Expression of Podoplanin in Nevoid Basal Cell Carcinoma Syndrome-Associated Keratocystic Odontogenic Tumours

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Abstract. Background: Keratocystic odontogenic tumour (KCOT) is a benign oral neoplasm of odontogenic origin. The majority of KCOT develop sporadically. The main differential diagnosis of KCOT is from other odontogenic cysts and ameloblastoma. In the rare nevoid basal cell carcinoma syndrome (NBCCS, synonym: Gorlin-Goltz-Syndrome), however, KCOTs are frequently detected and may be the initial sign of this clinical syndrome. Podoplanin is a mucin-type transmembrane protein found in podocytes of human kidneys homologous to T1α-2. The expression of podoplanin in some other non-endothelial tissues raised our interest in studying this antibody in tissues of odontogenic origin. Recently, we reported podoplanin expression in sporadic cases of KCOT. We intended to investigate the podoplanin expression in KCOTs associated with NBCCS. Materials and Methods: Archival paraffin embedded tissues from six KCOTs from patients with known NBCCS were analyzed immunohistochemically with antibodies to podoplanin (D2-40) and p63. Results: We observed a continuous linear immunoreactivity of basal epithelial cells for podoplanin in all cases. The staining intensity was strong and did not differ from that for KCOT in previously reported sporadic cases. Strong nuclear P63 expression was detected in basal cell layers and diminished in suprabasal layers. Conclusion: KCOTs exhibited enhanced podoplanin expression in a clinical setting of NBCCS. Although the biological functions of podoplanin have not yet been fully recognized, the overexpression of this protein is capable of promoting the formation of elongated cell extensions, and increasing adhesion and migration of inflammatory cells. Podoplanin expression in KCOT is possibly associated with slow invasion of the adjacent structures and the well-known frequent local tumour recurrences of this odontogenic tumour.

The nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome, is an autosomal inherited disease with a plethora of signs and symptoms (1-3). In the oral and maxillofacial region, keratocystic odontogenic tumour (KCOT) of the jaws is associated with this syndrome (4, 5). KCOT is a benign uni- or multicystic intraosseous tumour of odontogenic origin. The microscopic features of KCOT are characteristic: the cyst is lined by a parakeratinized stratified squamous epithelium, usually about 5 to 8 cell layers thick, that lacks rete ridges. Beside a serious impact on proper emergence and position of teeth and often severe impairment of preserving teeth due to tumour extension and tumour recurrences, this tumour is also of diagnostic importance: KCOT in NBCCS often develop multilocularly in affected individuals and usually develop much earlier in life than in sporadic cases, and thus can be the first diagnostic sign of NBCCS in children and adolescents (7, 8). Differential diagnosis of KCOT is from odontogenic cysts (8). Differential diagnosis may be hampered in cases with local inflammation and insufficient material for diagnosis (9). Podoplanin is a mucin-type transmembrane glycoprotein identified in kidney podocytes and is homologous to T1α-2, an antigen expressed on the apical surface of alveolar type I cells (10, 11). Podoplanin is expressed in lymphatic but not in blood vessel endothelial cells (12). However, podoplanin expression has been revealed in different organs, including odontogenic tissues (13). In a recent study, podoplanin was found to be strongly expressed in sporadic KCOT (13). Data on podoplanin expression in syndromatic KCOT have not yet been published. The aim of this study was to define the expression pattern of podoplanin in epithelial lesions frequently found in the oral and maxillofacial region of NBCCS patients.

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Materials and Methods

The KCOT of six patients with NBCCS were investigated. Clinical findings diagnostic for NBCCS are described elsewhere in detail (8). KCOT were from the maxilla (n=1) and mandible (n=5). Cysts were immediately stored in buffered formalin after removal and fixed in paraffin. Routinely processed slides were hematoxylin-eosin stained to establish the diagnosis. Podoplanin (D2-40; Signet, Dedham, USA) and P63 (A4A, M7247; Glostrup, Dako, Denmark) immunostaining was performed as described elsewhere (13).

Results

The KCOT of NBCCS patients exhibited the typical parakeratinized epithelial layers without cellular atypia. Immunohistochemically, KCOT of patients with NBCCS revealed a strong membranous and cytoplasmic reaction for podoplanin of the basal cell layers (Figure 1) identical to the staining pattern observed in sporadic cases (13).

P63 immunoreaction was observed in the basal and parabasal layer of the epithelial lining of the KCOT. Those superficial epithelia that showed initial parakeratinization were P63 negative.

Discussion

This study reveals podoplanin expression in syndromatic and sporadic KCOT to be identical. A number of odontogenic cells are capable of podoplanin expression: odontoblasts, secreting ameloblasts, stellate reticulum and stratum intermediate cells, as well as different epithelial cells in benign odontogenic tumours (13). Podoplanin function is presently unknown. However, the overexpression of podoplanin can promote the formation of elongated cell extensions, and increase adhesion, migration and tube formation of vascular endothelial cells (14). These findings suggest a role for podoplanin in the reorganization of the cytoskeleton and cell migration. Recent findings on the ability of tumour cells to induce podoplanin expression as a promoter of cell migration support these hypotheses (15). The association of podoplanin expression with migratory cells was also assumed in oral tissues with no evidence of malignant transformation: podoplanin is expressed in inflamed gingiva (16). The expression was restricted to inflamed regions and was not found in unaffected oral tissues (16). Indeed, the surprising findings of podoplanin-positivity in oral sulcular and junctional epithelium was interpreted to be associated with the severe inflammation of gingival connective tissues and assumed to be an early sign of periodontitis (16). The immunoreaction with anti-podoplanin in basal epithelium of both reactive non-neoplastic and tumoural cystic odontogenic lesions suggests a similar mechanism of cell adhesion, epithelial mesenchymal transition and invasion involved in the formation of benign expansive growing cystic odontogenic tumours (17).

Our findings of basal and parabasal cell layer P63 positive reaction in the epithelial nuclei was similar to that reported by Dong et al. (18). These results, however, were contrary to that reported by Foschini et al., who observed less frequent nuclear positivity in KCOT associated with NBCCS (19). This may possibly be explained by the different antibodies used in these studies.

Figure 1. Keratocystic odontogenic tumour (KCOT) of the left mandibular wisdom tooth region of an 8-year-old girl with NBCCS. A: Haematoxylin-eosin stain showing the thick epithelial lining of the cystic neoplasm filled with keratin lamellae. B: Under higher power of the sections in (A) the epithelial lining displayed characteristic palisading of the basal cell nuclei and slightly parakeratinization of the surface epithelium. C: The basal cells were strongly positive for D2-40 antibody. D: Strong P63 immunoreaction was observed in both basal and parabasal cell layer nuclei but it was absent from the superficial cells with initial parakeratinization in KCOT of NBCCS patients (Original magnification: A ×50, B-D: ×200).
Conclusion

KCOT may be the first clinical finding in the setting of NBCCS that is identified in childhood (20, 21). Inflammation of an odontogenic cyst can impair the histological diagnosis (22). Podoplanin expression in KCOT may support histological diagnosis. Podoplanin expression pattern does not differ between KCOT diagnosed in sporadic and that in inherited cases. Oral diagnosis is mandatory in patients suspected of being affected by NBCCS (23).

References