ORIGINAL ARTICLE

Inflammatory histopathogenesis of nasopalatine duct cyst: a clinicopathological study of 41 cases

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OBJECTIVE: The aim of this study is to characterize immunohistochemical profiles of lining epithelia of nasopalatine duct cyst (NPC) as well as to correlate those findings with their clinicopathological features to understand the histopathogenesis of NPC.

MATERIALS AND METHODS: Forty-one surgical specimens from NPC were examined for clinical profiles and expression of keratin-7, 13, MUC-1, and P63 by immunohistochemistry, compared to radicular cyst (RC) and maxillary sinusitis.

RESULTS: Nasopalatine duct cyst was clinically characterized by male predominant occurrence: 44% of the cases involved tooth roots, and 70% with inflammatory backgrounds. Lining epithelia of NPCs without daughter cysts were immunohistochemically distinguished into three layers: a keratin 7-positive (+) ciliated cell layer in the surface, a keratin-13+ middle layer, and a MUC-1-/P63+ lower half, indicating that they were not respiratory epithelia, and the same layering pattern was observed in RC. However, those immunolocalization patterns of the main cyst lining with daughter cyst were exactly the same as those of daughter cyst linings as well as duct epithelia of mucous glands.

CONCLUSIONS: Two possible histopathogeneses of NPC were clarified: one was inflammatory cyst like RC and the other was salivary duct cyst-like mucocèle.

Keywords: nasopalatine duct cyst; inflammatory cyst; immunohistochemistry; mucous retention cyst; radicular cyst

Introduction

Nasopalatine duct cyst (NPC), also known as incisive canal cyst, was first reported by Meyer in 1914 (Meyer, 1914). Since then, several reports have characterized its clinicopathological features (Abrams et al, 1963; Allard et al, 1981; Escoda Francoli et al, 2008; Killy et al, 1977; Nelson and Linfesty, 2010; Shear and Speight, 2007; Swanson et al, 1991; Vasconcelos et al, 1999; White and Pharoa, 2000), and NPC has basically been regarded as a non-odontogenic developmental jaw cyst arising from epithelial remnants of the nasopalatine duct (Kramer et al, 1992; Shear and Speight, 2007). However, some inflammatory backgrounds including bacterial infection have been suggested for the histopathogenesis of NPC (Abrams et al, 1963; Shear and Speight, 2007), although there has been insufficient evidence to support such an inflammation-based causative hypothesis.

Histopathological diagnosis of jaw cysts is not always easy when epithelial linings of the cyst wall are modified by inflammation. However, their differential diagnosis is important because such neoplastic lesions as cystic ameloblastoma or keratocystic odontogenic tumor are included in jaw cysts. To resolve this challenging issue, we have introduced several combinations of immunohistochemistry for epithelial linings to routine diagnostic services, because hematoxylin and eosin-stained sections did not work in the differential diagnoses of inflamed cystic jaw lesions (Saku et al, 1991; Murata et al, 2000; Ida-Yonemochi et al, 2002, 2011; Yamazaki et al, 2004; Tsuneki et al, 2008a,b, 2010). Our diagnostic criteria for cystic jaw lesion with immunohistochemical aids cover the five most common cystic lesions: cystic ameloblastoma, keratocystic odontogenic tumors, dentigerous cyst, lateral periodontal cyst, and radicular cyst (RC) (Saku et al, 1991; Tsuneki et al, 2008b; Tsuneki et al, 2010). However, NPC has not been included as an object for the differential diagnosis,

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because its occurrence is much rarer than that of the five cystic lesions as mentioned earlier and because the diagnosis of NPC is considered to be apparently easier due to its typical pear-shaped and well-circumscribed radiolucency in the anterior maxilla (Killy et al., 1977; Vasconcelos et al., 1999; White and Pharoa, 2000; Shear and Speight, 2007; Escoda Francolí et al., 2008). In the meantime, we have occasionally experienced NPC cases that involved non-vital teeth or teeth with advanced periodontitis. In addition, there have been reports of keratocystic odontogenic tumor cases in the median maxilla, which has the same location as that of NPC (Neville et al., 1997; Gonzalez-Alva et al., 2008). Thus, we have started to consider that it is necessary to study cases which were diagnosed from the other backgrounds or to examine how NPC is differentially diagnosed cases, diagnosed not only by histopathological findings, but also by clinical and radiological findings. Lining epithelia in seven cases of RC and covering epithelia of 12 specimens of maxillary sinus mucosa were similarly examined.

Histopathology

Tissue sections from 41 cases of NPC were reviewed histopathologically, and their characteristic features were analyzed in terms of lining epithelia, daughter cysts, mucous glands, blood vasculatures, nerves, and inflammatory cells within the cyst walls. Lining epithelia in seven cases of RC and covering epithelia of 12 specimens of maxillary sinus mucosa were similarly examined.

Antibodies

Mouse monoclonal antibodies against human keratin 7 (K7, clone OV-TL 12/30, IgG1), K13 (DE-K13, IgG2a), and p63 protein (P63) (4A4, IgG1) were purchased from Dako (Glostrup, Denmark). A mouse monoclonal antibody against human mucin 1 (MUC-1/CD227, clone DF3, IgG1) was obtained from Fujirebio, Inc. (Tokyo, Japan).

Immunohistochemistry

Immunohistochemical staining was performed by using the ChemMate Envision™ system (Dako) (Tsuneki et al., 2010). For K7, sections were autoclaved in 10 mM Tris buffer (pH 9.0) containing 1 mM EDTA at 121°C for 10 min. For K13 and P63, sections were autoclaved in citric acid buffer (pH 6.0) at 121°C for 10 min. After the pretreatment, the sections were rinsed in PBS containing 0.5% milk protein (Morinaga Milk Industry Co. Ltd., Tokyo, Japan) and 0.05% Triton X-100 (T-PBS) and treated with 0.3% hydrogen peroxide in methanol for 30 min at room temperature to block endogenous peroxidase activities. After rinsing in T-PBS, they were incubated with 5% milk protein in T-PBS for 1 h at room temperature to block non-specific protein binding sites. They were then incubated overnight at 4°C with the primary antibodies directly (DF3) or diluted at 1:50 (4A4), 1:100 (OV-TL 12/30), 1:200 (DE-K13) in T-PBS. After incubation, the sections were rinsed in T-PBS and incubated with the secondary antibodies that were conjugated with peroxidase-labeled dextran polymers for 1 h at room temperature. After rinsing with T-PBS, they were treated with 0.02% 3,3′-diaminobenzidine in 0.05 M Tris–HCl buffer (pH 7.6) containing 0.005% hydrogen peroxide to visualize the reaction products. Finally, the sections were counterstained with hematoxylin. For control studies on antibodies, the primary antibodies were replaced with preimmune mouse IgG subclasses (Dako).

Results

Age and sex

The age and sex distribution in the 41 cases of NPC are summarized in Figure 1. Those NPCs accounted for 2.6% of the 1552 of jaw cysts documented in the file during the same period. They were ranked fourth in jaw cysts, among

Materials and methods

Patients and specimens

Surgical specimens of 41 cases of NPC, 7 of RC of the mandible, whose cyst linings contained ciliated/goblet cells, and 12 cases of maxillary sinusitis, in which normal respiratory epithelial parts and squamous metaplastic ones were simultaneously present in the mucosa, were collected for the present study from the surgical pathology files of the Division of Oral Pathology, Niigata University Graduate School of Medical and Dental Sciences, during a 12-year period from 2000 to 2011. During the same period, 1552 jaw cysts were documented. The 41 NPC cases were typical cases, diagnosed not only by histopathological findings but also by clinical and radiological findings. Maxillary median cysts that were suspicious and suggestive of RCs, dentigerous cysts, and lateral periodontal cysts were not included in this study. The surgical samples were fixed in 10% formalin and decalcified with Planck Rychlo’s solution, which contained 8.5% hydrochloric acid and 5% formic acid, for up to 2 h when cyst walls contained small bone fragments in the periphery. They were then routinely processed and embedded in paraffin. Serial sections cut at 4 μm from paraffin blocks were used for immunohistochemical stainings. The experimental protocol for analyzing surgical material was reviewed and approved by the Ethical Board of the Niigata University Graduate School of Medical and Dental Sciences (Oral Life Science).

Clinical findings

In addition to clinical data of NPCs documented in patients’ clinical records, such as patients’ age, sex, and location, the relationship with tooth and conditions of associated teeth (vitality or periodontal diseases) were carefully determined in every case by analyzing simple X-ray and CT images in comparison with the documented clinical records by referring to the conventional criteria of NPC (Killy et al., 1977; White and Pharoa, 2000; Shear and Speight, 2007).
which RC was the most common (889 cases, 57.2%), followed by dentigerous cyst (252, 16.2%) and keratocystic odontogenic tumor (116, 7.5%). The mean age of the patients was 46.8 years (47.9, men; 45.7, women) with a range from 21 to 73 years old. There were 29 men (70.7%) and 12 women (29.3%) patients. In male patients, there were bimodal age incidences in the 31–40- and 61–70-year-old groups, while there was a normal distribution with a peak at 41–50 years of age among female patients.

**Tooth association**

Nearly half of the NPCs (23 cases, 56.1%) were not associated with the tooth roots (Figure 2a), and the tooth roots were closed to the cystic lumen in 18 cases (43.9%) (Table 1). Half of the teeth associated with the cysts (9/18 cases, 50.0%) were determined to be non-vital by electric pulp tests but were not only evidenced by the presence of root canal fillings on preoperative radiographs (Figure 2b). In addition, opposite-side incisor teeth in those nine cysts were confirmed to be vital and possessed intact lamina dura on radiographs (Figure 2b). In spite of radiographic findings suggesting tooth root treatment histories, their clinical diagnoses of NPC were recommenced by oral surgeons and radiologists based on their location and radiographic findings. Histopathological findings for these nine cases associated with non-vital teeth fulfilled the conventional criteria of NPC, such as cystic linings by ciliated epithelia and the presence of rather large arterioles, venules, and nerve fibers within the cyst wall connective tissue. In Table 1, the nine cases associated with non-vital teeth were parenthesized and separated from the other nine cases associated with vital teeth (Figure 2a). Three of the nine vital teeth (3/9, 33.3%) that were involved in the cysts were associated with advanced periodontal diseases (Table 1).

**Histopathology**

The histological features of lining epithelia of NPCs varied from area to area in the cyst walls. In the present series of NPC, there were two major types: ciliated columnar epithelia with or without mucous retention (goblet cells) (Figure 3a) and stratified squamous epithelia with no apparent keratinization (Figure 3b). The ciliated ones looked like pseudostratified epithelia, and most of the cells seemed to be attached to the basement membrane as usually seen in the upper respiratory tract. Mucous retention seemed to be limited to the surface zone of the epithelial layer, although it looked to be goblet cells lying on the top of the lining (Figure 3a). Squamous epithelia were stratified in most of the part with flat basal lines or minimal short rete ridges. However, single or two-cell layered squamous epithelial cells were occasionally observed. One case (2.4%, respectively) each was with ciliated or cuboidal cells only, two cases (4.9%) were with stratified squamous only, 18 cases with mixed ciliated and stratified squamous (41.9%), five cases with mixed ciliated and cuboidal (12.2%), one case with mixed stratified squamous and cuboidal (2.4%), and 13 cases with all epithelial types

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**Table 1** Nasopalatine duct cyst cases by associations with teeth, mucous glands, and daughter cysts

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**Figure 2** Occlusal radiographs for nasopalatine duct cyst (NPC) cases associated with teeth. (a) NPC intervened by intact incisor teeth, (b) NPC associated with one treated incisor tooth that was not so closely located to the cyst

**Figure 1** Age and sex distribution of patients with nasopalatine duct cysts (NPCs) from Niigata University Hospital, 2000–2011. Black bars in upper half, male; gray bars in lower half, female. There were no child patients. Bimodal peaks in the fourth and seventh decades among male patients, with a gentle peak in the fifth decade among female patients.
Ciliated columnar cells with mucous retention in the surface zone (goblet cells) were found in 16 cases (39.0%). Regarding inflammatory cell infiltrates in the cyst wall, 13 cases (31.7%) were free of inflammatory cells, while 14 cases (34.1%) had mild infiltrates, 9 (22.0%) moderate, and 5 (12.2%) severe. Within the cyst wall, there were peripheral nerve fibers (41 cases, 100%) and blood vessels with muscular walls (41 cases, 100%). In addition, there were daughter cysts (19 cases, 46.3%) and mucous glands (17 cases, 41.5%) in NPC cyst walls (Figure 6a,b, Table 1). Interestingly, daughter cysts were found in 17 of the 17 cases containing mucous glands (100%), 13 of which were not associated with tooth roots (76.5%) and four with periodontal diseases (23.5%) (Table 1).

The luminal surface of cyst walls of RC cases selected for the present study was lined by epithelia with ciliated pseudostratified appearances (Figure 4a) as well as with stratified squamous epithelia at the same time (Figure 4b). The mucosa of the maxillary sinus was covered by pseudostratified ciliated epithelia (Figure 5a) as well as by stratified squamous epithelia in the presence of inflammation (Figure 5b).

**Immunohistochemistry**

In a preliminary experiment, K4, K5/6, K10, K13, K17, K18, K19, K20, podoplanin, proliferating cell nuclear antigen (PCNA), and Ki-67 were screened for their specific stainings in NPC linings as were performed for the differential diagnoses of cystic jaw lesions (Tsuneki et al., 2010), and K13 was chosen among them for its characteristic localization in the middle zone of NPC linings. In addition, we selected K7 as a marker for ciliated respiratory epithelial cells. MUC-1 was chosen for confirming

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**Figure 3** Immunohistochemical profiles of lining epithelia of nasopalatine duct cyst (NPC). (a, b) Hematoxylin and eosin (HE) stain; immunoperoxidase stain for keratin (K) 7 (c, d), K13 (e, f), mucin 1 (MUC-1) (g, h), and p63 gene product (P63) (i, j), hematoxylin counterstain. (a, c, e, g, i), ciliated epithelial part; (b, d, f, h, j), squamous epithelial part. (a–j), ×120. Scale bar, 100 μm. In lining epithelium parts with pseudostratified appearances by the presence of ciliated cells (a), K7 was characteristically localized in the superficial layer (c). K13 was localized in the middle layer except for in the superficial and basal layers (e). MUC-1 was mainly localized in the lower half (g), and P63 positive (+) cells were found in the lower half with faint extensions to the upper layer (l). In the squamous epithelial part (b), there was no positive staining for K7 (d). The K13+ area was spread in the whole layer except for the basal layer (f). MUC-1 was evenly localized in the whole layer (h). P63+ cells were diffusely found in the whole layer (j)
the mucous gland duct epithelial differentiation. P63 was selected as a stable marker for the basal cell of pseudostratified epithelia of the respiratory tract, though its function in the basal cells has not been clarified. We also tried chromogranin A immunohistochemistry for endocrine basal cells of the respiratory epithelium (Sieskiewicz et al., 2007). However, there were no chromogranin A-positive cells in mucosal epithelia of the maxillary sinus. Thus, in the present study, immunohistochemical profiles for K7, K13, MUC-1, and P63 were compared between lining epithelia of NPC and RC, mucosal epithelia of the maxillary sinus, and daughter cysts and mucous glands within the NPC walls. The results are described separately below for the four groups.

**Nasopatine duct cyst.** When the ciliated epithelial parts (Figure 3a) were immunohistochemically investigated, K7 was positive (+) only in the ciliated or goblet zone in the surface but not in the lower part (Figure 3c), indicating that the lining was composed of multiple-layered epithelial cells but not of ciliated pseudostratified ones. In contrast, K13 was localized in the middle layer except for superficial and basal layers (e). MUC-1 was positive in the lower layers (g). P63+ cells were irregularly scattered in the whole layer except for ciliated/goblet cells (i). In the squamous epithelial part (b), K7 was not positive (d). K13 was evenly positive in the whole layer except for the basal layer (f). MUC-1 was evenly localized in the entire epithelia (h). P63+ cells were spread unstably in the whole layer (j).

**Figure 4** Immunohistochemical profiles of radicular cyst (RC). (a, b) HE stain; immunoperoxidase stain for K7 (c, d), K13 (e, f), MUC-1 (g, h), and P63 (i, j); hematoxylin counterstain. (a, c, e, g, i), ciliated epithelial part; (b, d, f, h, j), squamous epithelial part. (a–j), ×120. Scale bar, 100 μm. In the ciliated epithelia of RC (a), K7 was positive only in the superficial layer (c). K13 was localized in the middle layer except for superficial and basal layers (e). MUC-1 was positive in the lower layers (g). P63+ cells were irregularly scattered in the whole layer except for ciliated/goblet cells (i). In the squamous epithelial part (b), K7 was not positive (d). K13 was evenly positive in the whole layer except for the basal layer (f). MUC-1 was evenly localized in the entire epithelia (h). P63+ cells were spread unstably in the whole layer (j).
lining cells, and P63+ cells were more frequently found in the lower part of the squamous part than in the ciliated part (Figure 3j). These immunohistochemical profiles were shared by the 41 cases examined. The result obviously indicated that the lining epithelia of NPC were basically composed of squamous epithelial cells with ciliated/goblet cells appearing on the epithelial surface but that they were not true ciliated pseudostratified epithelia seen in the upper respiratory tract. This was also supported by the fact that there were no such surface ciliated cells on squamous epithelial part of the sinus mucosa as described later.

Radicular cyst. In the ciliated epithelial part of RC (Figure 4a), K7 was confined to the superficial layer of ciliated/goblet cells (Figure 4c) as seen in NPC (Figure 4c). K13 was localized in the middle layer but not in the surface and basal layers (Figure 4e), while MUC-1 was localized more widely than K13 including in the basal cells but not in the surface (Figure 4g). P63+ cells were scattered in the whole layer (Figure 4i). The findings were basically the same as those in NPC. On the other hand, in the stratified squamous epithelial part (Figure 4b), K7 was not localized in the whole layer (Figure 4d), and the K13+ areas were spread in the middle layer but not in the basal layer (Figure 4f). MUC-1 was evenly localized in the lining epithelia (Figure 4h). P63+ cells were less frequently spread in the squamous part than in the ciliated part (Figure 4j). The findings indicated that those immunohistochemical as well as histopathological profiles of the lining epithelia with ciliated/goblet cells were basically shared by NPC and RC, and hence that NPC cyst linings are possibly derived from epithelial rests of Malassez as RC linings were.
Maxillary sinus mucosa. K7 was localized in the whole layer (Figure 5c) of pseudostratified epithelia including the surface ciliated zone (Figure 5a), while K13 was not positive in the maxillary sinus (Figure 5e). MUC-1 (Figure 5g) and P63 (Figure 5i) were clearly localized in the basal layer. In the squamous metaplasia part due to inflammation (Figure 5b), K7 was not positive (Figure 5d), while K13 was positive in the whole layer except for in the basal layer (Figure 5f). MUC-1 was evenly localized in the whole layer (Figure 5h). P63+ cells were spread more in the middle layer, although their staining intensities were most enhanced in the lower layer including the basal cells (Figure 5j). These immunohistochemical profiles for the sinus mucosal epithelia were shown to be different from those for ciliated epithelia of NPC and RC. There was no ciliated cell in the surface of metaplastic-squamous epithelial parts of the sinus mucosa.

Daughter cysts and mucous glands in NPC. K7 was localized in the whole epithelial layer (Figure 6d) of both daughter cysts as well as in normal ducts (Figure 6a,b) of mucous glands within the cyst wall, though MUC-1 was localized in the basal cells of daughter cyst but only faintly in the luminal surface of duct epithelial cells (Figure 6h). K13 was not positive at all in the whole layer of daughter cyst linings nor in the duct of mucous glands (Figure 6f). P63 was positive in the basal cells of daughter cyst linings as well as in mucous gland ducts (Figure 6j). In addition, such immunohistochemical profiles for K7, K13, MUC-1, and P63 in the daughter cyst linings (Table 2) were confirmed to be the same as those in the main cyst linings (Figure 6a,c,e,g, i, Table 2). Since similar immunohistochemical profiles were demonstrated among mucous gland ducts and daughter cyst linings as well as main cyst linings (Table 2), it was thus considered that, in addition to epithelial rests of Malassez as indicated previously, some of the NPC cases might have originated from duct epithelial cells which also caused salivary duct cyst or mucocele in soft parts when mucous glands were involved in the cyst wall and even if tooth roots were not involved.

Discussion

Since the first case of NPC was reported by Meyer (Meyer, 1914) in 1914, the clinicopathological features of NPC have been documented (Abrams et al., 1963; Allard et al., 1981; Escoda Francoli et al., 2008; Nelson and Linfesty, 2010; Shear and Speight, 2007; Swanson et al., 1991; Vasconcelos et al., 1999), and they have suggested that NPCs arise due to the proliferation of epithelial remnants from the nasopalatine duct (Abrams et al., 1963; Allard et al., 1981; Shear and Speight, 2007), although the histopathogenesis of NPC still remains controversial because no actual evidence for the nasopalatine duct origin has yet to be demonstrated. In the present study, we have analyzed clinicopathological features of 41 cases of NPC, which we had diagnosed according to the conventional standard (Kramer et al., 1992). Their relative frequency of 2.6% among our series of jaw cysts (a total 1552 cases) was rather smaller than that reported in the literature (Shear and Speight, 2007), indicating that our diagnostic criteria were sufficiently strict. Using these strictly selected NPC cases, we demonstrated for the first time detailed immunohistochemical profiles of NPC lining epithelia, which have never been previously investigated. Eventually, we were able to propose two possible histopathogenetic pathways for NPC, both of which belong to inflammatory processes: one is associated with periapical periodontitis as seen in RCs in which cyst linings are derived from epithelial rest cells of Malassez, and the other is like salivary duct cyst or mucous retention cyst and related to mucous glands in the maxillary sinus or nasal mucosa. Therefore, a simple developmental pathogenesis originating from the nasopalatine duct is not likely in NPC.

The mean age of 46.8 years in NPC patients in our present series was consistent with that reported from western countries (Abrams et al., 1963; Allard et al., 1981; Swanson et al., 1991; Vasconcelos et al., 1999; Escoda Francoli et al., 2008), which indicates that NPC is a disease in adulthood, although there have been a few exceptional case reports of NPC in children under 10 years old (Swanson et al., 1991; Velasquez-Smith et al., 1999; Ely et al., 2001; Scolozzi et al., 2008). In our series, NPCs were 2.4 times more common in males (70.7%) than in females (29.3%), which was similar to that of most of the previous reports (Vasconcelos et al., 1999; Shear and Speight, 2007), although other studies (Abrams et al., 1963; Swanson et al., 1991) revealed equal gender frequencies. The present clinical characteristics mentioned earlier do not always indicate developmental backgrounds but rather some reactive events in adult stages among those NPC cases. The present study demonstrated that tooth roots were involved in the cystic lumen in half of the NPC cases (43.9%). Tooth association with NPCs has not been discussed in detail in the literature. However, about 70% of the teeth involved in our series of NPC were in fact not vital or associated with advanced periodontal diseases, even though they had no history of root canal treatment or tooth caries in their clinical records. Although previous reports speculated that trauma or bacterial infection could stimulate the formation of NPC (Abrams et al., 1963; Swanson et al., 1991; Shear and Speight, 2007), those articles did not demonstrate any actual evidence to support such hypotheses.

According to Abrams et al. (1963), the nasopalatine duct epithelium in the fetal stage is variable depending on location even in physiological conditions, and it is categorized into three types: (i) stratified squamous, (ii) primitive or cuboidal, and (iii) pseudostratified columnar. While NPC linings have been believed to originate from the nasopalatine duct epithelium, the idea seems to be rather conceptual and not based on any actual evidence for their origin. In the present study, we intended to characterize lining epithelia of NPC by using immunohistochemistry, as no immunohistochemical investigation had ever been performed in NPC. We selected the four antigens, K7, K13, MUC-1, and P63, because we had found that these four were most helpful in separating three epithelial layers of the NPC linings among commercially available antibodies which can be easily obtained by anyone. We adopted mandibular RC cases with ciliated epithelial linings as
control for ciliated/goblet cell metaplasia in the squamous epithelium. We examined the maxillary sinus mucosa as control for authentic upper respiratory epithelia because we were unable to obtain normal human fetal tissues with nasopalatine ducts due to legal and technical reasons. The four protein expression profiles in the ciliated epithelial parts were the same between NPC and RC but were completely different from those in the true ciliated pseudostratified epithelium of the maxillary sinus mucosa. K7, which is known to be a marker for pseudostratified respiratory epithelium (Chu and Weiss, 2002), was specifically localized in the surface ciliated cells in NPC and RC linings, and such superficial expression profiles were not found in the maxillary sinus, where K7 was expressed in the whole layer, which consisted of pseudostratified cells residing on the basement membrane. K13, a marker for

Figure 6 Immunohistochemical comparison between main cyst, daughter cyst, and mucous gland in NPC walls. (a, b) HE stain; immunoperoxidase stain for K7 (c, d), K13 (e, f), MUC-1 (g, h), and P63 (i, j), hematoxylin counterstain. (a–j), ×125. Scale bar, 100 μm. Mucous glands and daughter cysts (or dilated excretory ducts) were simultaneously present in the cyst wall of NPC (a, b). K7 (d) was evenly positive in the epithelial cells of both daughter cysts and ducts of mucous glands, while K13 was not positive in them (f). MUC-1 was localized in the basal cells of daughter cysts as well as in the luminal surface of ducts (h). P63+ cells were aligned in the basal layer of daughter cysts and ducts (j). Such immunohistochemical profiles of daughter cyst linings and mucous gland ducts were basically the same as those of NPC main cyst linings (a, c, e, g, i).
prickle cells of non-keratinizing stratified squamous epithelia (Chu and Weiss, 2002; Tsuneki et al., 2010), was distinctively localized in the middle layer of NPC and RC but was not positive in the maxillary sinus. MUC-1 and P63 were restricted to the basal cells of the maxillary sinus epithelia, while they were conspicuous over the stratified squamous epithelial parts of NPC and RC. Thus, these immunohistochemical findings conclusively indicate that the NPC lining is basically stratified squamous epithelium, and that the emergence of ciliated/goblet cells is due to metaplasia in the very surface part of stratified squamous epithelia. It is hence unlikely that NPC is a developmental cyst from the nasopalatine duct, if ciliated/goblet cells are considered to be the evidence for its nasopalatine duct origin, because the NPC ciliated/goblet cells are actually now shown not to be of the respiratory tract nature. Some of the NPCs and RCs seem to share their origin of cyst epithelial linings from epithelial rests of Malassez. In other words, nearly half of the NPC cases (43.9%), which are clinically related to tooth roots, are considered to be RC located in the median region of the maxilla involving the incisive canal. The nearly equal frequencies between the association with non-vital teeth in nine cases (50%) and that with vital teeth in nine cases (50%) may indicate that the nine cases were RC, although their clinicopathological features, except for non-vital teeth, were typical to NPC.

On the other hand, around half (43.9%) of the present series of NPC contained mucous gland tissues within the cyst wall, while this frequency of mucous gland in NPC cyst walls was slightly higher than that of previous reports (31.1%) (Abrams et al., 1963). Surprisingly, however, all of the present cases with mucous glands were completely free from such dental-inflammatory backgrounds as involvement of non-vital teeth or advanced periodontitis. In addition, the majority (17/19 cases, 89.4%) of the cases with daughter cysts contained mucous glands within their cyst walls. The simultaneous involvement of daughter cysts and mucous glands was further correlated with each other by their similar immunohistochemical profiles between daughter cyst linings, mucous gland ducts, and main NPC cyst linings. These findings indicate that at least almost half of NPCs could be considered to be a kind of salivary duct cyst or mucous retention cyst arising in the mucous gland located in the maxillary sinus or nasal mucosa. In fact, one case of the present series had a fully retained mucous material coagulated in the cystic lumen, which was not at all different from that of clinical and histopathological features of salivary duct cyst.

In the present study, we could correlate clinicopathological characteristics with two fairly possible pathways of histopathogenesis in NPC based on the comparative study between immunohistochemical and clinical data. Similar to the terms ‘globulomaxillary cyst’ or ‘branchial cyst’, which are no longer in use due to their wrong reference to fetal tissue remnants (Wu et al., 2009), the term NPC should not prudently be used either, when maxillary median cysts are carefully examined by pathologists keeping in mind the fact that RCs can develop along the incisive canal when severe inflammation continues in the sinonasal base. It is now time to quit using disease terms that are much too conceptual and abstract. However, it still remains unknown how the terminal differentiation toward ciliated or goblet cells occurs in the surface part of the cyst lining squamous epithelia; this is something, which must be experimentally elucidated in the next step.

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Author contributions

M. Tsuneki designed the study, performed histopathological experiments, analyzed data and prepared manuscript, tables, and figures. S. Maruyama supervised experiments and analyzed histopathological data. M. Yamazaki helped experiments and analyzed
References


