in vivo *26*: 453-458 (2012)

Nasolabial Cyst: Case Report with Respect to Immunohistochemical Findings

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Abstract. *The nasolabial cyst is a rare, usually unilateral lesion arising in the soft tissues adjacent to the alveolar process of the anterior maxilla, above the apices of frontal teeth and below the alar base. The typical clinical features of nasolabial cysts are: swelling between the upper lip and nasal aperture caused by a smooth and fluctuant, well defined space-occupying lesion, elevation of the nasal ala and obliteration of the nasolabial fold. This report describes some clinical, radiological and morphological findings in a nasolabial cyst. The cyst was lined up with bilayered epithelium showing scattered goblet cells. The immunohistochemical analysis revealed that the basaloid epithelial cells exhibited nuclear positive reactions for p63. The proliferative activity of the epithelial cells was low (<5%). Reaction for podoplanin was only discretely positive in basal cells within the non-inflamed portions but was enhanced in areas with inflammatory changes of the cyst wall. Cytokeratin subtyping showed a distinct expression of intermediate filaments in the nasolabial cyst. Nasolabial cysts are developmental cysts that can be cured by adequate surgical techniques. The expression pattern of podoplanin in this entity points to an association of this protein expression with inflammatory reactions to the cyst.*

The nasolabial cyst is an uncommon, non-odontogenic, benign, extraosseous lesion located in the paramedian region of the anterior maxilla and below the nasal ala (1-3). According to recent reviews on this item, nasolabial cyst is rarely diagnosed in Western countries but may be more frequent in others regions, *e.g.* Eastern Asia (4). The pathogenesis of nasolabial cyst is still a matter of debate (1-3, 5-9). Recent morphological studies support earlier views on this entity as its being a remnant of nasolacrimal duct epithelium (10). Immunohistochemistry was rarely applied to analyse nasolabial cysts (10). Recently, we determined the expression pattern of podoplanin in maxillary lesions of odontogenic origin (11). Here, we investigated the expression of podoplanin and other markers in a case of nasolabial cyst.

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Key Words: Nasolabial cyst, podoplanin, p63, cytokeratin, dysontogenetic cyst, non-odontogenic cyst.

Case Report

A 41-year-old Caucasian female attended the outpatient clinic of Hamburg University Hospital for treatment, for a lesion located in her anterior upper jaw. Physical investigation revealed complete dentition of the anterior maxilla with neither pathological motility nor malposition of the anterior teeth. The teeth proved sensitive to cold. The mucosa superior to the apical portion of the right upper incisors appeared to be slightly protruding. On palpation, a roundish, firm mass of about 2 cm in diameter became palpable. The nasal entrance showed a slight elevation of the floor but the integument was unaffected. The patient reported about a resection for a low-grade sarcoma of the ovary 10 years previously and expressed her anxiety about tumor spread.

Radiology. The cyst was not identified on panoramic radiograph of the jaws. On computed tomograms, a roundish hyperintense lesion was delineated below the alar base. A distinct impression of the maxilla was depicted, but no local invasion of the space-occupying lesion into the bone was seen (Figure 1A and B).

Macroscopy and histology. The cyst, 17 mm in maximum diameter approximately was filled with transparent fluid. The inner surface of the cyst appeared smooth. The lesion was cut into parallel sections and was completely embedded in paraffin. The sections were stained with haematoxylin- eosin, Astra and periodic acid-Schiff (PAS) staining methods. For immunohistochemical analysis, we used a panel of antibodies (Table I). The immunohistochemical analysis was validated through positive and negative controls (by omitting the primary antibody).

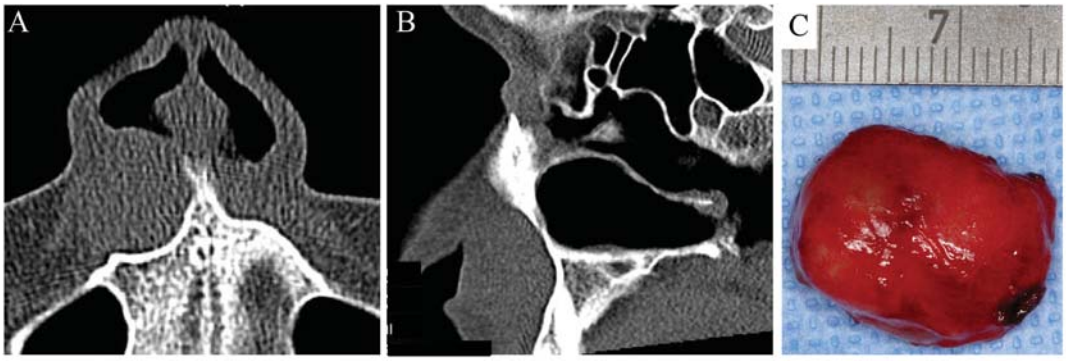

Figure 1. *Radiographic and macroscopic findings of nasolabial cyst. On axial computed tomogram (A), the roundish lesion has caused an impression of the aperture. The adjacent cortical bone shows continuous coverage of the spongiosa. On sagittal image (B), the thinning of the aperture's curvature is remarkable. The excised cyst (C) has a firm wall.*

Table I. *List of antibodies applied for immunohistochemical analysis in nasolabial cyst (CK=cytokeratin, SMA=smooth muscle actin, MUC=mucin).*

Antibody	Clone	Supplier	Dilution
CK5/6	D5/16B4	Dako, Glostrup, Denmark	1:100
CK7	OV-TL 12/30	Dako	1:50
CK14	LL002	Novocastra, Newcastle, UK	1:100
CK19	RCK108	Dako	1:100
CK20	Ks20.8	Dako	1:50
MUC-2	CCP58	Novocastra	1:100
MUC-5AC	CLH2	Novocastra	1:50
AE1/AE3	AE1/AE3	Dako	1:50
CAM5.2	CAM 5.2	Becton Dickinson, San Jose, CA, USA	non-diluted
Podoplanin	D2-40	Signet, Dedham, MA, USA	1:40
p63	4A4	Dako	1:800
Ki67	MIB-1	Dako	1:400
αSMA	1A4	Dako	1:400

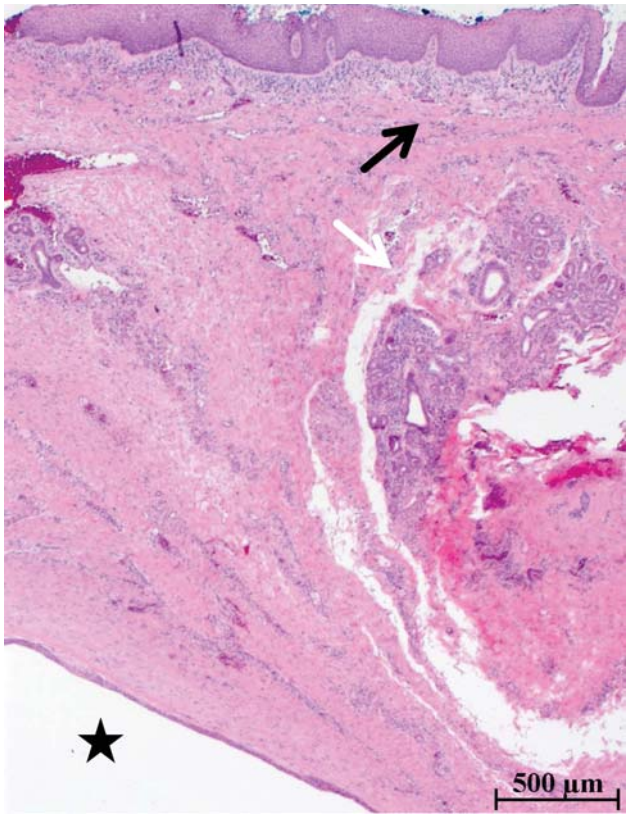

Figure 2. *Overview of histology of nasolabial cyst. Under low power, underneath the moderately inflamed mucobuccal vestibule (black arrow) a thin cyst wall (black star) was apparent. Few moderately inflamed small salivary glands (white arrow) were seen within the submucosa. (stain: haematoxylin-eosin, original magnification: ×25).*

Treatment. Excision of the tumor was performed under general anaesthesia using the intraoral approach. Following the incision of the mucosa and easy detachment of the cyst wall from the oral tissues, the lesion was found to be firmly attached to the nasal floor. Finally, the cyst had to be released from the base of the nasal cavity by sharp dissection and was removed completely (Figure 1C). The lining of the nasal cavity was preserved and the defect was closed by primary intention from the oral side. Healing was uneventful and the patient did not develop any local recurrence during a 12-month follow-up.

Microscopically, the cyst was located underneath the mucobuccal vestibule under the oral submucosa exhibiting moderate chronic subepithelial inflammation and small salivary glands without atypia. The cyst wall contained hypocellular fibrous tissue without calcified particles or odontogenic epithelia. The cyst wall was lined by bilayered epithelium with basaloid cell layers and columnar superficial cell layers along with few goblet cells. Neither squamous

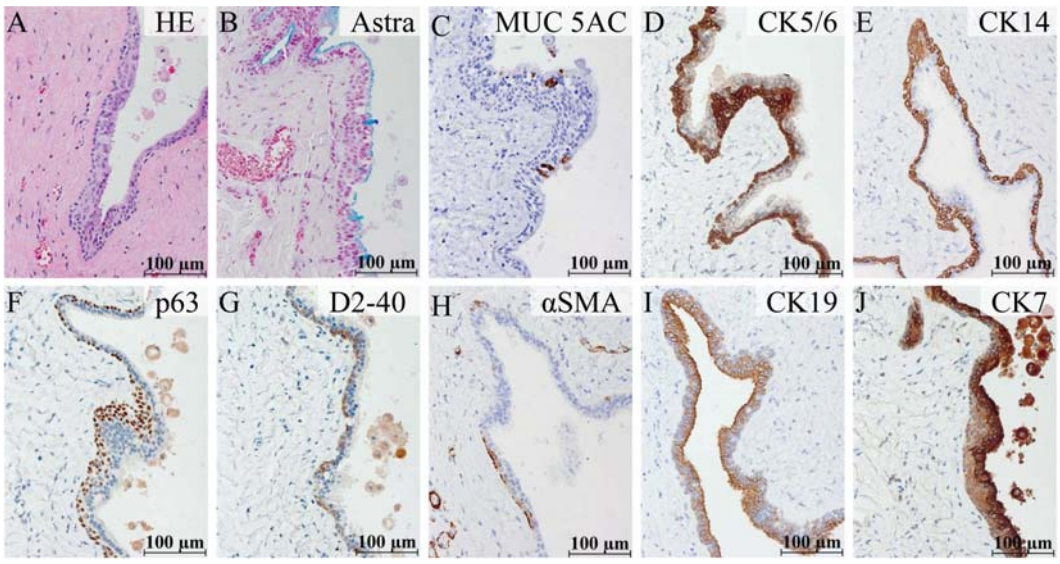

Figure 3. *Detail of histology of nasolabial cyst. The cyst was lined with bilayered epithelium which appeared multilayered in areas with reactive proliferated basaloid cells (A) (Stain: Haematoxylin-eosin). Interspersed scattered goblet cells were highlighted with Astra stain (B) and exhibited a positive reaction for MUC-5AC (C). Basal cells were immunohistochemically positive for CK5/6 (D) and CK14 (E) and also exhibited positive reaction for p63 (F). Scattered basal cells were positive for podoplanin (G). Few cells exhibited positive reaction for αSMA (H). Even though the luminal cells were positive for CK19 (I) and CK7 (J), the basal cells were negative for both markers. (A-J: original magnification: ×200).*

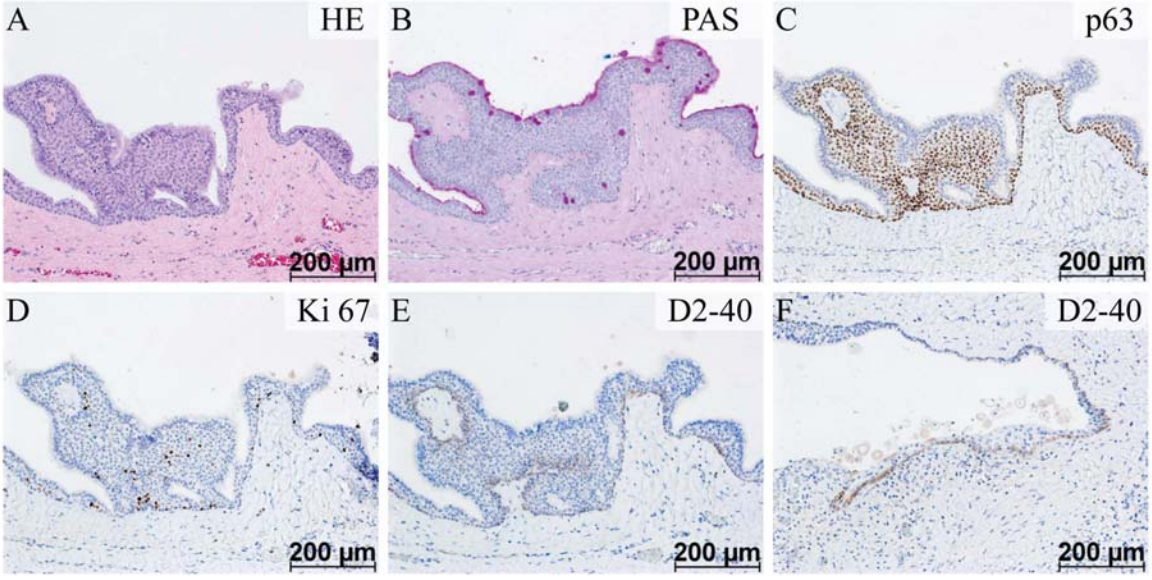

Figure 4. *Additional microscopic findings for nasolabial cyst. The cyst epithelium appeared focally multilayered in areas with proliferative basaloid cells (A) (stain: haematoxylin-eosin). Goblet cells were present in the luminal layer (B) (stain: periodic acid-Schiff). All basal cells exhibited positive nuclear staining for p63 (C) and low proliferative activity with Ki67 antibody (D). Although only discrete positivity for podoplanin (D2-40) was observed in the non-inflamed cyst wall (E), the reaction was enhanced in areas with inflammatory changes (F). (A-F: original magnification: ×100).*

differentiation nor cellular atypia were detected. Focal inflammatory changes of the cyst wall were associated with moderate epitheliomatosis and lymphoplasmacellular infiltrates (Figure 2). Immunohistochemically, the basaloid epithelial cells had a positive reaction for cytokeratins (CK) 5/6 and 14 as well as a nuclear reaction for p63. Interestingly, scattered basal cells were positive for D2-40 (podoplanin). The reaction for podoplanin was enhanced in

Table II. *Nasolabial cyst: immunohistochemical results (for abbreviations: see text).*

Antibody	Staining pattern (staining intensity)
CK5/6	Basal cells (strong)
CK7	Luminal cells (strong)
CK14	Basal cells (strong)
CK19	Luminal cells (moderate)
CK20	Negative
MUC-2	Negative
MUC-5AC	Goblet cells (strong)
AE1/AE3	All epithelial cells (strong)
CAM5.2	All epithelial cells (strong)
Podoplanin	Few basal cells (slightly/moderate in inflamed areas)
p63	Nuclei of basal cells (strong)
Ki67	Nuclei of few (<5%) basal cells (strong)
αSMA	Basal myoepithelial cells (strong)

areas with proliferative basaloid cells associated with inflammatory changes of the cyst wall. Moreover, few cells located within the basal layer had a positive reaction for alpha smooth muscle actin (αSMA), consistent with myoepithelial differentiation. The goblet cells stained positively with both Astra and PAS staining methods and were immunohistochemically positive for MUC-5AC (MUC=mucin). The reaction for MUC-2 showed no staining in the cystic lining. The anti-CK antibodies to AE1/AE3 and CAM5.2 stained strongly positively in all epithelial cells but CK20 was not detected. The luminal epithelial layer exhibited positive reactions for CK19 and CK7. The proliferative activity of the basaloid epithelial cells was low (Ki67 labelling index <5%). The morphological findings are illustrated in Figures 3 and 4, and summarized in Table II.

Discussion

This case report describes the clinical course of a patient who developed a nasolabial cyst that was surgically treated as well as some radiological and morphological findings.

In many cases the nasolabial cyst becomes apparent due to a distinct facial asymmetry (4, 8). Indeed, the facial deformity caused by the nasolabial cyst was even suggested to be pathognomonic (8). However, the growth directions of adjacent cysts may simulate the appearance of a nasolabial cyst and even malignant neoplasias may initially exhibit unilateral swelling around the ala with a smoothened nasolabial fold (12).

Differential diagnosis. This slowly growing lesion is frequently listed in classifications of jaw cysts despite its strict origin from and extension into soft tissues (9). The differential diagnosis of the nasolabial cyst includes several entities: cyst of the salivary duct (mucous retention cyst), heterotopic gastrointestinal cyst, dermoid or epidermoid cyst, and lesions derived from the jaw bones, such as nasopalatine duct cyst, periapical cyst, dentigerous cyst (all with cortical perforation), and even the rare case for extraosseously extending glandular odontogenic cyst (10). The long-term pressure of a cyst may result in resorption of adjacent maxilla, thereby demanding the differential diagnosis from further osseous (10) or extraosseous (12) lesions.

Pathogenesis. It is believed that the nasolabial cyst is of developmental origin (9). This theory is reinforced by recent morphological investigations (10), a frequency of about 10% of bilateral nasolabial cysts (13-15), and the association of nasolabial cysts with affections of the lacrimal drainage system (15). Nasolabial cysts are predominantly diagnosed in women (4, 9), as in the current case. As already proposed by Brüggemann (2), current concepts on the pathogenesis of the nasolabial cyst are based on embryological observations on the development of the nasolacrimal duct (16). After fusion of the margins of the maxillary and lateral nasal process, the ectoderm along the edge between them induces a continuous, rope-shaped cellular line, called the nasolacrimal ridge. This ridge develops as a linear elevation of the surface, then sinks into the mesenchyme and is removed completely from the ectoderm. The solid cellular rod extends in both the cranial and caudal directions. As a result, the caudal portion comes into contact with the caudal region of the lateral nasal wall. The cranial portion connects with the developing conjunctival sac and the whole rod becomes canalized over time (9, 17, 18). The location of the nasolabial cyst lateral to the inferior part of the nasal wall supports the hypothesis that the cells of origin which proliferate in the cyst are remnants of the embryonic nasolacrimal duct or even derived from the mature duct (9). However, this theory does not explain the preponderance of nasolacrimal cysts arising on the left side of the body as addressed in several reports (4, 9, 19), and the world-wide notice that females are predominantly affected (4, 9, 19).

The convincing theory of nasolacrimal duct remnants as being the origin of nasolabial cyst is the reason that other theories on the pathogenesis are rejected, such as the entrapping of epithelium at fissural lines (3), or epithelial remnants of the lateral nasal cleft (6). The nasolabial cyst is not a cyst arising from a region of the maxilla, in particular the alveolar process. Consequently, the misnomer "nasoalveolar cyst" (5) should no longer be in use (9). However, extraosseous extension of other intraosseous cysts of developmental origin may exhibit physical findings similar to those for nasolabial cysts (20).

Histology. Histological studies on nasolabial cysts have repeatedly shown that the cysts are lined by a non-ciliated pseudostratified columnar epithelium (9). Goblet cells are

frequently embedded in this epithelial lining, but may not always be present (9). Squamous metaplasia is sometimes found distributed in a macular pattern (9). The epithelial lining is occasionally incomplete (9), probably due to secondary infection of the cyst. In larger series on nasolabial cysts, stratified or cuboidal epithelium were found in addition to the predominant pseudostratified columnar epithelium. Therefore, the presence of ciliated cells in nasolabial cysts was questioned by Su *et al*. (21) but emphasized by Yuen *et al*. (4).

We detected a positive reaction of the basal epithelial cells for CKs 5/6 and 14 as well as a nuclear reaction for p63. Furthermore, a positive reaction to the podoplanin antibody was enhanced in areas with proliferative basaloid cells associated with inflammatory changes of the cyst wall. Moreover, few cells located within the basal layer showed positive reaction for αSMA, consistent with myoepithelial differentiation. Although the goblet cells stained positively with both Astra and PAS staining methods and were immunohistochemically positive for MUC-5AC, the reaction for MUC-2 was negative. The antibodies to CAM5.2 and AE1/3 were strongly positive in all epithelial cells. The luminal epithelial layer had positive reactions against CK19 and CK7. Our results were similar to a previous immunohistochemical study on a nasolabial cyst showing continuous expression of CK7 and 19, and high molecular weight CK in the nasolabial cyst. Distinct populations of basal layer epithelium were selectively immunoreactive for CK5/6 (10). These findings are in accordance with the predominant pseudostratified differentiation of cystic epithelium.

Imaging. Visualization of the nasolabial cyst on radiographs varies according to the size of lesion and the applied technique. Earlier reports on the value of occlusal radiography pointed to distinct landmarks, such as posterior convexity of a radiopaque line that appears to form the bony border of the nasal aperture, ipsilateral to the side of the cyst (22, 23). This finding is not present regularly on occlusal radiographs in cases with nasolabial cysts (24). Panoramic radiographs of the jaw may also not be informative with regard to osseous involvement in close proximity to the nasal aperture (24). The application of sectional imaging to visualize nasolabial cysts has proven advantageous over the use of plain radiographs. CT and magnetic resonance imaging (MRI) have been applied in nasolabial cyst diagnostics (24, 25). CT delineates the osseous impression and the displaced cortical rim, as shown in our case (Figure 1A and B). MRI appears to reveal the cyst content more clearly than does CT (24). However, other entities arising inferior to the *ala nasi* may appear very similar to nasolabial cyst on MRI (25). Ultrasonography was recommended as an additional tool to diagnose space-occupying lesions in this region (12, 24, 26).

Treatment. Nasolacrimal cysts are extraosseous lesions that lie subperiostally (9). Surgical enucleation is easily achieved *via* a transoral sublabial approach (14). Recently, the alternative transnasal route was proposed by some authors (27). The sublabial approach allows the attachment of the mucoperiosteum to the bone and thus the attachment of soft tissues in physiological layers, leaving the osseous impression unchanged. The endoscopic approach extends the nasal floor to the former cystic cavity and thus prepares an air-containing sinus. This technique appears to allow sufficient drainage of the new sinus and there were no signs of cyst recurrence (21). At present, both techniques appear to show good and definite therapeutic results (4, 21).

In summary, nasolabial cysts are very rare lesions in Western Europe [6% of all non-odontogenic jaw cysts, 0.1% of all jaw cysts, extraosseous jaw cysts vs. intraosseous jaw cysts 0.25%:97.75%, N=6410, (28)]. Morphological studies support the hypothesis of developmental disorders of the nasolacrimal duct as the cells of origin giving rise to nasolabial cysts. Podoplanin expression in nasolabial cyst is associated with inflammatory reactions (29). Extirpation of the cyst provides definite cure.

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Received February 2, 2012
Revised March 5, 2012
Accepted March 6, 2012