A Case of Sinonasal Low-Grade Nonintestinal Adenocarcinoma That Was Difficult to Diagnose Preoperatively

Yoshie Mizoguchi[1] Sunao Tanaka[1] Shigeru Kikuchi[1]

[1] Department of Otolaryngology, Saitama Medical Center, Saitama, Japan

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Address for correspondence Sunao Tanaka MD, PhD, Department of Otolaryngology, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe-shi, Saitama 350-8550, Japan (e-mail: cipher@saitama-med.ac.jp).

Abstract

We report a case of sinonasal low-grade, nonintestinal adenocarcinoma (LG non-ITAC). The patient, a 56-year-old woman, was referred to our university hospital for a left nasal tumor with nasal obstruction, epistaxis, and nasal discharge. Nasal endoscopy revealed a nasal polypoid tumor with a smooth margin occupying the left nasal cavity. The sinonasal tumor was diagnosed as an exophytic papilloma by histopathology. Sinonasal contrast computed tomography (CT) confirmed homogeneous opacification of the left frontal, maxillary, and ethmoidal sinuses. There was no evidence of a potential bone defect. T2-weighted magnetic resonance imaging (MRI) showed a relatively uniform high signal intensity area in the left maxillary and frontal sinuses. An area of high signal intensity was also found in a part of the left ethmoid sinus. Left transnasal endoscopic ethmoidectomy was performed under general anesthesia. The tumor in the nasal cavity was prone to bleeding. We defined the site of tumor attachment as the suprabullar cell. The anterior ethmoidal artery was exposed, and the tumor was carefully dissected and removed. Based on the findings of these radiological and histological examinations, the sinonasal tumor was diagnosed as a LG non-ITAC. Sinonasal non-ITAC is an adenocarcinoma without the histopathological characteristics of salivary or intestinal-type adenocarcinoma. Non-ITAC is additionally classified into the high-grade and LG types. LG non-ITAC is very uncommon. Thus far, there is only one published report in the literature on the clinical and therapeutic characteristics of LG non-ITAC in Japan. Non-ITAC has a good prognosis, with a low risk of metastasis. Therefore, it is imperative to suspect and distinguish non-ITAC from other sinonasal tumors with similar symptoms preoperatively.

Keywords

- sinonasal adenocarcinoma
- low-grade
- non intestinal type

Introduction

Nonintestinal adenocarcinoma (non-ITAC) is a type of adenocarcinoma without the histopathological characteristics of salivary or intestinal-type adenocarcinoma. Non-ITAC is additionally classified into high-grade (HG) and low-grade (LG) types. LG non-ITAC is very rare, and to date, there is only one published report on the clinical and therapeutic characteristics of LG non-ITAC in Japan.[1] We report the case of a woman who was diagnosed with sinonasal LG non-ITAC at our hospital.

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Case Presentation

Patient
The patient is a 56-year-old woman.

Chief Complaints
Chief complaints of the patient were nasal obstruction, nasal discharge, and epistaxis.

Medical History
The patient had a history of hypertension and childhood asthma.

History of Present Illness
Two months before the initial examination at our department, the patient had left nasal obstruction, nasal discharge, and epistaxis, and had consulted her local clinic. Endoscopic examination had revealed a polypoid lesion in the left nasal cavity; thus, the patient was referred to our department for consultation and further examinations.

Findings at the Initial Examination
A white polypoid lesion with a smooth surface was observed in the left middle nasal meatus (►**Fig. 1**).

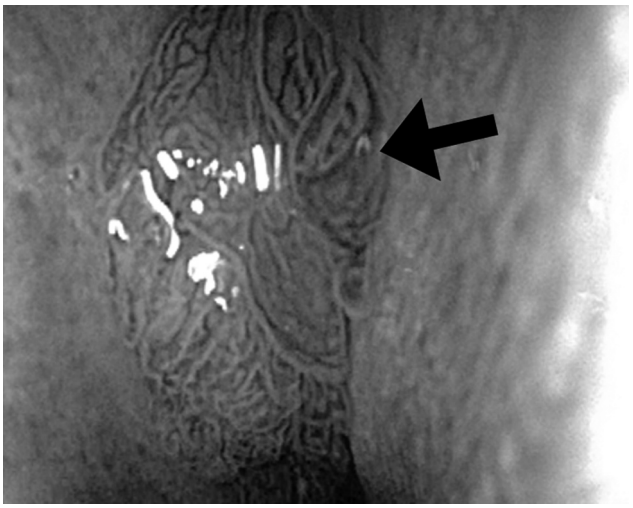

Fig. 1 Findings at the initial examination. Endoscopic findings of the left nasal cavity. A white neoplastic lesion with a smooth surface was found in the left middle nasal meatus (*arrow*).

Test Findings
Plain computed tomography (CT) of the paranasal sinus showed homogenous opacification in the soft part of the left maxillary sinus (►**Fig. 2**). This lesion in the left maxillary cavity continued inside the left nasal cavity, and a mildly dense soft-tissue lesion was also observed in the left side of the ethmoidal sinus. There was no evidence of a bone defect, including in the left maxillary sinus. Plain magnetic resonance imaging (MRI) of the paranasal sinus revealed a faint hyperintense signal on T1-weighted imaging in the left maxillary sinus, but the signal was not reduced on fat-suppressed T1-weighted imaging. A hyperintense signal was seen on T2-weighted short-term inversion recovery (T2 STIR). All hyperintense signals were relatively uniform, and mucus retention was suspected (►**Fig. 3**). A hyperintense signal on T2 STIR and an isointense area of thickening on T1-weighted imaging in the left ethmoidal sinus also were observed. Based on the intranasal and imaging findings, the anterior ethmoid sinus was considered the primary onset site.

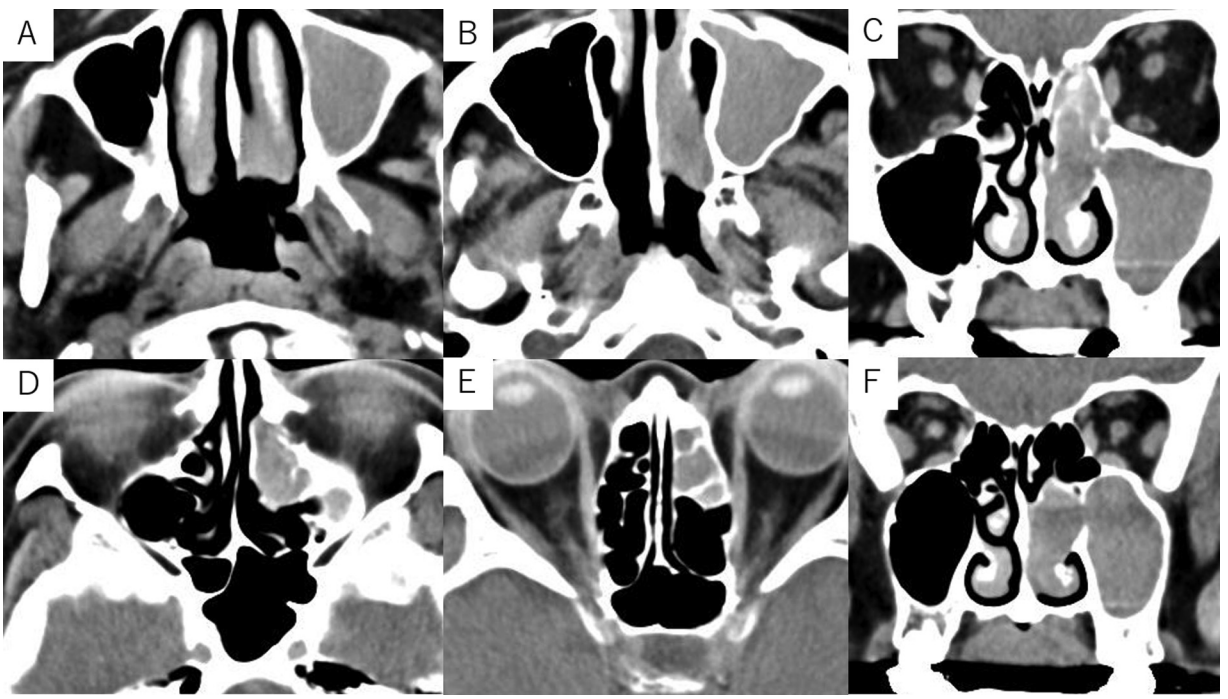

Fig. 2 Plain computed tomography of the paranasal sinus. (**A**,**B**,**D**,**E**) Axial sections. (**C**,**F**) Coronal sections. Opacification in the soft part of the left maxillary sinus, frontal sinus, and ethmoidal sinus, with no evidence of bone defect.

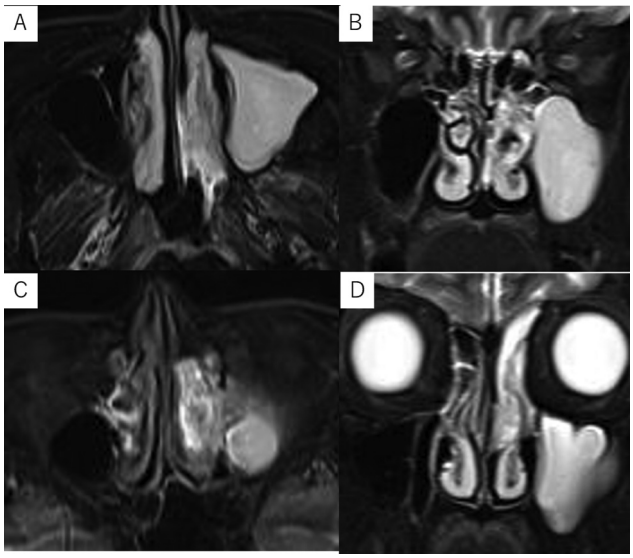

Fig. 3 Plain magnetic resonance imaging (MRI) of the paranasal sinus (T2 short-term inversion recovery). (**A, C**) Axial and (**B, D**) coronal sections. High signal intensity with relative uniformity is shown in the left maxillary sinus and frontal sinus. A partial region of high signal intensity is shown in the left ethmoidal sinus.

Preoperative Histopathological Findings

Biopsy of part of the tumor was performed on an outpatient basis, and the samples were submitted for pathological testing. The removed $7 \times 4 \times 3$ mm tumor specimen had a brownish color and a fibrous structure, and there were no clear solid components. Histologically, externally protruding papillary proliferation of pseudostratified ciliated epithelia was observed (►**Fig. 4**). In the epithelium, gobletlike cavities were observed. The mucosal interstitium was edematous and showed lymphocyte and plasma cell infiltration. These results led to the diagnosis of exophytic papilloma.

Clinical Progress

Surgery was scheduled to treat the exophytic papilloma, and at 5 months after the initial examination, a left paranasal sinus tumorectomy was performed (►**Fig. 5**). In the middle nasal meatus, a tumor was observed that was prone to bleeding. While covering the tumor with 1:5,000 bosmin-soaked gauze, we proceeded to perform a blunt dissection and partial resection of the tumor, after which the resected specimen was submitted for pathological testing. During this process, the ethmoidal sinus was opened, and upon proceeding with the dissection, we determined that the tumor was attached to the suprabullar cells. The anterior ethmoidal artery was exposed, and the remaining tumor was carefully dissected and then surgically removed. Examination of the inside of the maxillary sinus showed pooling of a white viscous fluid; however, the tumor could not be confirmed. Upon confirming hemostasis, surgery was completed. The operative duration was 1 hour and 44 minutes, and there was approximately 75 mL of blood loss. The postoperative course was uneventful, and the patient was discharged on postoperative day 6.

Postoperative Histopathological Findings

There were two resected specimens that measured $27 \times 20 \times 25$ and $17 \times 13 \times 11$ mm in size. Both specimens had micropapillary surfaces with mucus attached, and several cysts could be seen on the cut surface (►**Fig. 6**). Histologically, the tumor consisted of high columnar ciliated epithelium with papillary proliferation, and the epithelial cells had a large intestinal adenoid tumorlike form (►**Fig. 7**). Some muciphagelike clear cells could be seen in the epithelium, but no neutrophilic abscess or mucinous cyst was observed in the epithelium. Immunohistochemically, the atypical cells were negative for the intestinal markers CK20, CDX2, and MUC2. Furthermore, the cells also tested negative for the neuroendocrine markers CD56, chromogranin A, and synaptophysin. The CK7 test result was positive, and the PAX8 result was slightly positive, whereas the results for S-100 protein, TTF-1, and thyroglobulin were negative. The Ki-67-positive rate was low at only a few percent. The resection stump was difficult to assess. These results suggested a diagnosis of sinonasal LG non-ITAC (pT2N0M0).

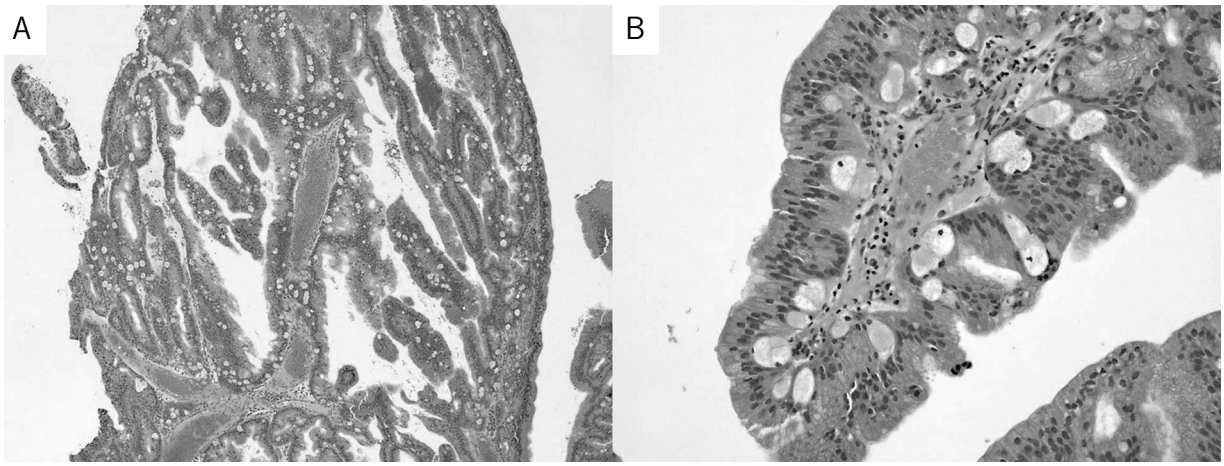

Fig. 4 Preoperative histopathological findings. (**A**) Hematoxylin and eosin (HE) stained sample (×40 magnification). Externally protruding papillary proliferation of pseudostratified ciliated epithelia. (**B**) HE-stained specimen (×100 magnification). Intraepithelial gobletlike cavities.

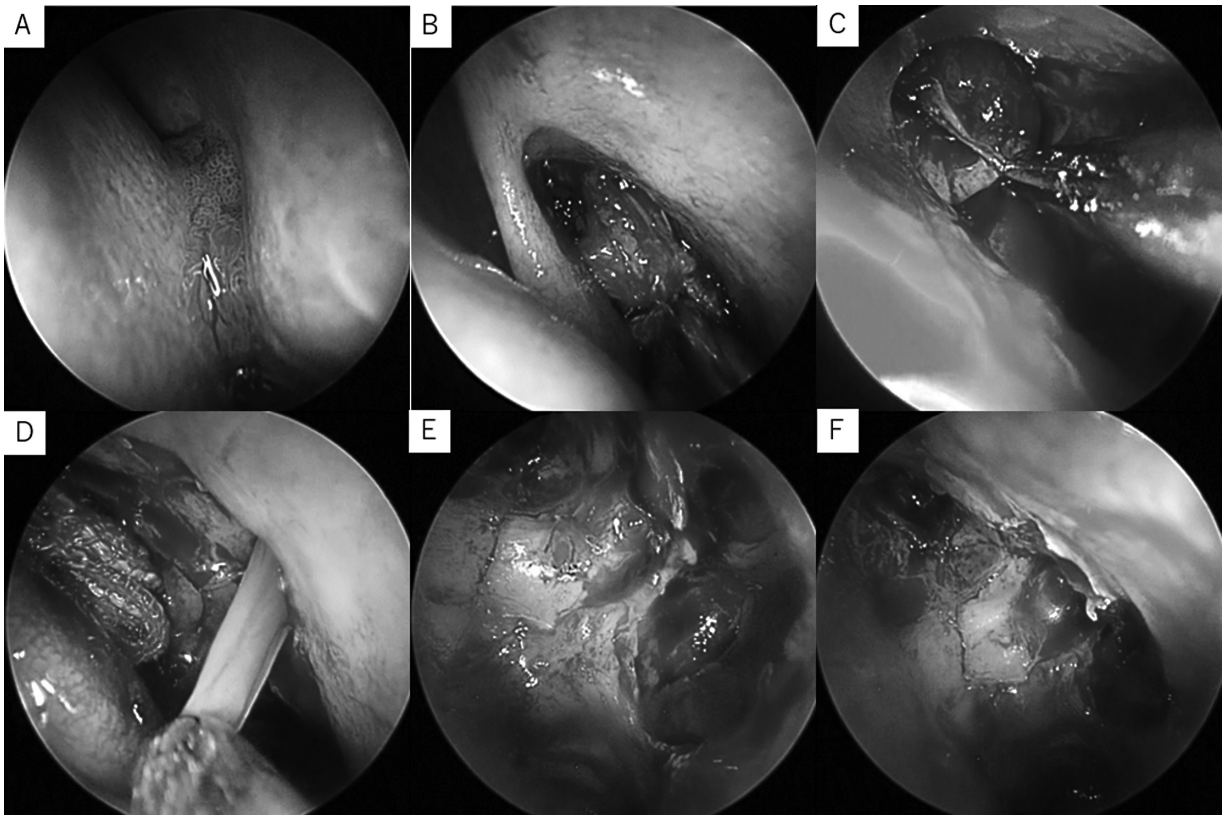

Fig. 5 Surgical findings. (**A**) In the middle nasal meatus, a tumor prone to bleeding is visible. (**B**) The blunt dissection with part of the tumor extracted is visible. During this procedure, the ethmoidal sinus has been opened. (**C**) The site of tumor attachment is the suprabullar cells. The remaining tumor is detached and removed. (**D**) A large volume of white viscous nasal mucus has pooled within the maxillary sinus. (**E**) No tumor is observed in the maxillary sinus. (**F**) Completion of surgery after confirming hemostasis.

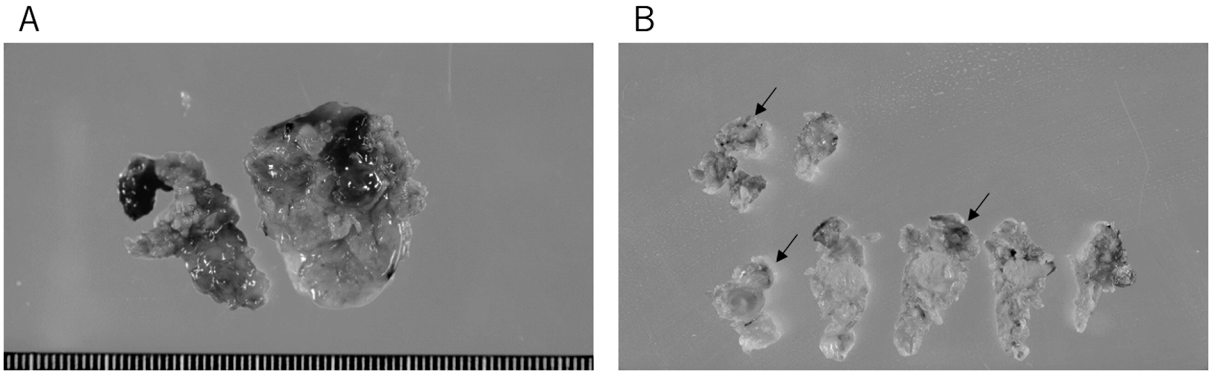

Fig. 6 Macrophotograph of the specimen. (**A**) Resected specimen. There were two specimens of $27 \times 20 \times 15$ and $17 \times 13 \times 11$ mm in size, and the surface of both specimens are micropapillary with mucus attached. (**B**) Specimen section. Several cysts can be seen on the cut surface (*arrow*).

Postoperative Progress

After surgery, the symptoms of nasal obstruction and nasal discharge disappeared. Unlike the preoperative inference, the postoperative diagnosis was a malignant tumor. Therefore, on postoperative day 58, fluorodeoxyglucose positron emission tomography (FDG-PET)/CT was performed. The paranasal sinus showed no abnormal uptake, and there were no signs of recurrence. Furthermore, no abnormal uptake was detected in the cervical lymph nodes or distal organs, suggesting the absence of a clear metastasis.

Although it was difficult to assess the resection stump, considering that there was no clear residual tumor or recurrence observed on FDG-PET/CT and after consulting with the patient, we decided to follow up with observation and without additional aggressive treatment. At postoperative 1 year, FDG-PET/CT and endoscopy showed no evidence of recurrence.

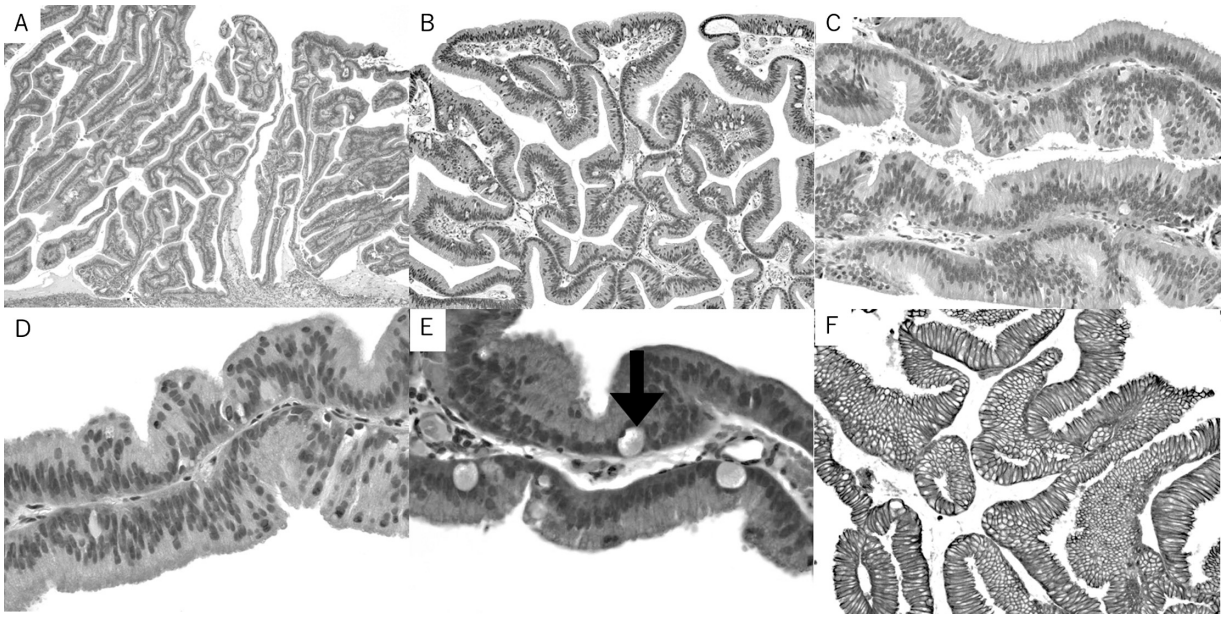

Fig. 7 Postoperative histopathological findings. (**A**) Hematoxylin and eosin (HE) stained specimen (×40 magnification). Atypical columnar epithelium with vigorous papillary proliferation is shown. (**B**) HE-stained specimen (×100 magnification). Atypical columnar epithelium with vigorous papillary proliferation is shown. (**C**) HE-stained specimen (×200 magnification) consisting of high columnar atypical epithelium, and mild pseudoreplication of the nucleus can be seen. However, the mild nuclear atypia is mild. (**D**) HE-stained specimen (×400 magnification) consisting of high columnar atypical epithelium and mild pseudoreplication of the nucleus can be seen. However, the mild nuclear atypia is mild. (**E**) HE-stained specimen (×400 magnification). Some muciphagelike clear cells can be seen in the epithelium (*arrow*). (**F**) Immunostaining CK7 (×200 magnification). Tumor cell positivity was found.

Discussion

Based on the 2017 World Health Organization (WHO) classification, paranasal sinus adenocarcinoma is classified into intestinal and nonintestinal types.[2] Non-ITAC is a type of adenocarcinoma without the histopathological characteristics of salivary or ITAC. The Non-ITAC type is subdivided into HG atypia type and LG atypia type. LG non-ITAC is very rare, and the report by Tachino et al is the only one in the literature on the clinical and therapeutic characteristics of LG non-ITAC in Japan.[1] Consequently, this is the second reported case (►**Table 1**). LG non-ITAC is observed in a wide range of age groups and primarily develops in the nasal cavity or paranasal sinuses, such as the ethmoidal and maxillary sinuses.[3] There are no clear risk factors, and in contrast to the relationship between ITAC and wood and leather dust exposure, no relationship between non-ITAC and environmental factors has been reported.[4]

The macroscopic characteristics of LG non-ITAC include papillary, cauliflower, and raspberry forms, and some are soft to somewhat hard and rough. Histologically, this is a well-differentiated lumen-forming tumor that presents papillary proliferation with an outward growth pattern. Most of these tumors are small adenocarcinomas consisting of columnar epithelium and ciliary cells. The constituent cells have clear eosinophilic bodies, and sometimes include oncocytes and squamous metaplastic cells. Nuclear division is rare, and nuclear atypia and clear nucleoli are not usually seen.[5] Morphologically, diseases requiring differential diagnosis include respiratory epithelial adenomatoid hamartoma, seromucinous hamartoma, and schneiderian papilloma.[4,6] Differential diagnosis of these diseases is often difficult by outpatient biopsy alone, and it is difficult to diagnose LG non-ITAC preoperatively.[7] On immunohistochemical staining, CK7 positivity combined with CK20 and CDX2 negativity is typically used.[2,4]

CK7 and CK20 are low-molecular-weight cytokeratins. Reportedly, CK7 is positive in the majority of intraepithelial tumors except for prostate cancer and colorectal cancer, whereas CK20 is positive in most patients with urothelial

Table 1 Japanese reported cases of sinonasal low-grade nonintestinal adenocarcinoma

Patient	Study	Age (y)	Sex	Onset site	Treatment method	Observation period (mo)	Prognosis
1	Tachino et al[1]	41	M	Ethmoidal sinus	Chemoradiotherapy and endoscopic paranasal sinus surgery	84	No recurrence
2	This study	56	F	Ethmoidal sinus	Endoscopic paranasal sinus surgery	12	No recurrence

cancer and colorectal cancer.[8] CDX2 is a homeobox gene expressed in the epithelial cell nuclei of the intestines from the duodenum to the rectum, and it encodes a transcription factor that has an important role in intestinal epithelial cell proliferation and differentiation.[9] CDX2 is expressed in primary and metastatic colorectal cancer, and it has also been identified in primary mucinous ovarian tumors, and metastatic mucinous carcinoma, including the ovaries. Therefore, as specific immunohistological markers of adenocarcinoma including intestinal adenocarcinoma, CK20 and CDX2 positivity combined with CD7 negativity are currently used. Our patient presented the characteristics of non-ITAC with CK7 positivity and CK20 and CDX2 negativity.

The incorrect preoperative diagnosis of the patient in the present case was exophytic papilloma, which is a benign epithelial tumor characterized by papillary proliferation. Exophytic papilloma arises in the nasal cavity and paranasal sinus mucous membrane covered by ciliated columnar epithelium called the schneiderian mucosa; thus, it shows proliferation of nonkeratinized squamous epithelium, transitional epithelium, and pseudostratified columnar epithelium with fibrovascular clusters. Exophytic papilloma was diagnosed presumably because glandular tumors of the nasal cavity are very rare, and most instances are salivary gland tumors. The present case did not show typical characteristics of salivary gland tumors, such as biphasic proliferation of the epithelium and myoepithelium. Furthermore, in the differential diagnosis of adenocarcinoma, a high level of atypia that would suggest adenocarcinoma was not observed, and immunostaining was deemed unnecessary for the morphological diagnosis of exophytic papilloma because outward-protruding papillary proliferation of the ciliated epithelium was observed. As stated earlier, LG non-ITAC presents papillary proliferation, with columnar epithelium, ciliated epithelium, and squamous epithelium, thereby resembling exophytic papilloma. The macroscopic characteristics of exophytic papilloma also resemble the findings of LG non-ITAC because the lesion morphology presents outward cauliflower or wartlike growths that are relatively hard. Therefore, exophytic papilloma and LG non-ITAC have many common characteristics in their macroscopic and histological findings; thus, differential diagnosis from a small tissue sample, such as that obtained by outpatient biopsy, was considered difficult. In the postoperative specimen, the attending physician had experienced a similar case in the past and conducted immunostaining after considering the possibility of LG non-ITAC. If the attending physician had not done this, we believe that deciding on a diagnosis would have been extremely difficult, considering that it was an extremely rare case of LG non-ITAC and the morphological features of the very LG disease did not strongly suggest a malignancy.

Sinonasal LG non-ITAC is primarily treated surgically, and in many cases, additional radiotherapy and chemotherapy are performed as the disease progresses. Turri-Zanoni et al reported that, in adenocarcinoma, there was no statistically significant difference between patients who underwent surgery alone and those who underwent surgery and radiotherapy for T1–T2 LG adenocarcinomas.[10] Bignami et al have reported that prognosis is better for LG non-ITAC than for HG non-ITAC and extensive resection is not absolutely necessary; thus, if the negative margin status can be confirmed on postoperative pathological analysis, then a long-term prognosis can be expected.[11] However, it is difficult to diagnose LG non-ITAC preoperatively, and it is possible that lack of diagnosis would result in insufficient resection. In this study, surgical monotherapy was selected to treat T1–T2 LG non-ITAC. Among these patients, there have been no reported cases of recurrences during the follow-up observation. Furthermore, it has been highlighted that prognosis is poorer for patients with T4a and T4b tumors than for patients with T1–T3 tumors, and adjuvant radiotherapy was administered to all patients who were diagnosed with T4a and T4b tumors. Choussy et al reported 418 patients with primary adenocarcinoma of the ethmoid sinus, including 23 patients with LG non-ITAC, and found that the prognosis was increasingly poorer if the lesion had invaded the sphenoidal bone, eye socket, brain, and dura mater.[12]

Regarding chemotherapy as perioperative adjuvant therapy, Tachino et al reported that remission was achieved by a patient with T4aN0M0 and stage IVa tumors after receiving cisplatin combined with radiotherapy followed by surgical treatment. At present, however, there is no established pharmacotherapy for LG non-ITAC.[1]

The 5-year survival rate of LG non-ITAC is good at $\geq$80%. On the other hand, HG non-ITAC is characterized by rapid tumor progression, and the 3-year survival rate is approximately 20%. Furthermore, even after administering postoperative radiotherapy, the 5-year survival rate is worse for HG non-ITAC than for LG non-ITAC. As stated earlier, progress is often good with appropriate treatment, and we believe that preoperative differential diagnosis is important before providing treatment. Although LG non-ITAC is very rare, if the disease is known, it could be possible to perform differential diagnosis when there are no features typical of salivary gland tumors and the pathological findings show lumen formation.[13,14]

Conclusion

At our hospital, we experienced a case of sinonasal LG non-ITAC that was difficult to diagnose preoperatively. Although this preoperative diagnosis is not easy, the characteristic findings can be used in the preoperative differential diagnosis to arrive at a probable diagnosis, which can improve the chance of administering the most appropriate treatment.

Funding
None.

Conflict of Interest
None declared.

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