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Odontogenic Keratocyst, Orthokeratinized Odontogenic Cyst and Epidermoid Cyst – an Immunohistochemical Comparison

Odontogena keratocista, ortokeratinizirana odontogena cista i epidermoidna cista – imunohistokemijska usporedba

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Abstract

Objectives: There are two types of keratinized cystic lesions arising in the jaw - developmental cysts of odontogenic origin (odontogenic keratocyst - OKC and orthokeratinized odontogenic cyst - OOC) and epidermoid cyst (EC) of undetermined origin. These lesions have overlapping histopathological features and their treatment depends on the correct diagnosis. The aim of our study was to determine diagnostically relevant differences between these cysts and to establish criteria for diagnosing intraosseous EC. **Materials and methods:** An immunohistochemical analysis comprised of various cytokeratins, carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), epithelial cell adhesion molecules family member BerEP4, apoptosis-related markers Bcl-2 and calretinin, stem cell marker CD44, tumor suppressor gene p63 and proliferation activity marker Ki-67 was performed on 25 OKCs, 8 OOCs and 11 ECs. **Results:** CK5/6 was positive in all layers of both OKCs and OOCs, but only in the basal layer of all ECs. CK8/18 and CK19 revealed strong basal and suprabasal positivity in all OKCs, weak basal positivity in OOCs, and negative expression in all ECs. BerEP4 and Bcl-2 revealed positivity in all OKCs while being negative in OOCs and ECs. **Conclusions:** The results of our study suggest that BerEP4 and Bcl-2 positivity may be useful in distinguishing between OKCs and the other keratinized jaw cysts. Orthokeratinized lesions within the jaw should be defined as OOCs, while intraosseal EC should be diagnosed only if immunohistochemical staining points to ectodermal origin, thus suggesting congenital or post-traumatic inclusion of the oral epithelium.

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Introduction

Cysts develop more frequently in the jaws than in any other bone because of the presence of residual developmental epithelial tissue of odontogenic origin (1). Keratinized cystic lesions which develop in jaw bones are infrequent. The most common among them is odontogenic keratocyst (OKC), a locally aggressive developmental odontogenic cyst with a high recurrence rate. The epithelial lining of OKC is composed of squamous epithelial cells with characteristic basal nuclear palisading and a corrugated parakeratinized surface. Orthokeratinized odontogenic cyst (OOC) is a rare, developmental odontogenic cyst which had been considered in the past to be a variant of odontogenic keratocyst (2), but is now recognized as a separate entity in the World Health Organization (WHO) Classification of Head and Neck Tumors (3), due to its different biological activity. It is lined with or-

Uvod

Ciste u čeljusti nastaju češće nego u bilo kojoj drugoj kosti zbog ostatnoga razvojnoga epitelnoga tkiva odontogenog podrijetla (1). Rijetke su keratinizirane cistične lezije koje nastaju u kostima čeljusti. Najčešća je odontogena keratocista (OKC), lokalno agresivna razvojna odontogena cista s visokom sklonošću prema recidivu. Epitelni pokrov OKC-a sastoji se od pločastih epitelnih stanica s karakterističnim bazalno palisadno poredanim jezgrama i nazubljenom parakeratiniziranom površinom. Ortokeratinizirana odontogena cista (OOC) rijetka je razvojna odontogena cista koja se u prošlosti smatrala varijantom odontogene keratociste (2), ali je u trenutačno valjanoj klasifikaciji tumora glave i vrata Svjetske zdravstvene organizacije (SZO) svrstana kao zasebni entitet (3) zbog svojega različitog biološkog ponašanja. Ona je obložena ortokeratiniziranim, višeslojnim pločastim epite-

thokeratinized, stratified squamous epithelium with a prominent granular cell layer, without palisading in the basal layer. Similar orthokeratinized epithelial lining can be found in epidermoid cyst (EC), an exceptionally rarely described intraosseous lesion of the jaw, which is histologically identical to EC of the skin. Depending on the pathogenesis, intraosseous ECs may be of two types. Congenital-type ECs arise from entrapped ectodermal tissue as a result of disturbances during the early stages of embryogenesis between the third and fifth week of gestation. Acquired type of intraosseous EC most probably arises from surgically or accidentally implanted epithelial cells into deeper tissues (4-6).

Clinical and radiological presentations as well as histopathological features of all these cysts are similar, but biological behavior differs. The treatment of keratinized cysts in jaw bones depends on the correct pathohistological diagnosis. OKCs have recurrence rates of up to 25% after enucleation, therefore these cases require resection. OOCs have much lower recurrence rates, up to 2% (3), and the treatment in these cases should be individual, depending on localization and size of lesion. The recurrence of intraosseous EC after enucleation was not reported.

In the present study, we performed an immunohistochemical analysis of expression of epithelial markers and calretinin, cancer stem cell markers, proliferation activity index labeling and antiapoptotic markers, in an attempt to differentiate between odontogenic and non-odontogenic origin of the epithelium lining the inner surface of these cysts, especially OOC which may be misdiagnosed as an EC. Another aim of this study was to identify the immunophenotype of keratinized cystic lesions of jaw bones, which may be useful in diagnostic pathology.

Materials and methods

Samples of 25 cases of OKCs and 8 cases of OOCs of the jaw bones, and 11 cases of ECs of the skin of the head and neck, were selected for immunohistochemical evaluation. Inclusion criteria for selecting the cases were clinically and/or radiologically confirmed cystic lesion of the jaw or of the head and neck skin, surgically excised and histologically analyzed at the Department of Pathology and Cytology at University Hospital Dubrava, Zagreb, Croatia. Exclusion criteria were histologically confirmed non-keratinized odontogenic cysts and cysts with insufficient epithelial lining for immunohistochemical analysis. All of the cases were histologically reviewed and reevaluated by authors. Age and gender of patients and localization of cysts are summarized in Table 1. All specimens were fixed in 10% neutral buffered formalin and embedded in paraffin. Four µm thick sections were prepared and stained with hematoxylin and eosin (HE) using standard technique. Immunostaining was carried out on deparaffinized tissue sections with different monoclonal antibodies (Dako Agilent Pathology Solutions) in a DakoCytomation Autostainer platform, according to the manufacturer's (Dako Denmark A/S) instructions.

The antibodies were used against various cytokeratins (CKAE1/AE3, CK5/6, CK7, CK8/18, CK19), carci-

lom s izraženim granularnim slojem, bez palisadno poredanih jezgara u bazalnom sloju. Slični ortokeratinizirani epitelni sloj nalazi se u epidermoidnoj cisti (EC), iznimno rijetko opisanoj intraosealnoj leziji čeljusti koja je histološki identična EC-u kože. Ovisno o patogenezi, dva su tipa intraosealnog EC-a. EC kongenitalnog tipa nastaje iz zarobljenog ektodermalnog tkiva kao posljedica poremećaja tijekom ranih stadija embriogeneze između trećega i petoga tjedna gestacije. Stečeni tip intraosealnog EC-a najvjerojatnije nastaje od kirurški ili slučajno usađenih epitelnih stanica u dublja tkiva (4 – 6).

Klinička i radiološka slika te patohistološke karakteristike svih ovih cista slične su, ali biološko ponašanje im je različito. Liječenje keratiniziranih cista u kostima čeljusti ovisi o ispravnoj patohistološkoj dijagnozi. OKC-i imaju učestalost recidiva do 25 % nakon enukleacije te takvi slučajevi zahtijevaju resekciju. Kad je riječ o OOC-ima, oni imaju mnogo nižu učestalost recidiva, do 2 % (3), te bi njihovo liječenje trebalo biti individualno, ovisno o lokalizaciji i veličini lezije. Recidivi intraosealnog EC-a nakon enukleacije nisu zabilježeni u literaturi.

U ovom istraživanju proveli smo imunohistokemijsku analizu izražaja epitelnih biljega i kalretinina, biljega tumorskih matičnih stanica, indeksa proliferacijske aktivnosti i antiapoptotičnih biljega kako bismo pokušali razlikovati odontogeno i neodontogeno podrijetlo epitela koji oblaže unutarnju površinu tih cista, pogotovo OOC-a koja se može pogrešno dijagnosticirati kao EC. Još jedan cilj ovog istraživanja bio je identificirati imunofenotip keratiniziranih cističnih lezija kosti čeljusti, što bi moglo biti korisno u dijagnostičkoj patologiji.

Materijali i metode

Uzorci 25 slučajeva OKC-a i 8 slučajeva OOC-a kosti čeljusti te 11 slučajeva EC-a kože glave i vrata izabrani su za imunohistokemijsku analizu. Kriteriji za uključivanje u izbor bili su klinički i/ili radiološki potvrđena cistična lezija čeljusti ili kože glave i vrata, kirurški uklonjena i histološki pregledana u Kliničkom zavodu za patologiju i citologiju Kliničke bolnice Dubrava. Kriteriji za isključivanje bili su histološki potvrđene nekeratinizirane odontogene ciste i ciste s nedovoljnim epitelnim pokrovom za imunohistokemijsku analizu. Sve slučajeve ponovno su histološki analizirali i potvrdili autori. Dob i spol bolesnika i lokalizacija cista sažeti su u tablici 1. Svi uzorci bili su fiksirani u 10-postotnom neutralnom puferiranom formalinu i uklopljeni u parafin. Učinjeni su rezovi debljine 4 µm te su uobičajenim postupkom obojeni hemalaun-eozinom (HE) . Imunohistokemijsko bojenje provedeno je na deparafiniziranim tkivnim rezovima s različitim monoklonalnim protutijelima (Dako Agilent Pathology Solutions) u platformi DakoCytomation Autostainer, prema uputama proizvođača (Dako Denmark A/S).

Korištena su protutijela za različite citokeratine (CKAE1/AE3, CK5/6, CK7, CK8/18, CK19), karcinoembrionalni antigen (CEA), epitelni membranski antigen (EMA), BerEP4, kalretinin, Bcl-2, p63, Ki-67 i CD44. Izraženost svih biljega

Table 1 Clinical characteristics of the present cases
Tablica 1. Klinička obilježja slučajeva

Category • Kategorija	No • Br	Age • Dob	Gender • Spol	Localisation • Lokalizacija
Odontogenic keratocyst (OKC) • Odontogena keratocista (OKC)	1	8	M	Maxilla, left • Maksila, lijeva
	2	8	M	Mandible, left angulus • Mandibula, lijevi angulus
	3	9	F • Ž	Mandible, right molar region • Mandibula, desna molarna regija
	4	10	F • Ž	Mandible, right molar region • Mandibula, desna molarna regija
	5	13	M	Mandible, right ramus • Mandibula, desni ramus
	6	17	M	Mandible, left angulus • Mandibula, lijevi angulus
	7	17	M	Mandible, front • Mandibula, prednji dio
	8	18	M	Mandible, right angulus • Mandibula, desni angulus
	9	18	F • Ž	Mandible, right angulus • Mandibula, desni angulus
	10	20	M	Mandible, right ramus • Mandibula, desni ramus
	11	20	M	Mandible, right angulus • Mandibula, desni angulus
	12	21	M	Maxilla • Maksila
	13	24	F • Ž	Mandible, right ramus • Mandibula, desni ramus
	14	31	M	Mandible, right angulus • Mandibula, desni angulus
	15	32	F • Ž	Mandible, right angulus • Mandibula, desni angulus
	16	37	M	Maxilla, front • Maksila, prednji dio
	17	43	F • Ž	Mandible, left angulus • Mandibula, lijevi angulus
	18	43	F • Ž	Maxilla, left • Maksila, lijeva
	19	51	M	Mandible, right molar region • Mandibula, desna molarna regija
	20	52	F • Ž	Mandible, left angulus • Mandibula, lijevi angulus
	21	59	M	Mandible, left angulus • Mandibula, lijevi angulus
	22	65	M	Mandible, right molar region • Mandibula, desna molarna regija
	23	69	M	Mandible, left molar region • Mandibula, lijeva molarna regija
	24	70	F • Ž	Maxilla, front • Maksila, prednji dio
	25	70	M	Maxilla, left • Maksila, lijeva
Ortokeratinized odontogenic cyst (OOC) • Ortokeratinizirana odontogena cista (OOC)	1	9	M	Mandible, right molar region • Mandibula, desna molarna regija
	2	19	M	Mandible, right angulus • Mandibula, desni angulus
	3	19	M	Mandible, left molar region • Mandibula, lijeva molarna regija
	4	22	F • Ž	Maxilla, front • Maksila, prednji dio
	5	27	M	Maxilla, right • Maksila, desna
	6	31	F • Ž	Mandible, left angulus • Mandibula, lijevi angulus
	7	32	F • Ž	Mandible, left angulus • Mandibula, lijevi angulus
	8	72	F • Ž	Maxilla, front • Maksila, prednji dio
Epidermoid cyst • Epidermoidna cista (EC)	1	17	F • Ž	Cheek • Obraz
	2	20	M	Cheek • Obraz
	3	23	M	Cheek • Obraz
	4	23	M	Cheek • Obraz
	5	28	M	Eyelid • Vjeđa
	6	41	F • Ž	Neck • Vrat
	7	43	M	Cheek • Obraz
	8	43	M	Lower lip • Donja usnica
	9	49	M	Cheek • Obraz
	10	55	M	Neck • Vrat
	11	56	F • Ž	Cheek • Obraz

noembryonic antigen (CEA), epithelial membrane antigen (EMA), BerEP4, calretinin, Bcl-2, p63, Ki-67 and CD44. The expression of all markers was analyzed in three layers of the epithelial lining (basal, suprabasal/granular and surface/keratinized). Immunoreactivity was scored semiquantitatively using a light microscope, and divided into three categories: negative (-), weakly positive (+), and moderately to strongly positive (++). The study was conducted in accordance with the Helsinki Declaration.

analiziran je u tri sloja epitelnog pokrova (bazalni, suprabazalni/granularni i površinski/keratinizirani). Imunoreaktivnost procijenjena je semikvantitativno koristeći se svjetlosnim mikroskopom i podijeljena u tri kategorije: negativno (-), slabo pozitivno (+) i umjereno do jako pozitivno (++). Istraživanje je provedeno u skladu s Helsinškom deklaracijom.

Results

OKCs analyzed in the present study were almost twice as frequent in male compared to female patients. The mandible was affected in 72% of cases. One third of cases were associated with an impacted tooth. Keratocysts were multilocular in three patients, one of them related to Gorlin's syndrome. Mean age of the patients with OKCs was 33 years.

OOCs were distributed equally among male and female patients, and occured slightly more frequently in the mandible then in the maxilla (5 and 3 respectively). The mean age of the patients was 28.8 years. Three OOCs (37.5%) enclosed a retained tooth.

All 11 ECs that were analyzed were from the skin of the head and neck regions of 8 male and 3 female patients, whose mean age was 33.2 years.

CK5/6 was positive in all layers of both OKCs and OOCs, but only in the basal layer of all ECs. CK7 was negative and CKAE1/AE3 was positive in all cysts analyzed. CK8/18 and CK19 revealed strong basal and suprabasal positivity in all OKCs, weak basal positivity in OOCs, and negative expression in all ECs. EMA and CEA were superficially positive in OKCs and OOCs and were negative in ECs. BerEP4 and Bcl-2 revealed moderate basal and suprabasal positivity in all OKCs, and negative reaction in all OOCs and ECs was obtained. Calretinin staining was negative in all cysts. CD44 and p63 revealed moderate membrane positivity in basal and suprabasal layers of all analyzed cysts. Proliferative activity assesed by Ki-67 labeling index was increased above the basal layers in OKCs when compared to other cyst types.

The results of the analysis of the immunohistochemical expression of markers used in the present study (median for each group) are summarized in Table 2.

Rezultati

OKC-i analizirani u ovom istraživanju bili su gotovo dvostruko češći kod pacijenata nego kod pacijentica. Mandibula je bila zahvaćena u 72 % slučajeva. Trećina slučajeva bila je povezana s impaktiranim zubom. Keratociste su bile multilokularne kod troje pacijenata, od kojih je u jednom slučaju bila povezana s Gorlinovim sindromom. Srednja dob pacijenata s OKC-om bila je 33 godine.

OOC-i su bili jednoliko raspoređeni prema spolu i malo češće su se nalazili u mandibuli nego u maksili (5 prema 3). Srednja dob pacijenata bila je 28,8 godina. Tri OOC-a (37,5 %) obuhvaćala su impaktirani zub.

Svih 11 analiziranih EC-a bili su iz kože glave i vrata 8 pacijenata i triju pacijentica. Njihova srednja dob bila je 33,2 godine.

CK5/6 bio je pozitivan u svim slojeva kod OKC-a i OOC-a, ali samo u bazalnom sloju svih EC-a. CK7 bio je negativan, a CKAE1/AE3 pozitivan u svim analiziranim cistama. CK8/18 i CK19 pokazali su snažni bazalni i suprabazalni pozitivitet u svim OKC-ima, slabi bazalni pozitivitet u OOC-ima i negativnu reakciju u svim EC-ima. EMA i CEA bili su površinski pozitivni u OKC-ima i OOC-ima i negativni u EC-ima. BerEP4 i Bcl-2 pokazali su umjereni bazalni i suprabazalni pozitivitet u svim OKC-ima te negativnu reakciju u svim OOC-ima i EC-ima. Bojenje na kalretinin bilo je negativno u svim cistama. CD44 i p63 pokazali su umjereni membranski pozitivitet u bazalnom i suprabazalnom sloju svih analiziranih cista. Proliferacijska aktivnost mjerena indeksom proliferacije Ki-67 bila je povišena iznad bazalnih slojeva u OKC-ima u usporedbi s drugim tipovima cista.

Rezultati analize imunohistokemijskih biljega korištenih u ovom istraživanju (medijan za svaku skupinu) sažeti su u tablici 2.

Table 2 A summary of immunohistochemical analysis results
Tablica 2. Sažetak rezultata imunohistokemijske analize

Immunohistochemical marker • Imunohistokemijski biljeg	EC (n=11)			OOC (n=8)			OKC (n=25)		
	B	SB	S	B	SB	S	B	SB	S
CK5/6	++	-	-	++	++	++	++	++	++
CK7	-	-	-	-	-	-	-	-	-
CKAE1/AE3	++	++	++	++	++	++	++	++	++
CK8/18	-	-	-	+/-	-	-	++	++	-
CK19	-	-	-	+/-	-	-	++	++	-
EMA	-	-	-	-	-	+	-	-	+
CEA	-	-	-	-	-	+	-	-	+
Ber-EP4	-	-	-	-	-	-	++	++	-
Calretinin	-	-	-	-	-	-	-	-	-
P63	++	++	-	++	++	-	++	++	-
Bcl-2	-	-	-	-	-	-	++	++	-
CD44	++	++	-	++	++	-	++	++	-
Ki-67	+/-	-	-	+	+	-	+	++	-

EC (epidermoid cyst), OOC (orthokeratotic odontogenic cyst), OKC (odontogenic keratocyst), B (basal layer of the epithelial lining), SB (suprabasal/granular layer of the epithelial lining), S (surface/keratinized layer of the epithelial lining), CK (cytokeratin), EMA (epithelial membrane antigen), CEA (carcinoembryonic antigen), - (negative), + (weakly positive), ++ (moderately to strongly positive), +/- (sporadic cells positive) • EC (epidermoidna cistt), OOC (ortokeratinizirana odontogena cista), OKC (odontogena keratocista), B (bazalni sloj epitela), SB (suprabazalni/granularni sloj epitela),S (površinski/keratinizirani sloj epitela), CK (citokeratin), EMA (epitelni membranski antigen), CEA (karcinoembrionalni antigen), - (negativno), + (slabo pozitivno), ++ (umjereno do jako pozitivno), +/- (pojedinačne stanice pozitivne)

Discussion

Cystic lesions of the jaws are fairly frequent. The pathogenesis may be developmental or nondevelopmental. Depending on the histogenesis, developmental cysts can be divided into cysts of odontogenic or of non-odontogenic origin. Stimulation of numerous potentially proliferative epithelial rests, originating from odontogenesis, and inclusions of ectodermal tissue during embryological development may result in a cystic lesion within the jaw (7). The vast majority of odontogenic cysts are inflammatory cysts, covered generally by nonkeratinized epithelium. On the contrary, jaw cysts lined by a keratinized epithelium are less frequent.

Keratinized odontogenic cysts (OKCs and OOCs) are developmental in nature and the process by which they arise remains obscure. Radiographical presentation in most cases is a well-circumscribed unilocular or multilocular radiolucency.

OKCs arise from the dental lamina. They represent 3-11% of all jaw cysts, and occur most commonly in the second to fourth decade of life, four times more frequently in the mandible than in the maxilla, with a strong predilection for the posterior mandible and ramus, and slightly more frequently in male patients (3, 8-10). The third of all cases of OKC are associated with unerupted teeth. Histologically, the epithelial lining of OKC is thin, composed of up to ten layers of squamous epithelial cells with characteristic basal nuclear palisading and a corrugated parakeratinized surface (Figure 1 A). The treatment modalities vary, depending on the size of the cyst. Small lesions may be treated by curettage or enucleation and larger lesions require surgical resection. Marsupialization may be performed to reduce the size of large cysts before removal (11, 12). Recurrence rate ranges between 20% and 30% after enucleation. Recurrence after resection is rare, occurring in less than 2% of cases (3).

Multiple cysts and somatic mutation of the PTCH gene have been documented in OKCs associated with the nevoid basal cell carcinoma syndrome (Gorlin-Goltz) (13, 14).

Odontogenic cystic lesion lined by an orthokeratinized epithelium was first described by Schultz (15) in 1927 as a dermoid cyst. In 1981 Wright (2) designated this lesion as an orthokeratinized variant of odontogenic keratocyst, and Li et al. (16) in 1998 suggested the term „orthokeratinized odontogenic cyst". OOC occurs eight times less frequently than OKC (17-19). It is a less aggressive lesion with a lower recurrence rate than OKC (20). The edition of the World Health Organization (WHO) Classification of Head and Neck Tumors (21), published in 2005, emphasized that cystic jaw lesions that are lined by orthokeratinizing epithelium do not form part of the spectrum of an OKC, which was, at that time, considered to be a benign keratocystic odontogenic tumor (KCOT). In the 5th edition of the WHO Classification of Head and Neck Tumors (3) OOC is included as a separate and specific entity. OOCs are characterized histologically by a thin squamous epithelium with a prominent granular cell layer and low cuboidal basal cells. The inner surface is covered by a noncorrugated, onion-skin-like orthokeratinization (Figure 1 B). Recurrence is rare, occurring in less than 2% of cases (3).

Rasprava

Cistične lezije čeljusti razmjerno su česte. Patogeneza može biti razvojna ili nerazvojna. Ovisno o histogenezi, razvojne ciste mogu se podijeliti u ciste odontogenog ili neodontogenog podrijetla. Stimulacija brojnih potencijalno proliferativnih epitelnih gnijezda nastalih tijekom odontogeneze te inkluzije ektodermalnog tkiva tijekom embrionalnog razvoja mogu rezultirati nastankom cistične lezije u čeljusti (7). Velika većina odontogenih cista su inflamatorne ciste, obično prekrivene nekeratiniziranim epitelom, a ciste čeljusti rjeđe su obložene keratiniziranim epitelom.

Keratinizirane odontogene ciste (OKC i OOC) razvojne su i proces njihova nastanka i dalje je nejasan. Radiološki se u većini slučajeva prezentiraju kao dobro ograničena unilokularna ili multilokularna prosvjetljenja.

OKC-i nastaju iz dentalne lamine. One čine od 3 do 11 % svih cista u čeljusti te se najčešće pojavljuju u dobi od drugoga do četvrtoga desetljeća, četiri puta češće u mandibuli nego u maksili, sa snažnom sklonošću prema pojavljivanju u stražnjoj mandibuli i ramusu, te malo češće kod muškaraca (3, 8 – 10). Trećina svih slučajeva OKC-a povezana je s neizniklim zubom. Histološki, epitelni pokrov OKC-a je tanak, sastavljen od najviše deset slojeva pločastih epitelnih stanica s karakterističnim palisadno poredanim jezgrama u bazalnom sloju i nazubljenom parakeratiniziranom površinom (slika 1. A). Način liječenja ovisi o veličini ciste. Male lezije mogu se liječiti kiretažom ili enukleacijom, a veće je potrebno kirurški resecirati. Može se provesti marsupijalizacija prije uklanjanja kako bi se smanjile velike ciste (11, 12). Učestalost recidiva poslije enukleacije iznosi između 20 % i 30 %. Pojava recidiva nakon resekcije je rijetka (u manje od 2 % slučajeva) (3).

Multiple ciste i somatska mutacija gena *PTCH* opisane su u OKC-ima povezanima sa sindromom nevoidnoga bazeocelularnog karcinoma (Gorlin-Goltz) (13, 14).

Odontogenu cističnu leziju obloženu ortokeratiniziranim epitelom prvi je put opisao Schultz (15) 1927. godine kao dermoidnu cistu. Godine 1981. Wright (2) je tu leziju nazvao ortokeratiniziranom varijantom odontogene keratociste, a Li i ostali (16) predložili su 1998. naziv *ortokeratinizirana odontogena cista*. OOC se pojavljuje osam puta rjeđe od OKC-a (17 – 19). To je manje agresivna lezija s manjom učestalosti recidiva od OKC-a (20). U izdanju Klasifikacije tumora glave i vrata Svjetske zdravstvene organizacije (SZO) objavljenom 2005. godine (21) istaknuto je da cistične lezije čeljusti obložene ortokeratiniziranim epitelom ne čine dio spektra OKC-a koji se tada smatrao benignim keratocističnim odontogenim tumorom (KCOT). U petom izdanju Klasifikacije SZO-a o tumorima glave i vrata (3), OOC je uključen kao zaseban i specifičan entitet. OOC je histološki karakteriziran tankim pločastim epitelom s izraženim granularnim slojem i niskim kubičnim bazalnim stanicama. Unutarnja površina prekrivena je nenazubljenom lameliranom ortokeratinizacijom (slika 1. B). Recidivi su rijetki, u manje od 2 % slučajeva (3).

Vrlo sličan ortokeratinizirani epitelni pokrov nalazi se u EC-u (slika 1. C). Iako su to najčešće kožne ciste, EC u usnoj

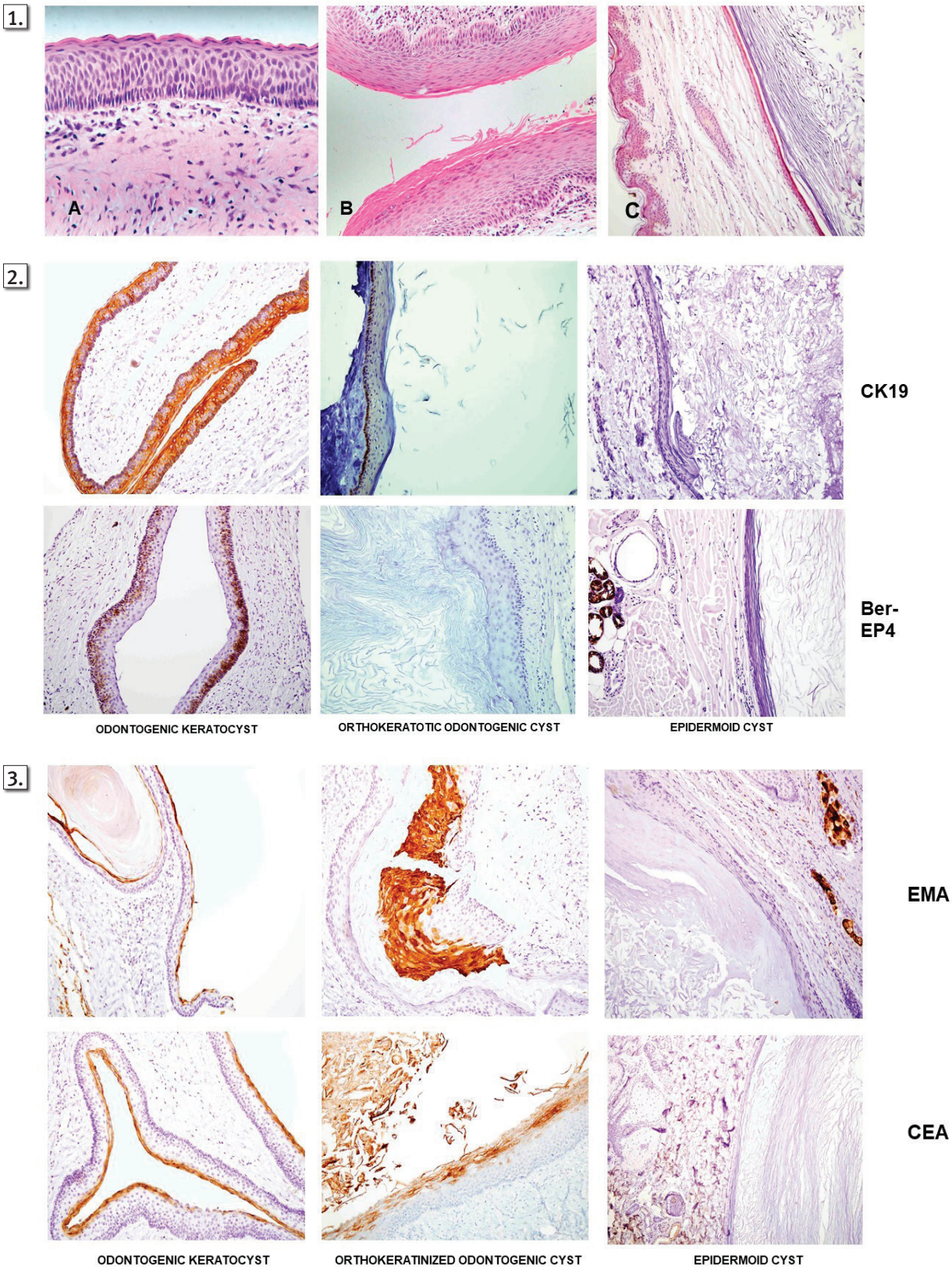

Figure 1 Histopathological images of odontogenic keratocyst (A, HEx400), orthokeratinized odontogenic cyst (B, HEx200) and epidermoid cyst (C, HEx100).
Slika 1. Patohistološke slike odontogene keratociste (A, HEx400), ortokeratinizirane odontogene ciste (B, HEx200) i epidermoidne ciste (C, HEx100)
Figure 2 Immunohistochemical expression of cytokeratin 19 (CK19) and epithelial cell adhesion molecule Ber EP-4 in analyzed cysts.
Slika 2. Imunohistokemijska izraženost citokeratina 19 (CK19) i epitelne adhezijske molekule Ber-EP4 u analiziranim cistama
Figure 3 Immunohistochemical expression of epithelial membrane antigen (EMA) and carcinoembryogenic antigen (CEA) in analyzed cysts.
Slika 3. Imunohistokemijska izraženost epitelnog membranskog antigena (EMA) i karcinoembrionalnog antigena (CEA) u analiziranim cistama

Very similar orthokeratinized epithelial lining can be found in EC (Figure 1 C). Although ECs are the most common cutaneous cysts, they rarely occur within the oral cavity. Approximately 7 % of these cysts occur in the head and neck, 1.6 % of which appear in the oral cavity (22). Budnik and Barnes (8) classify ECs as nonodontogenic, nondevelopmental cysts arising in oral soft tissue. Only a few cases in the literature describe ECs arising within the bone, occuring most frequently in the skull and in the distal phalanges of the fingers. ECs arising within the jaw bone have been extremely rarely described in literature (23-30). Most of these case reports were not supported by photomicrographs or immunohistochemical findings. Some of the available photomicrographs were, in our opinion, indistinguishable from OKC or OOC (4, 27, 31).

These cysts occur most often in patients in the second or third decade of life. Intraosseous ECs originate from a congenital inclusion of ectodermal tissue during embryological development (4, 5) or implantation of epithelium by either surgical or accidental trauma into deeper mesenchymal tissues (6). King (32) suggested the term „post traumatic cyst" considering that trauma always attributes to its formation. Considering the different biological behaviour of keratinized cystic lesions of the jaw, the therapeutic approach is dependent on the diagnosis.

Histopathologically, EC, OOC and OKC are very similar. Numerous studies investigated the expression of various immunohistochemical markers in the epithelial lining of different jaw cysts to elucidate their origin and pathogenesis, however conclusive results have not yet been reported. Cytokeratins (CK) were the most commonly analyzed markers. Cytokeratins are proteins of keratin-containing intermediate filaments found in the intracytoplasmic cytoskeleton of epithelial tissue. CK-10 is an early marker for mature keratinocytes, and CK-19 is expressed in odontogenic and secretory epithelium. One of the main clinical implications in the study of CK profile by immunohistochemistry techniques is its utility in investigating and identifying the source of origin of a tumor/cyst and its characterization (33). A compilation of data suggests that CK5/6, CK8/18 and CK19 are present in odontogenic cysts (33-36), but results vary. In the present study CK5/6 was positive only in the basal layer of all epidermoid cysts, and in all layers of both OKCs and OOCs, whereas CK8/18 and CK19 were negative in all ECs, sporadic cells were positive in OOCs, and strong basal and suprabasal positivity was evident in all OKCs (Figure 2). Coexpression of CK5/6, CK8/18 and CK19 appears to be characteristic of odontogenic epithelia (36). CK7, as a marker of enamel organ, has negative (20, 37) or weakly positive reactivity (19, 38) in odontogenic cysts. In our study CK7 was negative in all cysts. On the contrary, CKAE1/AE3 was intensely positive in all cysts, thus confirming previous findings that neither CK7 nor CKAE1/AE3 are useful in differentiating between jaw cysts (39, 40).

Epithelial membrane antigen (EMA) is normally present at the apical surface of almost all glandular and ductal epithelial cells and in eccrine and apocrine glands of the skin.

šupljini je rijedak. Oko 7 % tih cista pojavljuje se u području glave i vrata, od toga 1,6 % nastaje u usnoj šupljini (22). Budnik i Barnes (8) klasificiraju EC kao neodontogenu, nerazvojnu cistu koja se pojavljuje u oralnome mekom tkivu. Samo nekoliko slučajeva iz literature opisuje EC koji se pojavljuje u kosti, najčešće u lubanji i distalnim falangama prstiju. EC u kostima čeljusti iznimno je rijetko opisana u literaturi (23 – 30). U većini tih prikaza slučajeva ne nalaze se fotomikrografije, ni nalazi imunohistokemijske analize. Neke od dostupnih fotomikrografija ne može se, prema našem mišljenju, razlikovati od OKC-a ili OOC-a (4, 27, 31).

Te se ciste najčešće pojavljuju kod pacijenata u drugom i trećem desetljeću života. Intraosealni EC-i nastaju iz kongenitalnih inkluzija ektodermalnoga tkiva u embrionalnom razvoju (4, 5), ili slučajnim usađivanjem epitela u dublja mezenhimalna tkiva tijekom kirurškog zahvata, ili kao posljedica traume (6). King (32) je predložio termin „posttraumatska cista" s obzirom na to da trauma uvijek igra ulogu u njihovu nastanku. Keratinizirane ciste čeljusti različito se biološki ponašaju zbog čega liječenje ovisi o dijagnozi.

Histopatološki su EC-i, OOC-i i OKC-i vrlo slične lezije. Autori mnogobrojnih studija istraživali su izraženost različitih imunohistokemijskih biljega u epitelnom pokrovu različitih cista čeljusti kako bi razjasnili njihovo podrijetlo i patogenezu, ali zasad bez jasnih zaključaka. Najčešće istraživani biljezi bili su citokeratini (CK). Citokeratini su proteini intermedijarnih filamenata koji sadržavaju keratin, a nalaze se u intracitoplazmatskom citoskeletu epitelnog tkiva. CK-10 rani je biljeg zrelih pločastih stanica, a CK-19 izražen je u odontogenom i sekretornom epitelu. Klinički je proučavanje CK profila imunohistokemijskim metodama važno zato što je korisno u istraživanju i identifikaciji podrijetla tumora/ciste i njihove karakterizacije (33).

Mnogobrojni podatci govore u prilog tomu da se CK5/6, CK8/18 i CK19 nalaze u odontogenim cistama (33 – 36), ali rezultati istraživanja su različiti. U ovoj studiji je CK5/6 bio pozitivan samo u bazalnom sloju svih epidermoidnih cista u svim slojevima u OKC-u i OOC-u, a CK8/18 i CK19 bili su negativni u svim EC-ima, pokoja stanica bila je pozitivna u OOC-u, a jaki bazalni i suprabazalni pozitivitet nađen je u svim OKC-ima (slika 2.).

Čini se da je zajednički izražaj CK5/6, CK8/18 i CK19 karakterističan za odontogeni epitel (36). Kao biljeg caklinskoga organa CK7 negativan je (20, 37) ili slabo pozitivan (19, 38) u odontogenim cistama. U našem istraživanju bio je negativan u svim cistama. CKAE1/AE3 bio je snažno pozitivan u svim cistama, što potvrđuje nalaze u dosadašnjim istraživanjima da ni CK7 ni CKAE1/AE3 nisu korisni u razlikovanju cista čeljusti (39, 40).

Epitelni membranski antigen (EMA) normalno se nalazi na apikalnoj površini gotovo svih žljezdanih i duktalnih epitelnih stanica te u ekrinim i apokrinim žlijezdama kože. Tumorski biljeg, karcinoembrionalni antigen (CEA), nalazi se u odontogenim tumorima i keratocistama (41), ali njegovo značenje nije razjašnjeno. Autori dosadašnjih studija ističu da se CEA uvijek nalazi u zrelim stanicama smještenim u površinskim slojevima i difuzno je pozitivna u svim OKC-ima (39, 42). U našoj studiji i EMA i CEA bi-

The tumor marker carcinoembryonic antigen (CEA) has been detected in odontogenic tumors and keratocysts (41), but its significance is unclear. Previous studies showed that CEA reactivity was consistently detected in mature cells located in superficial layers and was diffusely positive in all OKCs (39, 42). In our study, both EMA and CEA were negative in ECs, but were superficially positive in both OOCs and OKCs, suggesting the identical origin of these cysts (Figure 3).

Ber-EP4 is an epithelial cell adhesion molecules (EpCAM) family member. Normal skin and oral epithelium does not stain with Ber-EP4. In several previous studies, it has been used as a marker for distinguishing intraoral basal cell carcinoma from peripheral ameloblastoma and mucosal OKC (43, 44).

To our knowledge, the present study is the first report on expression of Ber-EP4 in jaw cysts. At least weak positivity in basal and suprabasal layers of all investigated OKCs was evident, whereas all OOCs and ECs were negative with Ber-EP4 (Figure 2). This finding suggests that immunohistochemical staining for Ber-EP4 could be useful in cases where histological features alone are insufficiently conclusive to distinguish between these lesions.

Proliferation activity markers have often been used to demonstrate a higher proliferation rate in OKC compared to other cyst types. Increased Ki-67 expression above the basal layers is characteristic for OKC when compared to other cyst types (14, 18, 45-47).

Proliferation activity assesed by Ki-67, as well as the distribution of positive nuclei within the epithelial layers was consistent with previously reported data.

There is some evidence emerging that anti-apoptotic marker Bcl-2 may be specifically increased in OKC, but this needs confirmation and its diagnostic value should be evaluated (14, 48). Also, calretinin, a calcium-binding protein, has a possible role in the regulation of apoptosis. It has been found that it is expressed in stellate reticulum-like cells in ameloblastomas, but in odontogenic keratocysts either no positivity or positive staining to a much lesser extent is present (43, 47, 49).

Our analysis revealed moderately positive expression of Bcl-2 in basal and suprabasal layers of most OKCs analyzed, and negative reaction in all OOCs and ECs. No Bcl-2 staining was found in the analysis of a buccal EC by Costa et al (50), which is consistent with our results. This finding suggests that Bcl-2 could also be a useful immunohistochemical marker in diagnostically challenging cases.

No positive reactions with calretinin were revealed in our study.

The evaluation of the role of tumor stem cells in odontogenic lesions is important for a better understanding of the histogenesis of these lesions. Several benign and malignant odontogenic neoplasms have been reported to originate from the remnants of dental stem cells (51, 52), and the presence of stem cells was identified in the epithelial lining of various odontogenic cysts (53).

Tumor suppressor gene p63 plays a major role in the maintenance of epithelial stem cells and their terminal differ-

le su negativne u EC-u, ali površinski pozitivne i u OOC-u i u OKC-u, što upućuje na zajedničko podrijetlo tih cista (slika 3.).

Ber-EP4 član je obitelji molekula adhezije epitelnih stanica (EpCAM). Uredan kožni i oralni epitel negativan je na Ber-EP4. U nekoliko prethodnih istraživanja korišten je kao biljeg za razlikovanje intraoralnoga bazeocelularnog karcinoma od perifernog ameloblastoma i sluzničnog OKC-a (43, 44).

Prema spoznajama autora, ovo je prvo istraživanje u kojemu je analizirana izraženost Ber-EP4 u cistama čeljusti. U svim analiziranim OKC-ima nađen je barem slab pozitivitet u bazalnim i suprabazalnim slojevima, a svi OOC-i i EC-i bili su negativni na Ber-EP4 (slika 2.). Takvi rezultati upućuju na to da bi imunohistokemijsko bojenje na Ber-EP4 moglo biti korisno onda kada nije moguće razlikovati te lezije na temelju histoloških svojstava.

Biljezi proliferacijske aktivnosti često su korišteni za prikaz veće stope proliferacije u OKC-u u usporedbi s drugim vrstama cista. Povećana izraženost Ki-67 iznad bazalnih slojeva karakteristična je za OKC u usporedbi s drugim vrstama cista (14, 18, 45 – 47). U ovom istraživanju je proliferacijska aktivnost procijenjena s pomoću Ki-67, kao i raspodjela pozitivnih jezgri unutar slojeva epitela koja je bila u skladu s rezultatima iz već objavljenih istraživanja.

Rezultati pojedinih istraživanja upućuju na to da bi antiapoptotički biljeg Bcl-2 mogao biti specifično povišen u OKC-u, ali te podatke treba dodatno potvrditi i procijeniti njihovu dijagnostičku vrijednost (14, 48). Također kalretinin, protein koji veže kalcij, možda ima ulogu u regulaciji apoptoze. Utvrđeno je da je izražen u stanicama nalik na zvjezdasti retikulum u ameloblastomima, ali u odontogenim keratocistama nema pozitiviteta ili se on nalazi u mnogo manjoj mjeri (43, 47, 49).

Naša analiza pokazala je umjereno pozitivnu izraženost Bcl-2 u bazalnim i suprabazalnim slojevima većine analiziranih OKC-a, te negativnu reakciju u svim OOC-ima i EC-ima. U analizi EC-a sluznice obraza koju su obavili Costa i suradnici (50) nije pronađena izraženost Bcl-2, što je u skladu s našim rezultatima. Takav nalaz sugerira da bi Bcl-2 također mogao biti koristan imunohistokemijski biljeg u dijagnostički zahtjevnim slučajevima. U našem istraživanju nije bilo pozitivne reakcije na kalretinin.

Istraživanje uloge tumorskih matičnih stanica u odontogenim lezijama važno je za bolje razumijevanje histogeneze tih tvorbi. Utvrđeno je da nekoliko benignih i malignih odontogenih neoplazmi potječe od ostataka zubnih matičnih stanica (51, 52), a prisutnost matičnih stanica dokazana je u epitelnom pokrovu različitih odontogenih cista (53).

Tumor-supresorski gen *p63* izrazito je važan u održavanju epitelnih matičnih stanica i njihovoj završnoj diferencijaciji (54). Postoje dokazi koji upućuju na to da ciljana terapija usmjerena protiv određenih populacija tumorskih matičnih stanica (CSC) može rezultirati učinkovitijim liječenjem, sprječavanjem recidiva i smanjenjem morbiditeta kod pacijenata s malignim neoplazmama, a sličan učinak očekuje se i u slučaju odontogenih lezija (55). U našem istraživanju provedena je analiza izraženosti biljega matičnih stanica CD44

ferentiation (54). Evidence suggests that targeted therapies designed against particular cancer stem cell (CSC) populations may result in a more effective treatment, prevention of recurrences and reduction of morbidity in patients with malignant neoplasms, and a similar effect is expected with odontogenic lesions (55). In our study, an analysis of the expression of CD44 stem cell marker and p63 was perfomed, which revealed moderate membrane positivity in basal and suprabasal layers of all analyzed cysts.

A potential limitation of this study is that, due to their extreme rarity, no ECs of the jaw bones were included in the study. However, since intraosseous ECs and ECs of the skin have the same histogenesis and their only difference is localization, their histopathological and immunohistochemical characteristics should be considered identical. In the study which compared cytokeratin expression among orthokeratinized odontogenic cysts, epidermoid cysts and odontogenic keratocysts, Padmapriya et al (33) also analysed ECs of the skin instead of intraosseuous ECs because of their identical characteristics.

Conclusion

The results obtained in the present study show that immunohistochemistry may be helpful in distinguishing between keratinized cystic lesions of the jaw, especially in diagnostically difficult cases. In particular, the results of our study suggest that Ber-EP4 and Bcl-2 are useful in distinguishing between OKC and OOC, which is the biggest differential diagnostic problem and the choice of treatment depends on the diagnosis. According to the compilation of our results and other reported results, the authors suggest that orthokeratinized lesions within the jaw bone should be defined as orthokeratinized odontogenic cyst developed from odontogenic remnants. Intraosseal epidermoid cyst should be diagnosed only if immunohistochemical staining points to ectodermal origin, thus suggesting congenital inclusion EC or with evidence of traumatic inclusion of ectodermal epithelium, which suggests post-traumatic EC.

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Ethical approval: This research study was conducted retrospectively from data obtained for clinical purposes. The Institutional Review Board of University Hospital Dubrava determined that ethical approval was not required for our study.

Author's contribution: L. M. - Conceptualization, Methodology, Writing - Original Draft; **M. M.** – Validation, Formal analysis; **K. K.** – Writing - Review & Editing; **S. M.** – Writing - Review & Editing, Supervision; **S. S.** – Supervision

i *p63* koja je pokazala umjereni membranski pozitivitet u bazalnim i suprabazalnim slojevima svih analiziranih cista.

Potencijalno ograničenje ovog istraživanja jest to što, zbog njihove iznimne rijetkosti, u istraživanje nisu uključeni EC-i čeljusnih kostiju. Budući da intraosealni EC-i i EC-i kože imaju istu histogenezu i jedina im je razlika lokalizacija, za njihova histopatološka i imunohistokemijska svojstva treba smatrati da su identična. U istraživanju u kojemu se uspoređivala izraženost citokeratina među ortokeratiniziranim odontogenim cistama, epidermoidnim cistama i odontogenim keratocistama, Padmapriya i suradnici (33) također su analizirali EC kože umjesto intraosealnih EC-a zbog njihovih jednakih obilježja.

Zaključak

Rezultati u ovom istraživanju pokazuju da imunohistokemija može biti korisna u razlikovanju keratiniziranih cističnih lezija čeljusti u dijagnostički zahtjevnim slučajevima. Konkretno, rezultati našeg istraživanju upućuju na to da su Ber-EP4 i Bcl-2 korisni u razlikovanju OKC-a i OOC-a, što je najveći diferencijalnodijagnostički problem, a izbor liječenja ovisi o točnoj dijagnozi. Na temelju rezultata našeg i drugih istraživanja, autori predlažu da se ortokeratinizirane lezije u kostima čeljusti definiraju kao ortokeratinizirana odontogena cista nastala iz odontogenih ostataka. Dijagnozu epidermoidne ciste treba postaviti isključivo ako imunohistokemijsko bojenje upućuje na ektodermalno podrijetlo, što govori u prilog EC-a kongenitalnog tipa, ili ako postoje dokazi o traumatskoj inkluziji ektodermalnog epitela, što govori u prilog posttraumatskom EC-u.

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Doprinos autora: L. M. - Konceptualizacija, Metodologija, Pisanje, Izvorni nacrt; **M. M.** – Validacija, Formalna analiza; **K. K.** – Pisanje, Pregled i uređivanje; **S. M.** – Pisanje - Pregled i uređivanje, Nadzor; **S. S.** – Nadzor

Sažetak

Cilj rada: Postoje dva tipa keratiniziranih cističnih lezija koje mogu nastati u kosti čeljusti – razvojne ciste odontogenog podrijetla (odontogena keratocista – OKC i ortokeratinizirana odontogena cista – OOC) te epidermoidna cista (EC) nejasnoga podrijetla. Patohistološki izgled tih lezija preklapa se, a njihovo liječenje ovisi o točnoj dijagnozi. Svrha našeg istraživanja bila je utvrditi dijagnostički važne razlike među tim cistama te odrediti kriterije za postavljanje dijagnoze intraosealnog EC-a. **Materijali i metode:** Imunohistokemijska analiza koja je obuhvatila različite citokeratine, karcinoembrionalni antigen (CEA), epitelni membranski antigen (EMA), epitelnu adhezijsku molekulu BerEP4, biljege povezane s apoptozom Bcl-2 i kalretinin, biljeg matičnih stanica CD44, tumorsupresorski gen *p63* i biljeg proliferativne aktivnosti Ki-67, učinjena je na 25 OKC-a, 8 OOC-a i 11 EC-a. **Rezultati:** CK5/6 bio je pozitivan u svim slojevima OKC-a i OOC-a, ali samo u bazalnom sloju EC-a. CK8/18 i CK19 bili su snažno izraženi bazalno i suprabazalno u svim OKC-ima, slabo bazalno izraženi u OOC-ima, a negativni u EC-ima. Ber-EP4 i Bcl-2 bili su pozitivni u svim OKC-ima, a negativni u OOC-ima i EC-ima. **Zaključci:** Rezultati našeg istraživanja upućuju na to da izraženost Ber-EP4 i Bcl-2 može biti korisna za razlikovanje OKC-a od drugih keratiniziranih cista čeljusti. Ortokeratinizirane lezije unutar kostiju čeljusti trebaju se smatrati OOC-om, a dijagnoza intraosealnoga EC-a može se postaviti samo ako imunohistokemijska obrada potvrdi ektodermalno podrijetlo, što upućuje na kongenitalnu ili posttraumatsku inkluziju epitela.

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