalne fosfataze) obično su bolji nakon tri do šest tjedana od početka terapije. Nakon toga većina liječnika smanjuje dozu na 50 do 100 i.u. svaki drugi dan ili tri puta na tjedan. Taj lijek pozitivno utječe na normalizaciju alkalne fosfataze i ublažava simptome čak do 50 posto kod pacijenata s PBK (20). Popratne pojave tijekom parenteralne primjene kalcitonina su valovi vrućine, slabost, povraćanje, proljev i bolnost u području aplikacije lijeka. Simptomatska hipokalcijemija iznimno je rijetka, kao i preosjetljivost na lijek. Nedavno je proizveden lijek za intranazalnu primjenu, iako nije odobren za terapiju u slučaju PBK (9).

Bifosfonatni lijekovi prvi su izbor za pacijente s PBK-om, ali i kod mnogih drugih stanja kod kojih se razgrađuju kosti, primjerice u slučaju osteoporoze i koštanih metastaza. Bifosfanati su analogni anorganskom pirofosfatu za koji se smatra da je potreban u procesu mineralizacije kostiju. Molekula kisika koja se veže za dvije molekule fosfata na pirofosfatu se zamjenjuje ugljikom. Tako se centralni dio lijeka sastoji od polovice fosforiliranog ugljičnog fosfata, koji je, za razliku od centralne fosforilirane oksidne fosfatne jezgre pirofosfata, otporan na metaboličku degeneraciju. To svojstvo omogućuje oralnu primjenu lijeka, premda je nekoliko njih prilagođeno i za intravensku primjenu. Bifosfanati imaju jedinstveno svojstvo – privlače hidroksiapatit (21). Poput kalcitonina, ti lijekovi inhibiraju aktivnost osteoklasta, ali potpuno drugim mehanizmima. Raniji spojevi bifosfanata (etidronate i clodronate) inhibiraju aktivnost osteoklasta tako što stvaraju adenozin trifosfata koji se ne može hidrolizirati. Kasnije generacije bifosfanata, koje imaju jednu ili više amino skupina, inhibiraju farnesil-pirofosfatsku sintetazu, važan enzim u ciklusu limunske kiseline (22). Etidronate, kada se primjenjivao u oralnoj dozi od 400 miligrama na dan tijekom šest mjeseci, koristio se biokemijskim markerima koštane pregradnje kod pacijenata s Pagetovom bolesti i smanjivao ih do približno 50 posto. Pamidronate disodium bio je prvi aminobifosfanat koji se upotrebljavao u intravenskom obliku kod liječenja PBK. Premda je razvijeno još nekoliko bifosfonata za kliničku uporabu (uključujući tiludronate, olpadronate, neridronate), najbolji rezultati postignuti su tijekom istraživanja zoledronata. Čini se da je najsnažniji u porodici bifosanata te da je također lijek s najvećim afinitetom za hidroksilapatit (23). Osteonekroza čeljusti identificirana je kao moguća komplikacija, posebice u slučaju dugotrajne intravenske primjene bifosfanata kod onkoloških bolesnika (24). Ta nuspojava i komplikacije u terapiji vrlo su rijetke kod pacijenata s PBK-om koji se liječe bifosfanatima (9). Daljnja istraživanja potrebna su kako bi se odredilo mogu li se tim lijekovima prevenirati komplikacije kod simptomatičnih i asimptomatičnih pacijenata.

PDB and is still approved for the treatment of PDB. Patients usually notice a reduction of pain within four weeks of starting the treatment, and if they have no relief within three months, then the Paget's disease is probably not responsible for the pain. Treatment should then be stopped and other causes of pain sought; osteoarthritis may well be the culprit. The patient who responds to treatment usually relapses shortly after it is stopped so that the treatment has to be continued indefinitely. The patient who relapses clinically while using one form of calcitonin may respond to a different type (19). The usual starting dose is 100 U, subcutaneously, initially on a daily basis. Symptomatic benefit may be apparent in a few weeks, and the biochemical benefit (typically about a 50% reduction from baseline in serum alkaline phosphatase) is usually seen after 3 to 6 months of treatment. After this period, many clinicians reduce the dose to 50 to 100 U every other day or three times a week. This agent has been associated with normalization of alkaline phosphatase or symptom relief in up to 50% of patients (20). The main side effects of parenteral salmon calcitonin include flush, nausea, vomiting, diarrhea and pain at the site of injection. Symptomatic hypocalcemia is exceptional, as well as hypersensitivity to the compound. Recently, intranasal calcitonin has been developed, however it is not specifically approved for use in PDB (9).

Bisphosphonates are the treatment of choice of patients with PDB, as well as of many other conditions characterized by increased bone turnover such as osteoporosis and bone metastases. Bisphosphonates are analogs of inorganic pyrophosphate, a factor thought to be needed for the process of bone mineralization. The oxygen molecule that binds the two phosphate molecules of pyrophosphate is substituted by carbon. Thus, the central core of these drugs consists of a phosphorous-carbon-phosphorous moiety, which, unlike the central phosphorous-oxygen-phosphorous core of pyrophosphate, is resistant to metabolic degradation. This allows for the oral use of the drugs, although several have been evaluated for intravenous use. Bisphosphonates have the unique attribute of localizing to hydroxyapatite in bone (21). Like calcitonin, these agents inhibit osteoclast activity, but through entirely different mechanisms of action. The earlier bisphosphonates (etidronate and clodronate) inhibit osteoclast activity by generating nonhydrolyzable analogs of adenosine triphosphate. The later generations of bisphosphonates, with one or more amino groups, inhibit farnesyl pyrophosphate synthase, an important enzyme in the mevalonate pathway (22). Etidronate, given at an oral dose of 400 mg a day for 6 months, was widely used and it reduced biochemical markers of bone turnover in patients with Paget disease by ~50%. Pamidronate disodium has been the first aminobisphosphonate to be used as intravenous regimen in PDB. Although several other bisphosphonates have been developed for clinical use (including tiludronate, olpadronate, neridronate), the most impressive data reported so far have emerged from studies of zoledronate. It seems to be the most potent of the bisphosphonate family, as well as the agent with the highest affinity for hydroxyapatite (23). Osteonecrosis of the jaw has been identified as a potential complication, particularly with

long-term, high dose intravenous bisphosphonate therapy in malignant diseases (24). This complication seems extremely rare in patients with PDB treated with a bisphosphonate (9). Further studies are required to determine whether prevention of possible complications in symptomatic and asymptomatic patients is achievable with these agents.

Abstract
Paget's disease of bone (PDB) is a chronic bone remodeling disorder characterized by increased osteoclast-mediated bone resorption with subsequent new bone formation resulting in a disorganized mosaic of woven and lamellar bone at affected skeletal sites. The disease is usually not clinically apparent under 40 years of age. The clinical manifestations may range from asymptomatic to painful deformity of more than one bone. PDB is most common in white people of European descent, but it also occurs in black population, whereas it is rare in people of Asian descent. With anti-osteoclast therapy such as calcitonin and bisphosphonates many of the symptoms are relieved. But the risk of future complications still remains. Unfortunately, very little evidence of long-term results is available. We report a case of Paget's disease of bone with a brief review of literature.

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Key words
Osteitis Deformans; Bone Remodeling; Bone Resorption; Hypercementosis; Osteoclasts; Calcitonin; Diphosphonates

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