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Sinonasal Low-Grade Adenocarcinoma:
Report of Three Cases with the Clinicopathologic and Immunohistochemical Findings

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Low-grade adenocarcinomas that primarily arise within the sinonasal tract are uncommon tumors. We report here on three cases of primary sinonasal low-grade adenocarcinomas. The patients were 2 females and 1 male with ages of 48, 57 and 64, respectively. Microscopically, the tumors had a well developed tubulopapillary growth pattern that consisted of columnar or pseudostratified cells with eosinophilic cytoplasm, round to oval nuclei and rare mitotic activity. On immunohistochemistry, the tumor cells were strongly positive for cytokeratin 7, but they were negative for cytokeratin 20, CDX-2 and p53. The Ki-67 labeling index was very low (mean: 1.9%). Two patients developed recurrent tumors at the primary site after the initial surgery, but all the patients are presently alive without metastasis 6 years 8 months, 8 years 8 months, and 11 months after the initial diagnosis. When considering the progress of these tumors, we think that it's important to understand the pathology of this entity to avoid underdiagnosis because a complete excision is required for effective treatment.

Key Words : Adenocarcinoma; Cytokeratin 7; Cytokeratin 20; CDX2 protein; p53; Ki-67 Antigen

Non-salivary type adenocarcinomas arising within the sinonasal tract are uncommon tumors, and they are often poorly recognized and misdiagnosed. The tumors can be divided into the intestinal-type and the non-intestinal type according to the World Health Organization (WHO) classification of sinonasal adenocarcinomas.[1] The intestinal-type adenocarcinomas (ITACs) are clinically aggressive and they generally present at an advanced stage with an overall mortality of 53%.[2] They are associated with occupational exposure to wood dust and leather dust, nickel and possibly smoking.[2] The majority of the non-intestinal type adenocarcinomas are of a histological low-grade and they show an excellent prognosis. Several studies have attempted to determine whether immunohistochemical markers could be useful in distinguishing sinonasal low-grade adenocarcinomas from the sinonasal intestinal-type adenocarcinomas and the metastatic colorectal adenocarcinomas.[3-5] We report here on three cases of primary sinonasal low-grade adenocarcinoma, and we investigated the expression of cytokeratin 7 (CK 7), cytokeratin 20 (CK 20), the homeobox gene product CDX-2, p53 and the Ki-67 labeling index, which are all known to be useful markers in determining the origin and grade of primary sinonasal adenocarcinomas.

CASE REPORT

CASE 1

A previously healthy 57-year old, non-smoking female was admitted to our hospital in June 1999 for further evaluation of her bloody rhinorrhea. She did not have any history of wood dust exposure. A computerized tomography (CT) scan of the paranasal sinus (PNS) confirmed a 1cm-sized mass in the right maxillary sinus. An excision was performed. The pathologic diagnosis was an oncocytic papilloma because of the observed papillary structures with bland nuclei without pleomorphism or mitoses.

The patient was free of disease until May 2001 when the bloody rhinorrhea developed again. A PNS CT demonstrated a 1.7 cm-sized mass that was located in the right maxillary sinus and it extended into the ethmoid sinus (Fig. 1). As there was the possibility of invasion, Denker's operation (turbinectomy and ethmoidectomy) was performed.

Histologic examination revealed that the tumor, which was similar to the initial tumor, consisted of papillary structures formed by pseudostratified columnar cells with abundant eosinophilic cytoplasm. The nuclei were uniform without significant pleomorphism. Very few mitoses were observed (Fig. 2). The diagnosis was low-grade papillary adenocarcinoma. The patient did not undergo further adjuvant treatment. Clinically, she remains well without any evidence of another recurrence.

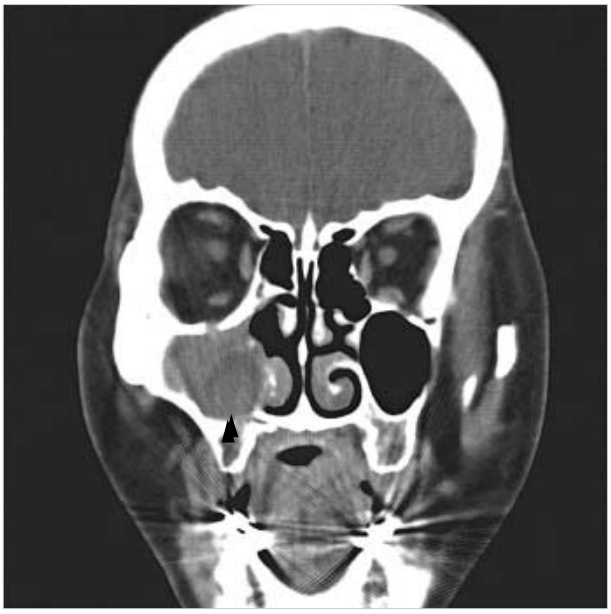

Fig. 1. CT findings of sinonasal low-grade adenocarconoma in Case 1. The tumor is located in maxillary sinus with possibility of bone invasion (arrow head).

CASE 2

A 64-year-old male who never smoked was admitted to our hospital for examination of nasal obstruction in May 1997. He had been working in an office and did not have any history of exposure to wood dust or other chemicals. A PNS CT showed a polypoid mass that was occupying the entire right nasal cavity and it extended to the ethmoid sinus. Right middle turbinectomy and ethmoidectomy were performed. The histological features of the tumor were that of a well differentiated adenocarcinoma without any histologic evidence of invasion. The patient did not receive any more active treatment. The routine follow-up examination was normal until November 2004, when the patient presented with nasal obstruction. A PNS CT showed a 4 cm-sized soft tissue density filling the right maxillary sinus and ethmoid sinus. Maxillectomy and ethmoidectomy were performed.

Microscopically, numerous uniform small tubular glands lined by a single layer of non-ciliated cuboidal cells were arranged in a back-to-back pattern. The cytoplasm was eosinophilic. The nuclei were uniform, round to oval and limited to the basal aspect of the cells. Mitoses and necrosis were absent. Sparse mucoid substances were observed (Fig. 3).

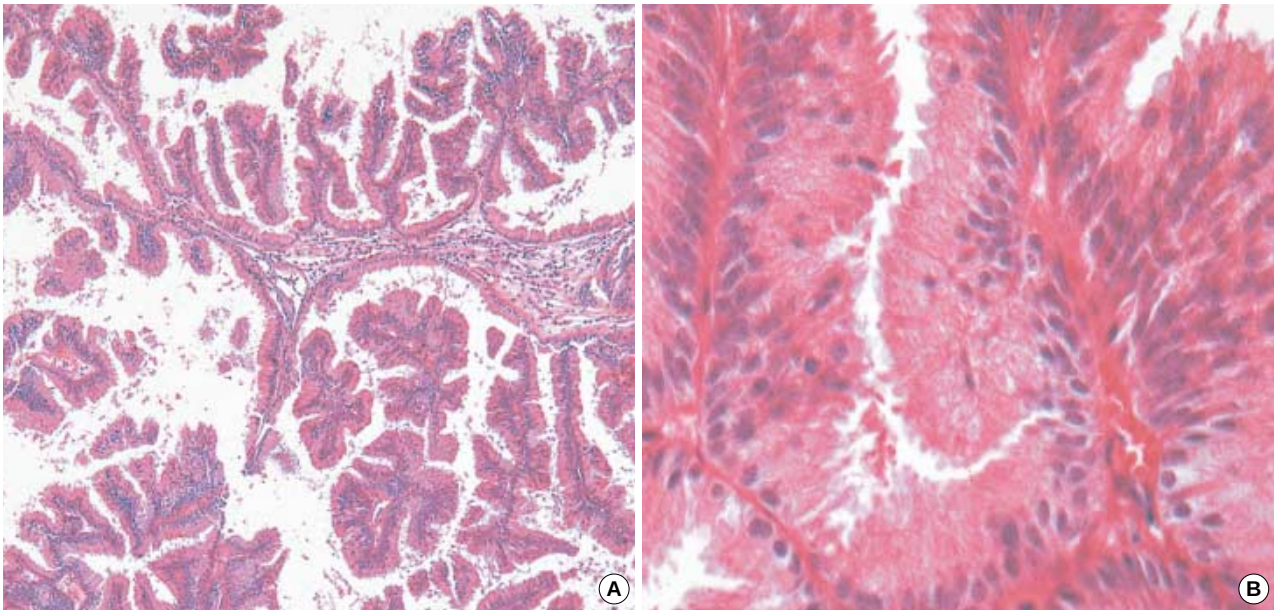

Fig. 2. The pathologic findings of Case 1. (A) The tumor has well developed papillary growth pattern with thin fibrovascular cores. (B) The tumor cells are composed of pseudostratified columnar cells with abundant eosinophilic cytoplasm. The nuclei are uniformly ovoid without significant pleomorphism.

The patient presently has no symptoms or signs of tumor and he has not undergone further treatment.

CASE 3

A 48-old non-smoking woman visited our hospital in March 2005 for further examination of her nasal obstruction. She had worked in a food company for ten years and her job had nothing to do with wood dust exposure or other chemicals. A PNS CT confirmed an ovoid shaped, 3 cm-sized mass in the right anterior ethmoid and maxillary sinuses with the possibility of adjacent bone destruction. Right maxillectomy and ethmoidec-

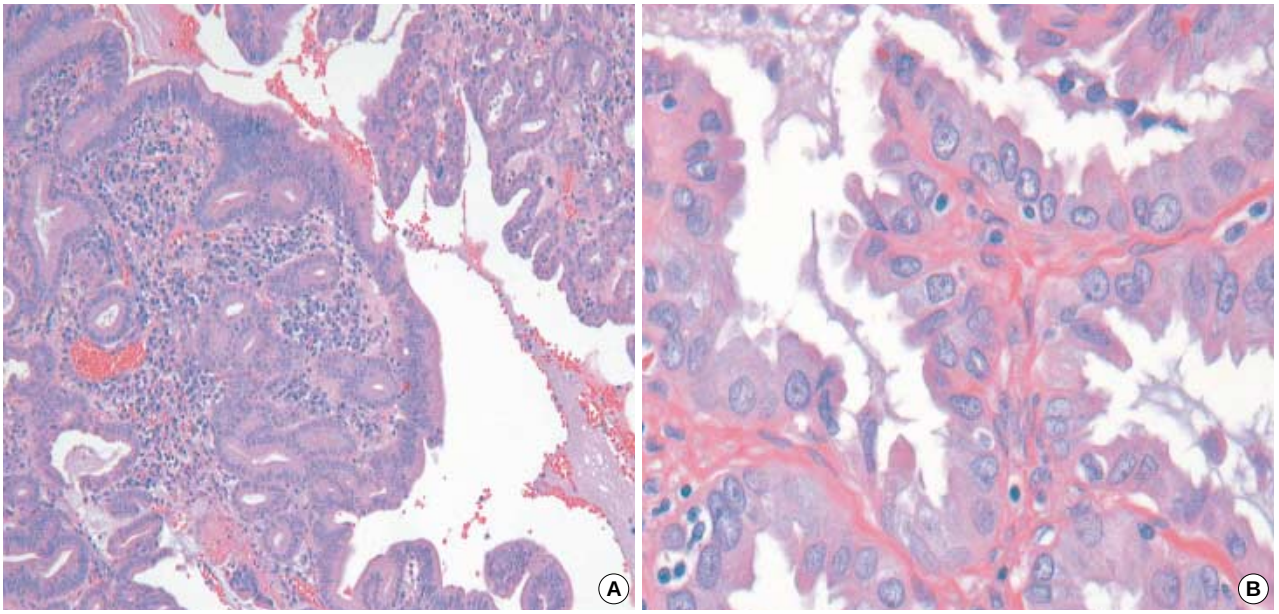

Fig. 3. The pathologic findings of Case 2. (A) The numerous uniform small tubular glands are arranged back to back. (B) The tumor cells are non-ciliated cuboidal cells with eosinophilic cytoplasms and sparse mucoid substances.

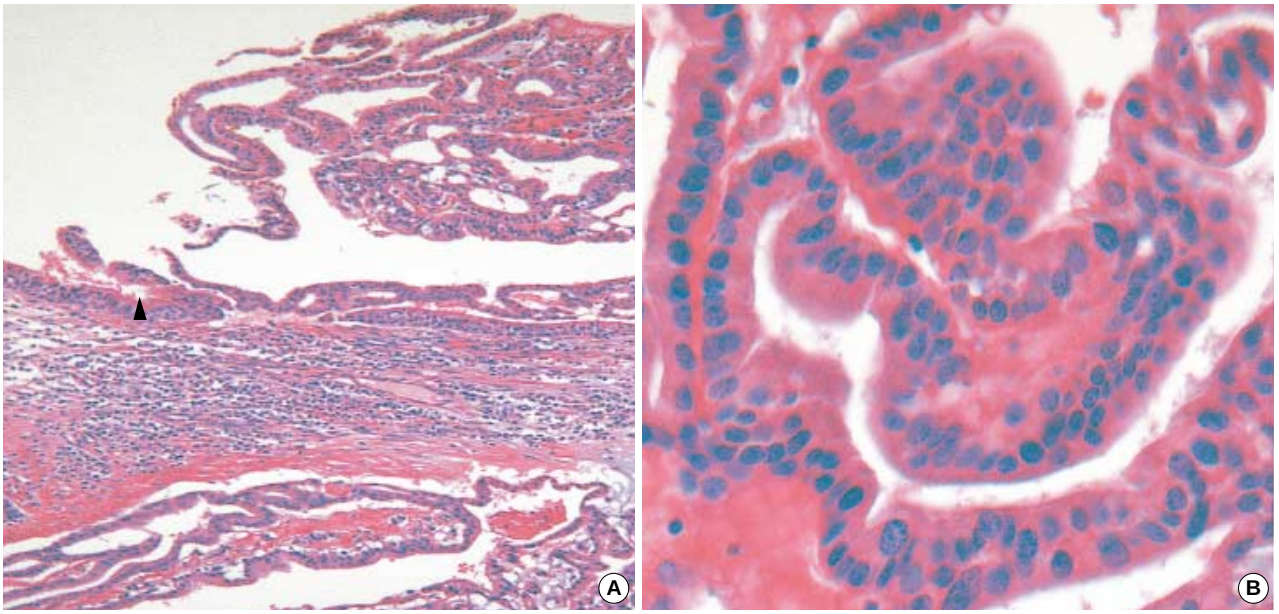

Fig. 4. The pathologic findings of Case 3. (A) The tumor have well differentiated villotubular growths with back-to-back arrangements. Transition from normal surface epithelium to neoplasm is seen (arrow head). (B) The cells are uniformly cuboidal with eosinophilic cytoplasms and uniform oval nuclei.

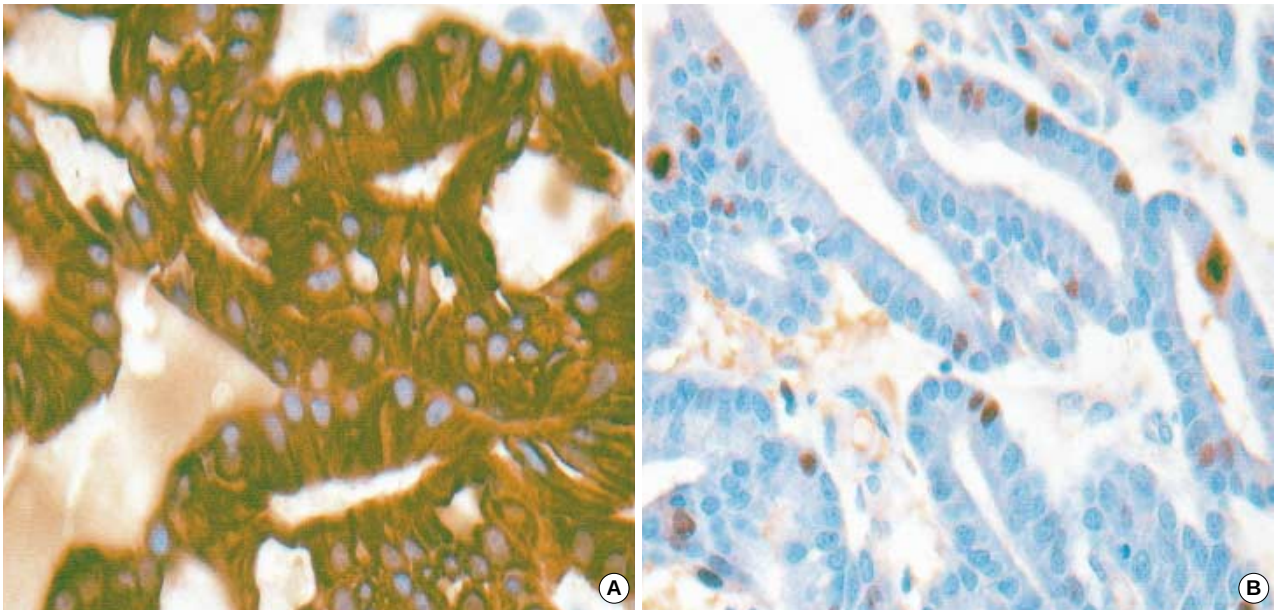

Fig. 5. (A) Immunostaining for CK 7 shows strong positivity in Case 3. (B) Ki-67 labeling index is low (1-4%, mean 1.9%).

Table 1. Clinical data for three cases of sinonasal low-grade adenocarcinomas

Case	Age/ Sex	Occupation	Risk factor	Symptoms	Size	Location	Treatment	Rec.	Follow-up
1	57/F	absent	non-smoker	bloody rhinorrhea	1.7×1.6×0.8 cm	maxillary sinus	excision	yes	6 yr 8 mo. NED
2	64/M	absent	non-smoker	nasal obstruction	4×3×1.5 cm	maxillary & ethmoid sinus	middle turbinectomy & ethmoidectomy	yes	8 yr 8 mo. NED
3	48/F	food company	non-smoker	nasal obstruction	3.8×3×0.9 cm	maxillary sinus	maxillectomy	no	11 mo. NED

NED, no evidence of disease; Rec., Recurrence.

tomy were performed.

Microscopically, the tumor had a well differentiated villotubular growth pattern with back-to-back arrangements. The cells were cuboidal with eosinophilic cytoplasm. The nuclei were oval and uniform; any mitotic activities were extremely scanty. Weak mucin production was observed (Fig. 4).

The patient has been free of tumor at 11 months after the operation.

The clinical information on each patient is summarized in Table 1.

Immunohistochemistry

In all three cases, the tumor cells were strongly positive for CK 7 (Fig. 5A), but they were negative for CK 20 and CDX-2. The proliferative activity was very low with a mean Ki-67 labeling index of 1.9% (range 1-4), although the recurrent tumors had a tendency to show slightly increased Ki-67 labeling indices (Fig. 5B). The initial tumors were negative for p53, but a focal positivity was noted (<1%) in the recurrent tumors of Cases 1 and 2.

Table 2. Summary of immunohistochemical findings

Anti-serum	Source	Dilution	Case 1-initial	Case 1-recurrence	Case 2-initial	Case 2-recurrence	Case 3
CK7	DAKO	1:200	+	+	+	+	+
CK20	DAKO	1:200	–	–	–	–	–
CDX2	Biogenex	1:200	–	–	–	–	–
p53	DAKO	1:1600	–	<1%	–	<1%	<1%
Ki-67	DAKO	1:200	1%	2%	–	4%	3%

CK, cytokeratin.

The immunohistochemical findings are summarized in Table 2.

DISCUSSION

We have described a series of three tubulopapillary low-grade adenocarcinomas that primarily arose from the sinonasal mucosa

and we investigated the expressions of CK 7, CK 20, CDX-2 and p53, and the Ki-67 labeling index. All three tumors were histologically of a low-grade, and they comprised a uniform population of cells that lacked nuclear pleomorphism. The growth patterns were characteristic, being tubulopapillary with back-to-back glands. There was only sparse mucus production.

Various subclassifications of the non-salivary type sinonasal adenocarcinomas have been proposed, beginning with that of Batsakis *et al*. in 1963, who divided them into the papillary, sessile and mucoid subtypes.[6] Klintenberg *et al*. split their cases into the papillary and alveolar subtypes.[7] Later, Batsakis *et al*. separated out the colonic or intestinal tumors from his original three groups.[8] Barnes *et al*. have grouped their series of tumors into the papillary, colonic, solid, mucinous and mixed types.[2] Kleinsasser and Schroeder proposed the classification of the papillary tubular cylinder cell type, the mucus-producing alveolar goblet cell type and the signet-ring cell types of adenocarcinoma of the inner nose.[9] Franquemont *et al*. have evaluated the Kleinsasser and Schroeder criteria and they further subdivided the papillary tubular cylinder cell cases into the low- and high-grade groups.[10] The current classification by the WHO is the intestinal and non-intestinal types.[1]

The extremely bland features of sinonasal low-grade adenocarcinomas may lead to an under-diagnosis. In our Case 1, the initial pathological diagnosis was oncocytic papilloma. Sinonasal low-grade adenocarcinoma and oncocytic (cylindrical cell) papilloma share several histological features such as cytologically bland eosinophilic epithelium, mucin-containing intraepithelial lumina, regular simple papillary structures, the absence of mitosis and the nuclear uniformity. The distinguishing features of oncocytic papilloma include the stratified epithelium and a lack of true glandular formation.[11] Moreover, despite its very uniform bland appearance, sinonasal tubulopapillary low-grade adenocarcinomas display a true invasive growth pattern and they can recur if they're treated inadequately.[11] As in our Case 1, an incomplete resection led to a recurrence.

The other differential diagnoses of low-grade sinonasal adenocarcinomas include ITACs and metastatic intestinal adenocarcinomas. Although metastatic tumors are even less common than primary sinonasal adenocarcinomas, colonic tumors have a probability to migrate to the sinonasal areas. In general, low-grade sinonasal adenocarcinomas show tubulocystic or papillary patterns and they are composed of a single layer of eosinophilic cuboidal or columnar cells. These tumors must be properly distinguished from ITACs because they have a much less aggressive clinical course and a better prognosis. The distinction between low-grade sinonasal adenocarcinomas and ITACs is based on the higher grade of most ITACs and their predominant population of cylindrical cells and goblet cells. ITACs frequently demonstrate extensive necrosis, inflammation, occasional hemorrhage and 0 to 6 mitoses per high-power field.[2] Yet this distinction can be difficult. Our Case 3 was also difficult to distinguish from ITAC because the structures were complex and they contained a number of mucous cells. However, low-grade papillary sinonasal adenocarcinomas do not share the same immunohistochemical expression profile of the intestinal type adenocarcinomas (ITACs) or the colonic adenocarcinomas.

The CK 7 and CK 20 profiles and the expression of CDX-2 were reported to be useful in distinguishing ITACs from low-grade sinonasal adenocarcinomas.[3-5] CDX-2 is a transcription factor product of the CDX-2 homeobox gene. This gene is one of the earliest genes involved in intestinal differentiation and it plays an essential role in the proliferation and differentiation of the intestinal epithelial cells.[12,13] The tumors with a CDX-2 expression that occur outside the gastrointestinal tract include ovarian mucinous and endometrioid carcinomas and adenocarcinomas of the urinary bladder.[3] Franchi *et al*. have demonstrated the nuclear expression of CDX-2 in 15 cases of ITAC.[12] On the other hand, low-grade adenocarcinomas have displayed CK 7 positivity, and they lacked both CK 20 and CDX-2 expressions, as in our cases.[4,14] Krane *et al*. reported the co-expression of CK 7 and CK 20 in five cases of ITACs. The co-expression of CK 7 and CK 20 largely excludes any metastasis from a colorectal adenocarconoma.[15] In brief, the immunoprofile of low-grade sinonasal adenocarcinoma is reasonable if it shows CK 7+/CK 20-/CDX-2-. On the contrary, the CK 7+/CK 20+/CDX-2+ phenotypes suggest ITACs. The metastatic colonic adenocarcinomas most commonly express the CK 7-/CK 20+/CDX-2+ immunophenotypes.

Recent studies have shown a high incidence of p53 abnormality in the ITAC that is associated with saw dust exposure.[16] None of our patients had a history of wood dust exposure or p53 immunopositivity. It is conceivable that the sawdust contributes to the development of a subset of ITAC via p53 mutation, and that a different pathway may play a role in the tumors that develop in the non-sawdust exposed patients.

A proliferative marker, i.e., the Ki-67 labeling index, is also helpful in making the diagnosis. Skalova *et al*. have reported on six sinonasal low-grade adenocarcinomas that demonstrated very low proliferative activities, wihich is in contrast to ITAC.[11,17] The Ki-67 labeling indices of the tumors presented in this report constituted too small a group to allow meaningful statistical

analysis; however, a comment can be made. The recurrent tumors in two cases had a tendency to show slightly increased Ki-67 labeling indices.

The histogenesis of sinonasal adenocarcinomas remains unknown because of the lack of suitable biomarkers and also due to lack of consensus between the published studies. Gnepp and Heffner suggested that sinonasal adenocarcinomas mostly originate from the surface mucosa and they are less commonly from the excretory ducts or seromucous glands.[18] Manning and Batsakis postulated a cancerous deviation from stem cells or reserve cells that are resident in 1) the surface epithelium, 2) the seromucous derivatives of the invaginated surface epithelium, and 3) the junctions between the two epithelia.[19] On the other hand, Kleinsasser and colleagues reported seven tumors originating from the medial wall of the middle concha and ethmoid sinus, and they called them terminal tubulus adenocarcinoma.[9,14] One of the tumors (Case 3) in this study showed a direct transition from the normal surface epithelium to the neoplasm, suggesting a surface epithelial origin.

The low-grade sinonasal tubulopapillary adenocarcinomas have a tendency to recur, as was seen in our cases, but they show no distant metastasis. Therefore, we think that it is important to understand the pathology of this entity because a complete excision is required for proper treatment.

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