

## Original

## Comparative study of cytokeratin and langerin expression in keratinized cystic lesions of the oral and maxillofacial regions

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**Abstract:** Dermoid cysts (DMCs) and epidermoid cysts (EDMCs) usually arise in soft tissues, whereas orthokeratinized odontogenic cysts (OOCs) and keratocystic odontogenic tumors (KCOTs) develop in the jaw. In this study, we performed immunohistochemical analysis of cytokeratins (CKs) to examine differences in the lining epithelium of DMCs, EDMCs, OOCs, and KCOTs. In addition, we carried out immunohistochemical examination of langerin to clarify the biological characteristics of the orthokeratinized lining epithelium of DMCs, EDMCs, and OOCs. Seven DMCs, 30 EDMCs, 11 OOCs, and 28 KCOTs were examined immunohistochemically using antibodies against CK10, 13, 14, 16, 17, 19, and langerin. Immunoreactivities for CKs and langerin in oral DMCs and EDMCs were similar to those of lesions affecting the skin. Positive reactivity for CK13 and 17 was evident in OOCs, but not in DMCs/EDMCs. CK10 was significantly positive in all layers except for the basal layer in OOCs, but was negative in KCOTs. CK17 was positive in all layers in KCOTs, and in all layers except for the basal layer in both OOCs and

dentigerous cysts. CK19 was negative in OOCs. Langerhans cells were found mainly in OOCs, but were hardly evident in KCOTs. These results suggest that DMCs/EDMCs, OOCs and KCOTs are independent diseases. (J Oral Sci 57, 287-294, 2015)

Keywords: keratinized cystic lesion;  
immunohistochemistry; cytokeratin (CK);  
langerin; Langerhans cell.

### Introduction

Among the keratinized cystic lesions of the oral and maxillofacial regions, dermoid cysts (DMCs) and epidermoid cysts (EDMCs) usually occur in soft tissues, whereas orthokeratinized odontogenic cysts (OOCs) and keratocystic odontogenic tumors (KCOTs) develop in the jaw. DMCs and EDMCs are commonly found in the skin but are relatively rare in the oral region. DMCs and EDMCs usually occur in the soft tissue of the oral region; however, several reports have indicated that DMCs and EDMCs can also occur in the jaw. Generally, the origins of DMCs and EDMCs in the jaw have been unclear, but two possible reasons have been suggested: sequestration of stomodeal ectoderm during embryogenesis, or derivation from an odontogenic epithelial remnant showing dermal metaplasia (1-5). Among the orthokeratinized cystic lesions, both dermoid and epidermoid cysts are lined by keratinized stratified squamous epithelium

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resembling epidermis. DMCs are characterized by the presence in the wall of one or more dermal appendages such as hair follicles, sweat glands or sebaceous glands. On the other hand, EDMCs do not have such appendages. The midline of the mouth floor is the most common location for both DMCs and EDMCs, which usually originate above the mylohyoid muscle. Histogenetically, they may be congenital or occur as a result of trauma (6).

In the 2005 World Health Organization (WHO) histopathological classification, cystic jaw lesions that are lined by orthokeratinizing epithelium do not form part of the spectrum of KCOTs. The mandible, especially at the angle, is involved more frequently than the maxilla, extending anteriorly and superiorly (7). These cysts are considered to arise from the dental lamina, enamel organ and its remnants (8).

In the present study, we performed an immunohistochemical analysis of cytokeratins (CKs) to examine the differences in the epithelial linings of DMCs, EDMCs, OOCs, and KCOTs. In addition, immunohistochemical staining for langerin was conducted to clarify the biological characteristics of the orthokeratinized lining epithelium of DMCs and EDMCs resembling that of skin in which Langerhans cells are normally present. Furthermore, we investigated the differences between neoplastic cystic lesions and developmental cysts, since KCOTs were reclassified as odontogenic tumors in the revised WHO classification in 2005 (7).

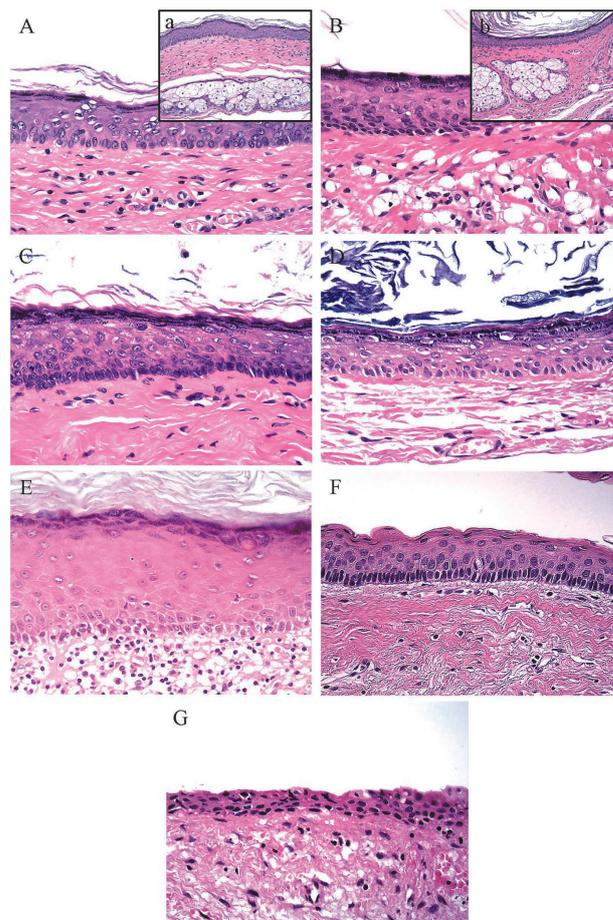
## Materials and Methods

### Tissue preparation

Seven DMCs, 30 EDMCs, 11 OOCs, and 28 KCOTs were collected from the archives of the Division of Pathology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry, covering the period from 1982 to 2013. Dentigerous cysts (DCs) were used as a control. KCOTs and OOCs were reclassified on the basis of the 2005 WHO histopathological classification (7). Samples were fixed in 10% buffered formalin, embedded in paraffin wax, and stained with hematoxylin and eosin for subsequent histological diagnosis (Figs. 1A-G). Clinical findings are summarized in Table 1. The study protocol was reviewed and approved by the Research Ethics Committee of Meikai University School of Dentistry (A1321).

### Immunohistochemistry

Each sample embedded in paraffin wax was sectioned and mounted on glass microscope slides. The deparaffinized sections were immersed in absolute methanol containing 0.3% (v/v) H<sub>2</sub>O<sub>2</sub> for 15 min at room temperature to block



**Fig. 1** Representative images of the histological features of DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs, and DCs. Hematoxylin and eosin staining of DMC (oral region) (A), DMC (skin) (B) [dermal appendages are present in the cystic wall (a, b)] (original magnification  $\times 100$ ), EDMC (oral region) (C), EDMC (skin) (D), OOC (E), KCOT (F) and DC (G) (original magnification  $\times 200$ ).

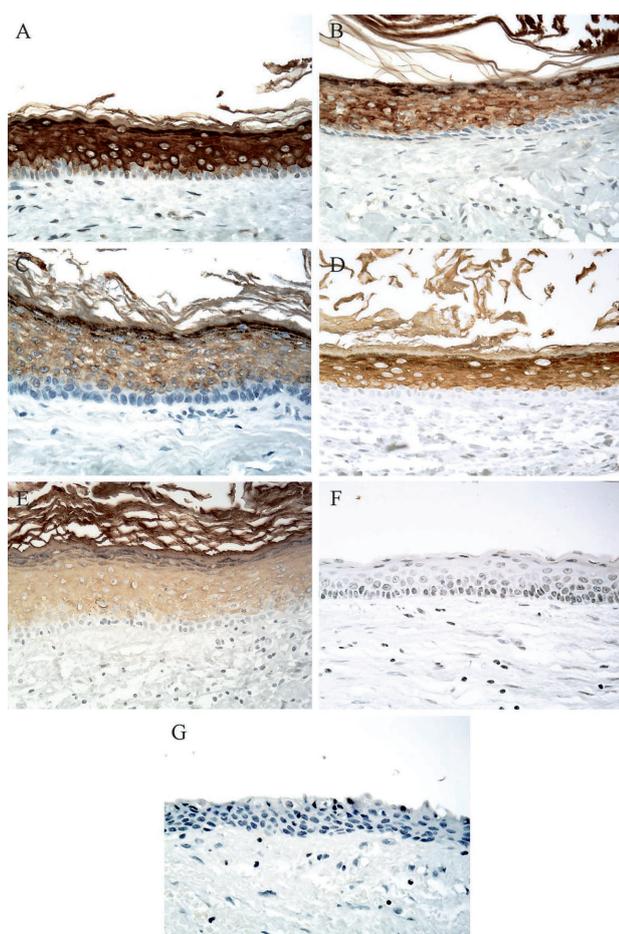
endogenous peroxidase activity. After washing with running water and phosphate-buffered saline (PBS, pH 7.4), the sections were immersed in 0.01 M citrate buffer (pH 6.0), and heated in a microwave oven for 15 min at low voltage. All sections were then incubated in 2% (w/v) bovine serum albumin in PBS (BSA-PBS) for 30 min at room temperature to block nonspecific reactions. Appropriately diluted primary antibodies shown in Table 2 were applied to each section for 1 h at room temperature followed by incubation with peroxidase-labeled dextran polymer, Simple Stain MAX-PO (Nichirei Bio Inc., Tokyo, Japan), for 30 min. They were then washed with PBS, immersed for 5 min in 0.05% 3,3'-diaminobenzidine tetrahydrochloride (DAB) (Nakarai Tesque, Inc., Kyoto, Japan) in 0.05 M Tris-HCl buffer (pH 7.6) containing 0.01% H<sub>2</sub>O<sub>2</sub>, and counterstained with Mayer's hematoxylin. For control studies, the serial sections were

**Table 1** Clinical findings

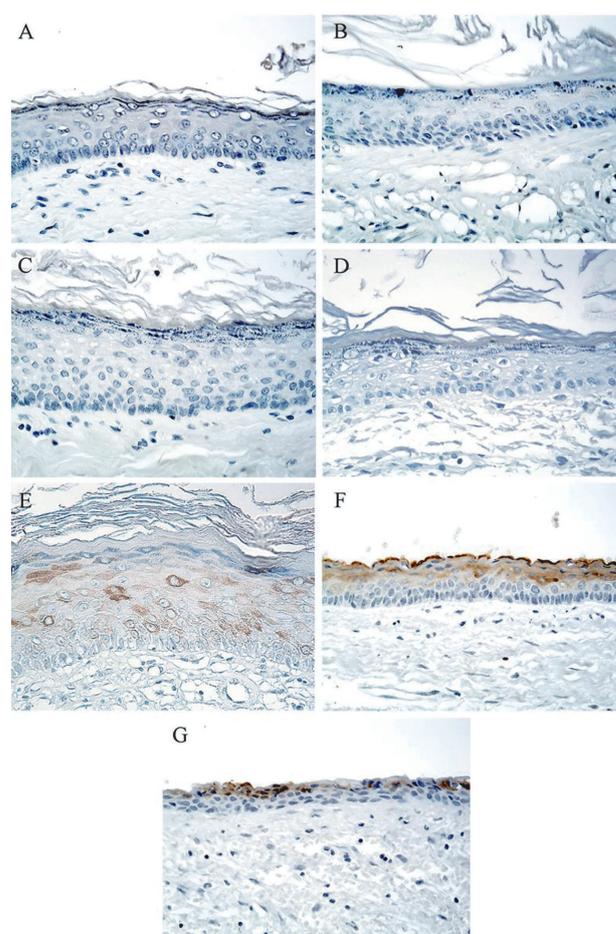
	Number	Gender		Mean age	Location			
		Male	Female		Oral region	Skin	Maxillary molar region	Mandibular molar region
DMC	7	6	1	42.9	2	5	–	–
EDMC	30	21	9	40.8	7	23	–	–
OOC	11	9	2	36.3	–	–	3	8
KCOT	28	17	11	33.5	–	–	5	23
DC	30	20	10	44.2	–	–	2	28

**Table 2** Primary antibodies

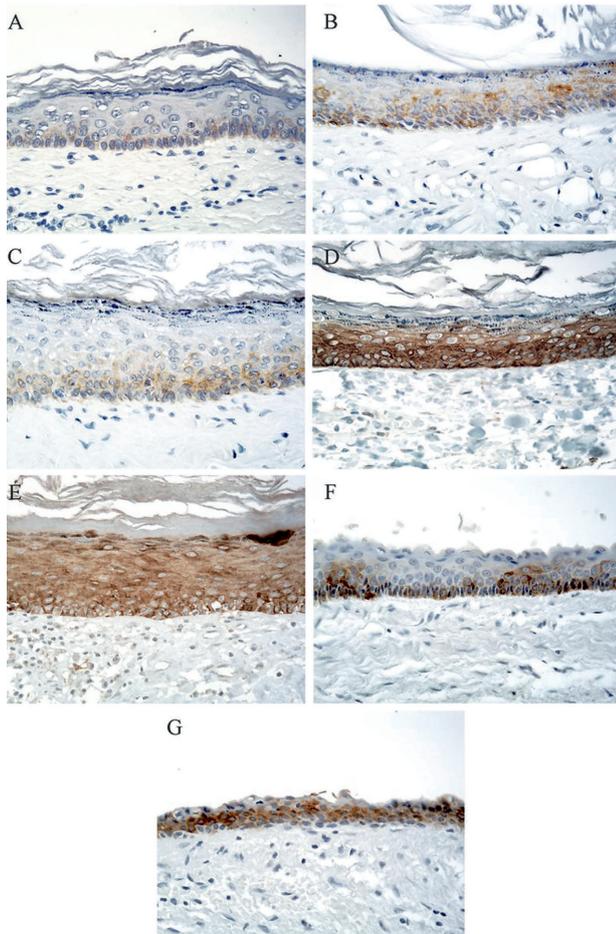
Antibodies	Source	Dilution
Anti-human CK10 mouse monoclonal antibody	Dako North America, CA, USA	1/50
Anti-human CK13 mouse monoclonal anti-body	Abcam plc, Cambridge, UK	1/100
Anti-human CK14 mouse monoclonal anti-body	Abcam plc, Cambridge, UK	1/100
Anti-human CK16 rabbit monoclonal anti-body	Abcam plc, Cambridge, UK	1/100
Anti-human CK17 mouse monoclonal antibody	Dako North America, CA, USA	Pre-diluted
Anti-human CK19 mouse monoclonal antibody	Dako North America, CA, USA	Pre-diluted
Anti-human Langerin mouse monoclonal anti-body	Abcam plc, Cambridge, UK	1/200



**Fig. 2** Representative immunoreactivity for CK10 in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs, and DCs. CK10 was positive in the Su and SP of DMCs (oral region and skin) (A, B), EDMCs (oral region and skin) (C, D) and OOC (E), but negative in all layers of KCOT (F) and DC (G) (original magnification  $\times 200$ ).



**Fig. 3** Representative immunoreactivity for CK13 in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs, and DCs. CK13 was negative in all layers of DMCs (oral region and skin) (A, B) and EDMCs (oral region and skin) (C, D), but positive in all layers of OOC (E), KCOT (F) and DC (G) except for the Ba (original magnification  $\times 200$ ).

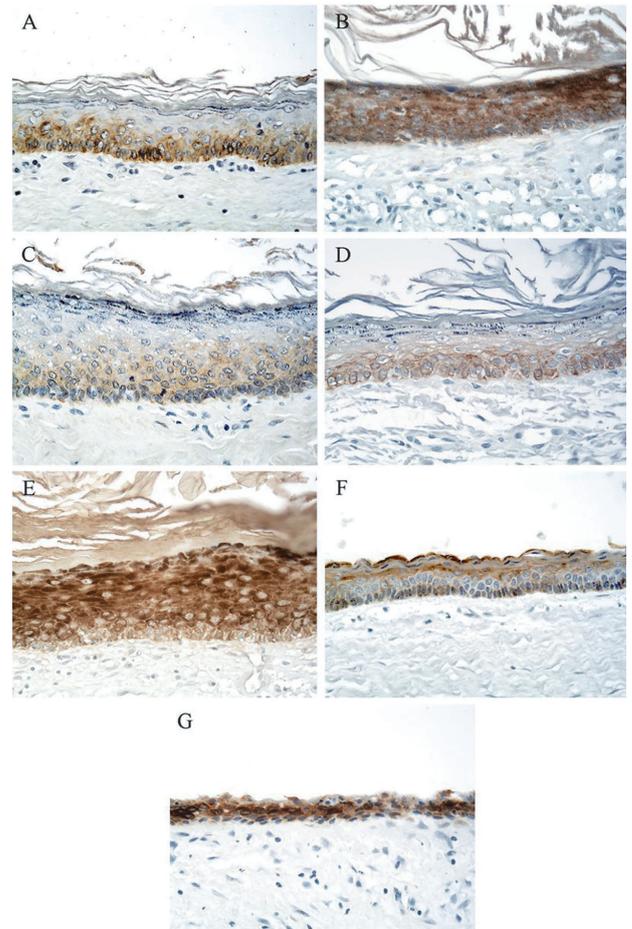


**Fig. 4** Representative immunoreactivity for CK14 in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs, and DCs. CK14 was positive in the SP and Ba of DMCs (oral region and skin) (A, B), EDMCs (oral region and skin) (C, D), OOC (E) and KCOT (F), and also positive in all layers of DC (G) (original magnification  $\times 200$ ).

treated with 2% BSA-PBS instead of the primary antibodies.

#### Immunohistochemical evaluation

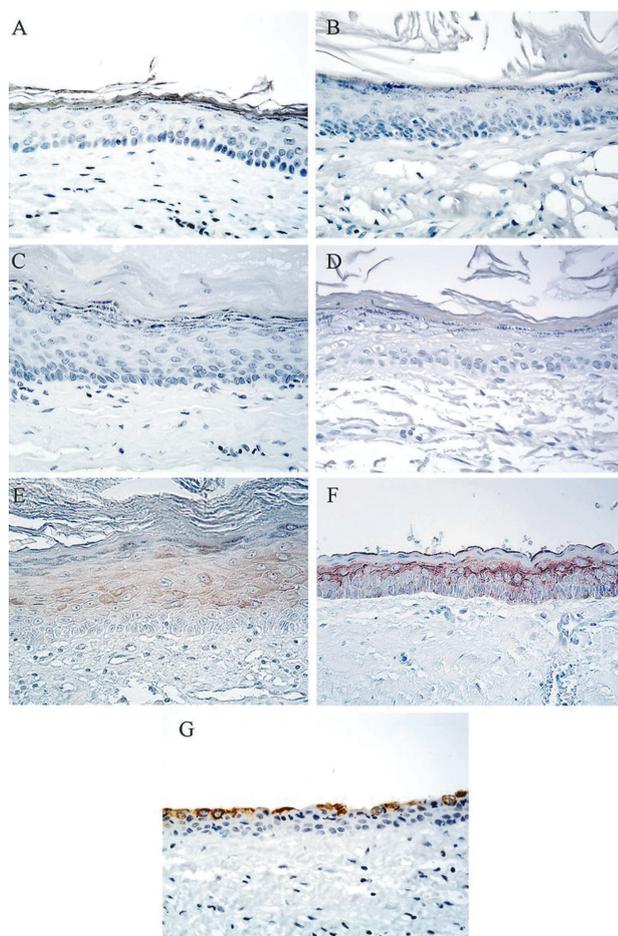
We evaluated the immunohistochemical reactivity of CKs by classifying the epithelial lining into three layers: the surface layer (Su; the keratinized epithelial lining including the granular layer), the spinous layer (Sp) and the basal layer (Ba). In DCs the epithelial lining was divided into two layers: Sp and Ba. With regard to CK and langerin expression, the specimens were classified into two groups: positive and negative in the cytoplasm, cell membranes or Langerhans cells, respectively. As positive controls for the orthokeratinized lining epithelium, sections of morphologically normal hard palate and skin and for the parakeratinized lining epithelium normal gingiva were used respectively.



**Fig. 5** Representative immunoreactivity for CK16 in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs and DCs. CK16 was positive in the SP and Ba of DMC (oral region) (A) and EDMCs (oral region and skin) (C, D) and also positive in all layers of DMC (skin) (B), OOC (E), KCOT (F) and DC (G) (original magnification  $\times 200$ ).

## Results

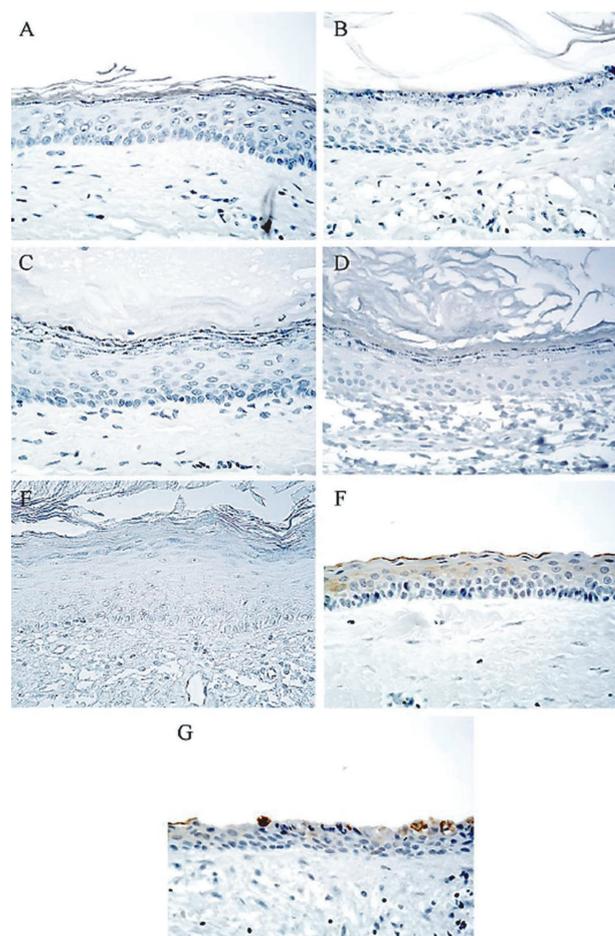
The representative expressions of each CK and langerin are shown in Figs. 2-8. For CK10 expression, immunohistochemical staining was positive in all layers of the keratinized squamous epithelium except for the Ba of DMCs (oral region and skin), EDMCs (oral region and skin) and OOCs (Figs. 2A-E), but negative in KCOTs and DCs (Figs. 2F and G). For CK13 expression, positivity was confirmed in all layers except for the Ba of OOCs, KCOTs, and DCs (Figs. 3E-G), but not in DMCs (oral region and skin) and EDMCs (oral region and skin) (Figs. 3A-D). For CK14 expression, immunoreactivity was shown in all layers except for the Su of DMCs (oral region and skin), EDMCs (oral region and skin), OOCs and KCOTs (Figs. 4A-F), as was the case for all layers of DCs (Fig. 4G). For CK16 expression, positivity was evident in all layers except for the Su of DMCs (oral region) and EDMCs (oral region and skin) (Figs. 5A, C,



**Fig. 6** Representative immunoreactivity for CK17 in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs and DCs. CK17 was negative in all layers of DMCs (oral region and skin) (A, B) and EDMCs (oral region and skin) (C, D), but positive in the Su and Sp of OOC (E), in all layers of KCOT (F) and in the Sp of DC (G) (original magnification  $\times 200$ ).

and D), as was the case for all layers in DMCs (skin), OOCs, KCOTs, and DCs (Figs. 5B, E-G). For CK17 expression, immunoreactivity was shown in all layers except for the Ba of OOCs and DCs (Figs. 6E and G) and in all layers of KCOTs (Fig. 6F), but not in DMCs (oral region and skin) and EDMCs (oral region and skin) (Figs. 6A-D). For CK19 expression, reactivity was evident in all layers except for the Ba of KCOTs and DCs (Figs. 7F and G), but not in DMCs (oral region and skin), EDMCs (oral region and skin) and OOCs (Figs. 7A-E). For langerin expression, positivity was evident in Langerhans cells in the Sp of DMCs (oral region and skin), EDMCs (oral region and skin) and OOCs (Figs. 8A-E), but hardly evident in KCOTs (Fig. 8F), and absent in DCs (Fig. 8G).

The immunohistochemical data for these CKs are shown as bar graphs (Figs. 9A-F). There was a similar pattern of reactivity for CK10, CK13, CK17, and CK19 in DMCs (oral region and skin) and EDMCs (oral region

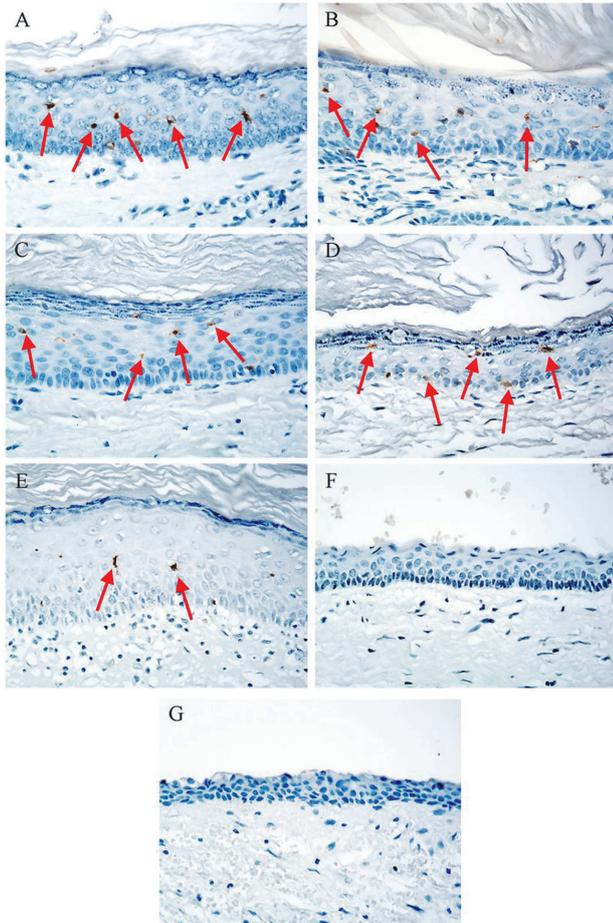


**Fig. 7** Representative immunoreactivity for CK19 in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs and DCs. CK19 was negative in all layers of DMCs (oral region and skin) (A, B), EDMCs (oral region and skin) (C, D) and OOC (E), but positive in the Su and Sp of KCOT (F) and in the Sp of DC (G) (original magnification  $\times 200$ ).

and skin) (Figs. 9A-D). There were differences in immunoreactivity for CK13 and CK17 between DMCs/EDMCs and OOCs (Figs. 9B and C). The immunoreactivities for CK10, CK17, and CK19 in OOCs, DCs as developmental cysts and KCOTs as neoplastic cystic lesions also differed (Figs. 9A, C, and D). With regard to CK14 and CK16 expression, no differences were evident among all the lesions. A similarity in the reactivity pattern for CK14 and CK16 was evident between DMCs (oral region and skin) and EDMCs (oral region and skin) (Figs. 9E and F), and a similar reactivity pattern for CK14 was evident between OOCs and KCOTs (Fig. 9E), and for CK16 among OOCs, KCOTs and DCs (Fig. 9F).

## Discussion

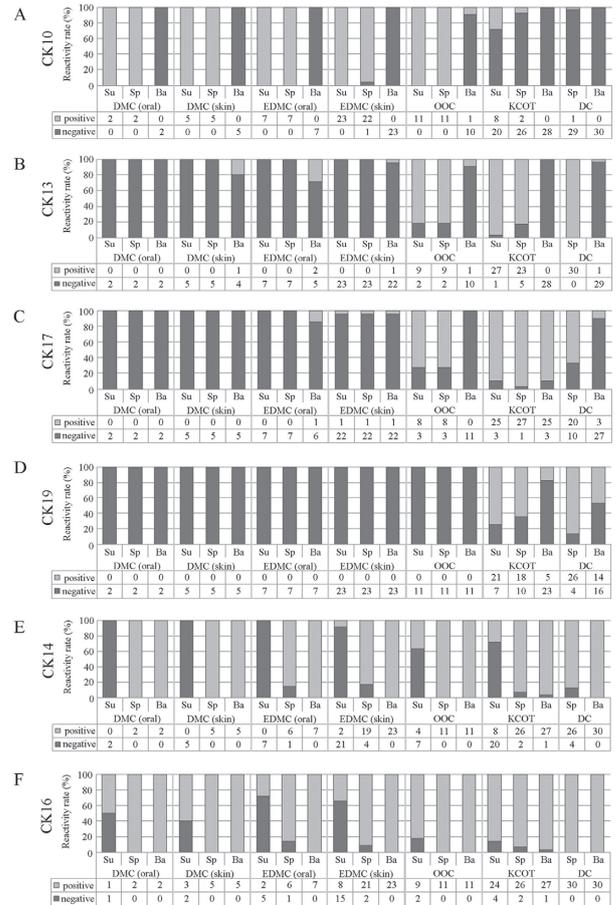
Although the first recorded orthokeratinized jaw cysts (OJCs) were identified by Schultz (9) in 1927, various subsequent reports have indicated that OJCs should



**Fig. 8** Representative immunoreactivity for langerin in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs, and DCs. Langerin was positive in the Sp of DMCs (oral region and skin) (A, B), EDMCs (oral region and skin) (C, D) and OOC (E), but negative in KCOT (F) and DC (G) (original magnification  $\times 200$ ). The red arrows indicate Langerhans cells.

be distinguished from OKCs (8,10-13). Furthermore, Pindborg et al. (14) stated that any kind of keratinized cysts should be independent from other odontogenic cysts. On the other hand, in 1960 Shear (15) classified primordial cysts (PCs) as OKCs, which was controversial because all PCs were not necessarily keratinized (11,16). In the 1992 WHO classification (17), OKCs and PCs were handled synonymously, but there was no reference to non-keratinized PCs. PCs have still not been officially defined; however, the term “PC” has been generally used for non-keratinized odontogenic cysts without impacted teeth (8). In the 2005 WHO classification, cystic jaw lesions that are lined by orthokeratinizing epithelium were considered not to form part of the spectrum of KCOTs (7).

CKs, which are intermediate filaments with a molecular mass range of 40-70 kDa and form 10-nm tonofilaments, are divided into two subfamilies: acidic



**Fig. 9** Immunohistochemical analyses of CKs in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs, and DCs. Each bar in the column and number represents percentages and cases, respectively, of CK-positive and negative reactivities. There were similar patterns of immunoreactivity for CK10 (A), CK13 (B), CK17 (C), and CK19 (D) between DMCs (oral region and skin) and EDMCs (oral region and skin). On the other hand, differences in immunoreactivity for CK10, CK17, and CK19 were observed among OOCs, DCs, and KCOTs. A similar pattern of immunoreactivity for CK14 was evident between Su OOCs and KCOTs (E), and for CK16 among OOCs, KCOTs, and DCs (F). Su: surface layer, Sp: spinous layer, Ba: basal layer of the keratinized epithelial lining.

(type I: CK9-21) and neutral-to-basic (type II: CK1-8) (18,19). The cytokeratin filaments of epithelial cells appear to be heteropolymers of these two protein types, and their expression patterns differ depending on each epithelial type (20-22). Our investigation of the differences in the six kinds of CKs in DMCs (oral region and skin), EDMCs (oral region and skin), OOCs, KCOTs and DCs indicated that the expression patterns of CKs in DMCs and EDMCs of the oral region were similar to those of skin.

Among orthokeratinized cystic lesions, positive immunoreactivity for CK13 and CK17 was not evident in DMCs and EDMCs affecting soft tissues, but was evident

in OOCs, indicating that they may show individual types of differentiation. CK13 (54 kDa) is present in the suprabasal layer of oral stratified squamous epithelium (23) and is expressed in odontogenic cysts and tumors (24-26). However, Tsuji et al. (27) and Hayashi et al. (28) reported that CK13 expression could not be confirmed in OOCs, being inconsistent with our present result. On the other hand, Koizumi (29) stated that CK13 was partially positive in OOCs, supporting of our result. In addition, Crivelini et al. (30) described that CK13 expression in odontogenic epithelium was consistent with its expression in dental lamina. Furthermore, several reports have indicated that CK13 is positive in lesions derived from odontogenic epithelium, such as radicular cysts, DCs, ameloblastomas and KCOTs (24-29). CK17 (46 kDa) is expressed in the anlage of sweat glands, hair follicles and teeth (31), and also in lesions such as odontogenic cysts and tumors (24-26,32). In a comparison between OOCs as representative of developmental cysts and KCOTs as neoplastic cystic lesions, differences in expression were evident among CK10, CK17, and CK19. CK10 (56.5 kDa) is expressed in keratinized stratified squamous epithelium, except for the basal layer (25,27,29). CK10 positivity was evident in the Su and SP of OOCs, indicating they differ from lesions such as KCOTs and DCs. Immunoreactivity for CK17 was found in all layers except for the basal layer in both OOCs and DCs, whereas it was partially weak but present in all layers in KCOTs, suggesting that KCOT has a more neoplastic nature. CK19 (40 kDa) is expressed in dental lamina, the enamel organ and epithelial rests of Malassez, suggesting that it may be considered an odontogenic epithelial marker (29,33-35). In fact, several reports have indicated that CK19 is positive in the basal layer of non-keratinized epithelium, or was negative in KCOTs (25,29). However, our present study showed that CK19 was negative in OOCs, suggesting that CK19 might not be a specific odontogenic marker, whereas positivity was evident in all layers except for the basal layer in KCOTs (80%) and DCs (90%).

Immunoreactivity for both CK14 and CK16 was found in the lining epithelium of all lesions in the present study. CK14 (40 kDa) is specifically expressed in the basal layer of stratified squamous epithelium or myoepithelial cells (20,36,37). CK16 (48 kDa) is expressed in the basal layer of the skin or proliferative epithelium, and in dermal appendages (38-41). Therefore, both CK14 and CK16 may be basic CK markers for stratified squamous epithelium.

Langerin (40 kDa) is a type II transmembrane C-type lectin associated with the formation of Birbeck granules

in Langerhans cells (42,43). Although the function of langerin has been unclear, it has been reported to prevent human immunodeficiency virus (HIV) infection (42). Immunohistochemical staining for langerin was positive in DMCs (oral region and skin), EDMCs (oral region and skin) and OOCs, whereas it was rarely positive in KCOTs and negative in DCs. The function of Langerhans cells in keratinized cystic lesions is unclear; however, the expression of langerin may be associated with immune reactions in the skin and oral mucosa.

In conclusion, the results of our immunohistochemical analyses of CKs and langerin in intraoral DMCs/EDMCs were similar to those for extraoral DMCs/EDMCs, indicating that DMCs/EDMCs, OOCs and KCOTs are independent diseases.

### Conflicts of interest

The authors have no potential conflicts of interest to declare.

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