Case Report

Thyroid-like low-grade nasopharyngeal papillary adenocarcinoma: a case report and literature review

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Abstract: Thyroid-like low-grade nasopharyngeal papillary adenocarcinoma (TL-LGNPPA) is a rare disease, and consensus regarding the diagnosis, clinical management, and prognosis for this population is lacking. This study aimed to assess the immunohistochemical features, clinical management, and prognosis of TL-LGNPPA through a comprehensive literature review. We reported a patient diagnosed with TL-LGNPPA in our institution. In addition, we reviewed the published literature from PubMed, Science Direct, Web of Science, Google Scholar, and China National Knowledge Internet to synthetically review the patient characteristics, treatments, and outcomes for TL-LGNPPA. We included 46 patients in this study, and most of them (76.1%) came from Asia. The most common symptoms were nasal obstruction, epistaxis, and bloody sputum. The tumors mainly occurred in the posterior roof of the nasopharynx or nasal septum. In patients with available immunohistochemical results, all patients were overexpression of thyroid transcription factor 1 (100%), CK7 (100%), CK19 (100%), Ckpan (100%), and epithelial membrane antigen (100%). In addition, the majority of them were Vimentin overexpression (94.7%). However, TL-LGNPPA patients were more likely to have lower-expression of CK20 (100%), smooth muscle actin (100%), Epstein-Barr virus-encoded RNA (100%), thyroglobulin (97.8%), CK5/6 (92.6%), S-100 (86.7%), and P63 (85.8%). All of the patients underwent surgery, and two of them received postoperative radiotherapy. With a median follow-up time of 16 months, and 16% of them were follow-up for more than five years, no locoregional recurrences or distant metastasizes occurred. In conclusion, TL-LGNPPA is an extremely rare entity with unique disease features and excellent prognosis. Surgery is the optimal treatment for this population.

Keywords: Thyroid-like low-grade nasopharyngeal papillary carcinoma; thyroid transcription factor 1 (TTF-1); treatment; prognosis; immunohistochemistry; case report

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor with significant differences in regional distribution, which has a high incidence in Southeast Asia, North Africa, and the Arctic regions, especially in southern China (1). In the 4th edition of the World Health Organization (WHO) classifications of head and neck tumors in 2017, NPC was classified into the following subtypes: non-keratinizing squamous cell carcinoma, keratinizing squamous cell carcinoma, basaloid squamous cell carcinoma, and nasopharyngeal papillary adenocarcinoma (NPPA) (2). NPPA includes conventional or mucosal surface origin type and the salivary gland type, and thyroid-like low-grade NPPA (TL-LGNPPA) belongs to the former one (3).

TL-LGNPPA, a rare neoplasm originating from the nasopharyngeal epithelium, accounting for 0.38–0.48% of all malignant neoplasms in the nasopharynx (4,5), which

was first defined by Carrizo *et al.* in 2005 (6). TL-LGNPPA is a low-grade malignancy, which has similar pathological and immunohistochemical findings compared to papillary thyroid carcinoma. The TL-LGNPPA is characterized by a linear arrangement of bland cuboidal to columnar cells with papillary lobes and dense glandular cells (3,4,7). In addition, overexpression of thyroid transcription factor 1 (TTF-1) was found in the majority of TL-LGNPPA patients (6,8).

Owing to the rarity of this entity, the clinicopathological characteristics, treatment modalities, and prognosis of TL-LGNPPA have not been well described. We reported a case of TL-LGNPPA in a 42-year-old female. Another purpose was to present the literature review of TL-LGNPPA by focusing on clinicopathological, immunohistochemical features, clinical management, and prognosis of this rare tumor. We presented the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/tcr-19-1973).

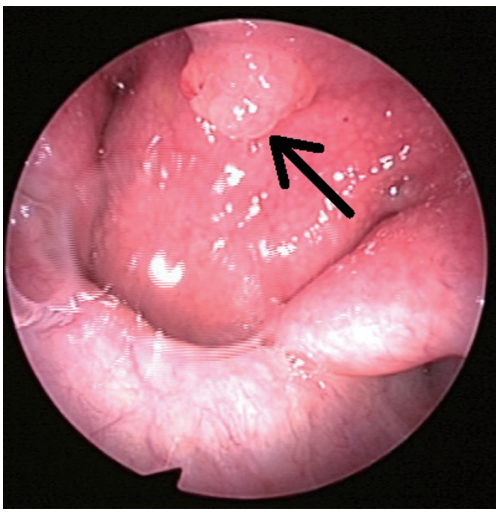


Figure 1 The location of the tumor in the junction of the nasopharyngeal wall and the free margin of nasal septum displayed using nasal endoscopy (black arrow).

Case presentation

A 42 years old non-smoking Chinese woman was admitted to our institution because of foreign body sensation in pharyngeal and dry throat for one month on December, 28, 2011. Nasal endoscopy showed a gray-red mass with a smooth surface at the junction of the nasopharyngeal wall and free margin of the nasal septum, which measured as 0.5 cm × 0.5 cm (*Figure 1*). A contrast-enhanced computed tomography (CT) was conducted on this patient, and the CT images showed a soft tissue at the junction of the nasopharyngeal wall and free margin of the nasal septum with no signs of local infiltration and bone erosion (*Figure 2*). In addition, there was no lymphadenopathy in the cervix and no lesion in the thyroid gland. Moreover, no family history of cancer was found.

The patient received surgical treatment and achieved complete excision on December 29, 2011. The tumor tissues were fixed with 4% formaldehyde, then dehydrated and embedded with paraffin, followed-by sectioned and stained with hematoxylin-eosin. Finally, a two-step

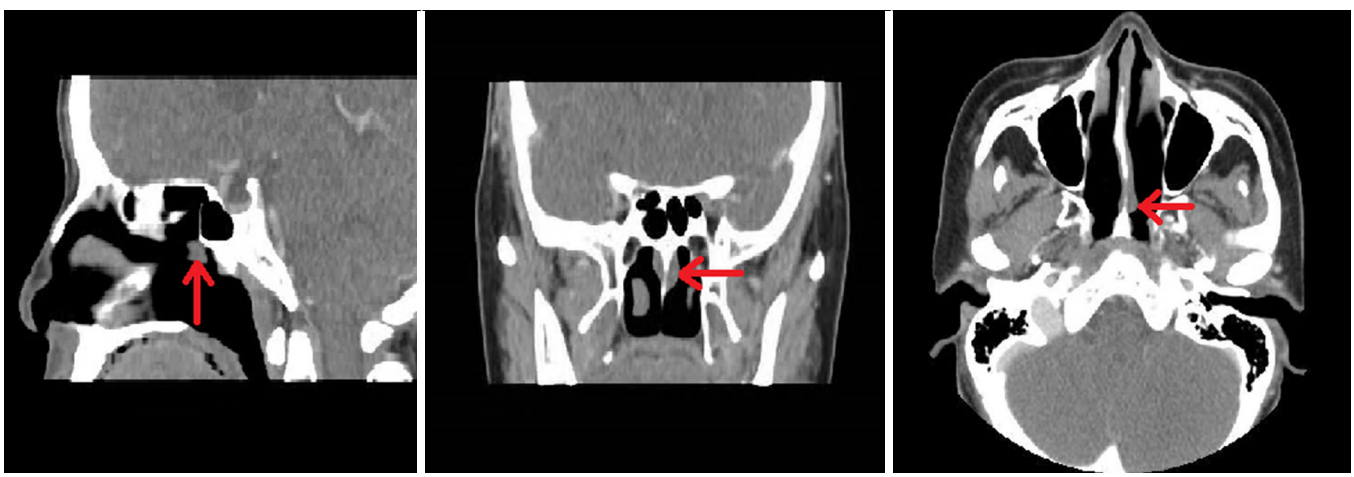


Figure 2 The location of the tumor in the junction of the nasopharyngeal wall and free margin of nasal septum displayed using computed tomography (red arrows).

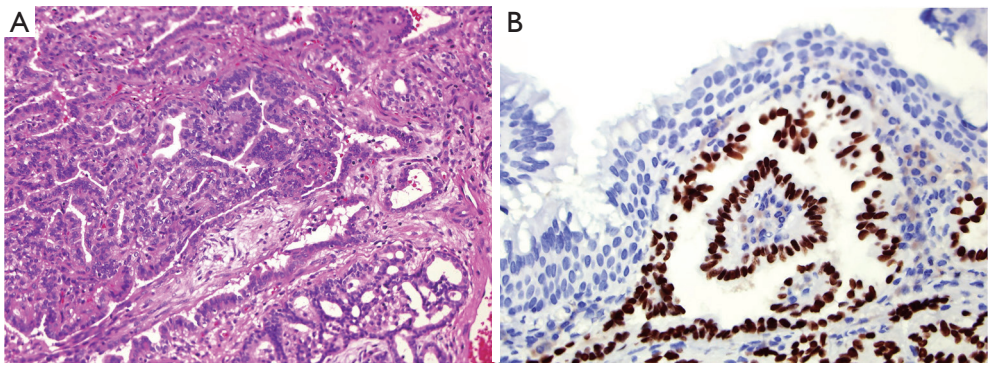


Figure 3 The pathological examination showed papillary structure and dense glandular cells in this disease (A) and overexpression of thyroid transcription factor 1 (B) in thyroid-like low-grade nasopharyngeal papillary adenocarcinoma (immunohistochemistry, ×200).

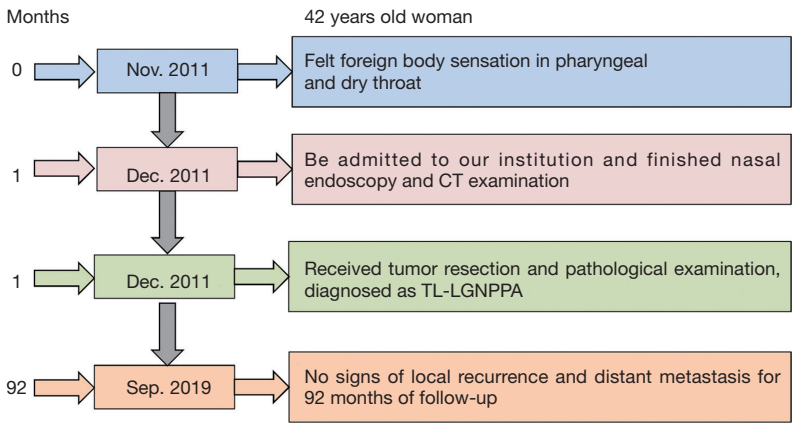
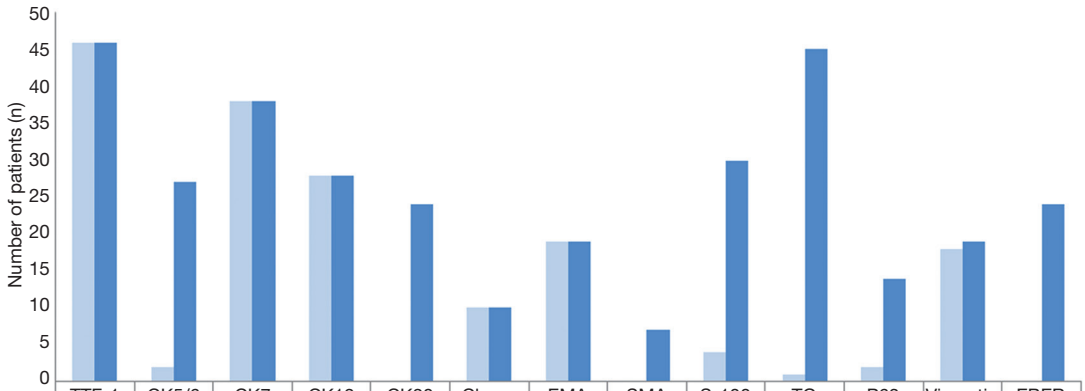


Figure 4 The timeline of the symptoms, interventions, and the corresponding survival in months by the patient.

EnVision method was used for the detection of TTF-1 expression. Microscopically, the tumor was present with papillary structure and dense glandular cells (*Figure 3A*). In addition, the tumor cells exhibited a diffuse expression of TTF-1 (*Figure 3B*). According to these findings, a diagnosis of TL-LGNPPA was started. No adjuvant chemotherapy or radiotherapy was performed following surgery. This patient was a follow-up for 93 months with no signs of local recurrence and distant metastasis from December 29, 2011, to September 20, 2019. No unanticipated events after surgery were reported in this patient. The timeline of the symptoms, interventions, and outcome of this case is listed in *Figure 4*. All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Affiliated Hospital of Xiamen University, and written informed consent was obtained from the patient for publication of this case report and any accompanying images (Approval number. KYH2019-044).

Search strategy for literature review

We conducted a comprehensive review of the current literature using the database from PubMed, Science Direct, Web of Science, Google Scholar, and China National Knowledge Internet up to September 26, 2019. The following keywords were used as effective index words: "nasopharyngeal papillary adenocarcinoma or low-grade nasopharyngeal papillary adenocarcinoma or thyroid-like nasopharyngeal papillary adenocarcinoma or thyroid-like low-grade nasopharyngeal papillary adenocarcinoma." The literature with "thyroid-like low-grade nasopharyngeal papillary adenocarcinoma" were identified, and we excluded patients diagnosed with nasopharyngeal adenocarcinoma, nasopharyngeal papillary adenocarcinoma, and low-grade



	TTF-1	CK5/6	CK7	CK19	CK20	Ckpan	EMA	SMA	S-100	TG	P63	Vimentin	EBER
Over expression of IHC markers (n)	46	2	38	28	0	10	19	0	4	1	2	18	0
Patients with known IHC results (n)	46	27	38	28	24	10	19	7	30	45	14	19	24

Figure 5 The expression of biomarkers in immunohistochemistry.

nasopharyngeal papillary adenocarcinoma. Thirty-four literatures were included from 2005 to 2019 (4-6,8-16) (*Table S1*).

Patient characteristics from the literature review

A total of 46 patients, including one from our institution were identified in the 34 literature, including 24 English literature and 10 Chinese literature. The patients' characteristics have shown in *Table S1*. The median age of diagnosis was 34 years (range, 9–68 years), and there was no sex predilection (males: females = 1:1.19). The distribution of main countries of the published literature was as follows: China (60.9%), Japan (10.8%), United States (8.7%), Argentina (4.3%), Turkey (4.3%), Vietnam (2.2%), Iran (2.2%), Spain (2.2%), United Kingdom (2.2%), and Italy (2.2%). The most common clinical manifestations were nasal obstruction (45.6%), epistaxis and bloody sputum (32.6%), foreign body sensation of the nasal cavity, nasopharynx, and pharynx (19.6%). In addition, 10.9% of the patients were diagnosed during the physical examination, and 8.7% of patients performed as snoring, sore throat, or headache. Imaging examination [CT, magnetic resonance imaging (MRI), or endoscope] found that most tumors originated from the unilateral or bilateral posterior roof of the nasopharynx (76.1%), and the others occurred in the posterior edge of the nasal septum (23.9%).

Immunohistochemistry findings, treatment, and prognosis

All patients received an excisional biopsy and histopathologic evaluation. In patients with available immunohistochemical results (*Figure 5*), all patients were overexpression of thyroid transcription factor 1 (100%), CK7 (100%), CK19 (100%), Ckpan (100%), and epithelial membrane antigen (EMA) (100%). In addition, the majority of them were overexpression of Vimentin (94.7%). However, TL-LGNPPA patients were more likely to have lower-expression of CK20 (24/24, 100%), smooth muscle actin (SMA) (7/7, 100%), Epstein-Barr virus-encoded RNA (EBER) (24/24, 100%), thyroglobulin (TG) (44/45, 97.8%), CK5/6 (25/27, 92.6%), S-100 (26/30, 86.7%), and P63 (12/14, 85.8%) for this population. All patients received surgical treatment, and only two patients (4.3%) received postoperative radiotherapy (the radiotherapy dose was not mentioned in the literature). No other adjuvant treatment strategies were found in all literature. With a median follow-up of 16 months (range, 3–240 months) (n=39), and 16% of them were follow-up for more than 5 years, no locoregional recurrences or distant metastasizes occurred.

Discussion

In this study, we reported one case of TL-LGNPPA and performed a comprehensive literature review to analyze the clinicopathological features, clinical management, and prognosis of TL-LGNPPA. Our results showed that TL-LGNPPA was a rare disease with unique clinical and immunohistochemical features, and excellent prognosis.

Different from the common histology of NPC, the pathogenesis and etiology of TL-LGNPPAs remain to be elucidated. This literature review found that most patients

were Asian (76.1%). Currently, no definitive risk factors, such as genetic predisposition, environmental, and radiation exposure, have been found to contribute to the development of the TL-LGNPPA (5). Epstein-Barr virus (EBV) has been confirmed to be associated with the development of NPC, especially in non-keratinizing histology (17). However, all patients with available EBER status were negative in our literature review. Therefore, the EBV status might not contribute to the development and progression of TL-LGNPPA. More studies are required to elaborate on the pathogenesis and etiology of this rare disease.

The diagnosis of TL-LGNPPA mainly based on the unique pathological and immunohistochemical features, including TTF-1 positive and TG negative. It should be distinguished with nasopharyngeal metastatic papillary thyroid carcinoma due to their similar pathological characteristics and similar expression of TTF-1 (9). TG was a useful biomarker to differentiate these two diseases. Lower expression of TG was found in TL-LGNPPA, and overexpression of TG was observed in nasopharyngeal metastatic papillary thyroid (11,18). TG is a secretory protein produced by vertebrate, which is synthesized in the thyroid cell, and stained positive in papillary thyroid carcinoma (8,19). In this literature review, all of the 46 patients stained positive in TTF-1, and of the 45 patients known the expression of TG, only one (2.2%) patient was positive for TG (16). Therefore, the expression of TG was also an important biomarker for the diagnosis of TL-LGNPPA.

It is also challenging to distinguish TL-LGNPPA from low-grade papillary adenocarcinoma of the salivary gland. Salivary gland types exclusively occur in the palate, but occasionally in the nasopharynx, which originate minor salivary glands. Almost all of them were found in older patients with more aggressive behaviors, including a higher risk of local recurrence and lymph node metastasis (20,21). However, the median age at onset of TL-LGNPPA in our study was 34 years, which was significantly younger than patients with low-grade papillary adenocarcinoma of the salivary gland, and was also significantly younger compared to common histology of NPC (median age at onset, 59 years) (22). In addition, salivary gland types showed overexpression of S-100, while TL-LGNPPAs were more likely to be lower expression of S-100 (5). Moreover, salivary gland types had an inferior outcome and required adjuvant systemic therapy, which was significantly different from TL-LGNPPAs that were surgically curable (21).

In our literature review, we found that CK7, CK19, Ckpan, EMA, and Vimentin were also overexpression in this rare disease. Therefore, these markers could also help to diagnose the TL-LGNPPA. In National Comprehensive Cancer Network guidelines, the common histological subtypes of NPC are mainly treated by radiotherapy and chemotherapy, and surgery is recommended in specific circumstances (23). In the imaging findings of TL-LGNPPA, the tumors exhibited exogenous growth without local invasion and lymph node metastasis, which was significantly different from the common histological subtypes of NPC (24). All patients in our literature review received surgical treatment, no locoregional recurrences or distant metastasizes occurred during the follow-up time. The woman in our institution also survived with no signs of local or distant recurrence after 93 months of follow-up. Therefore, surgery is the optimal treatment for this patient subset. In this literature review, two of them in our literature review received postoperative radiotherapy (8). The reasons for postoperative radiotherapy in these two patients were not described in the literature. Based on our findings, radiotherapy should be omitted for TL-LGNPPA.

To the best of our knowledge, our study had the largest sample size, including one patient from our institution and 45 patients from the literature review to assess the clinicopathological features, treatment, and prognosis of TL-LGNPPA.

Several limitations should be noted in this study. Firstly, there might be a selection bias that only English and Chinese literature were included. Secondly, among all biomarkers, only TTF-1 was examined due to the financial constraint of the patient at that time.

Conclusions

In conclusion, our study suggests that TL-LGNPPA is an extremely rare entity with unique disease features and excellent prognosis. Surgery is the optimal treatment for this population.

Acknowledgments

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-19-1973). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Affiliated Hospital of Xiamen University, and written informed consent was obtained from the patient for publication of this case report and any accompanying images (Approval number. KYH2019-044).

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Supplementary

Table S1 Clinical feature, treatment, and period of follow-up in the literature review of thyroid-like low-grade nasopharyngeal papillary adenocarcinoma

Author (reference)	Age (years)	Gender	Country	Symptoms	Tumor size	Treatment	Follow-up time
References in the main test							
Li *et al.* (4)	35	F	China	Dyspnea, nasal foreign body sensation, dry throat	1.5 cm × 1 cm × 0.8 cm	Surgery	16 months
Zhang *et al.* (5)	64	M	China	Nasal bleeding, nasal foreign body sensation	2 cm	Surgery	1 year
Carrizo *et al.* (6)	9	M	Argentina	Right nasal fullness, blood in the saliva	2.0 cm	Surgery	2 years
	13	M	Argentina	Unilateral nasal obstruction	1.5 cm	Surgery	15 years
Huang *et al.* (8)	26	F	China	Nasal obstruction, epistaxis, occasional rhinorrhea	1.5 cm	Surgery	8.8 years
	44	M	China	No associated symptoms	0.4 cm	Surgery + radiotherapy	5.5 years
	19	M	China	Nasal obstruction, epistaxis, occasional rhinorrhea	1.0 cm	Surgery	1.5 years
	29	M	China	Pharyngeal discomfort	1.0 cm	Surgery + radiotherapy	7 months
	36	F	China	Detection in physical examination	1.2 cm	Surgery	6 months
Li *et al.* (9)	15	F	China	Rhinorrhea, nasal congestion	2.5 cm × 2 cm	Surgery	2 years
Yang *et al.* (10)	27	F	China	Blocked nose, rhinorrhea, mild headache	2.1 cm × 1.8 cm	Surgery	3 years
	34	F	China	Tinnitus and loss of hearing	0.5 cm	Surgery	12 months
	23	M	China	Nasal discomfort	0.5 cm	Surgery	12 months
Baumann *et al.* (11)	26	M	United States	Headaches, nasal congestion, epistaxis	0.8 cm	Surgery	NA
Borsetto *et al.* (12)	15	F	Italy	Posterior nose bleeding	1.29 cm^3	Surgery	30 months
Sourati *et al.* (13)	35	F	Iran	Nasal obstruction with mild post-nasal drip	2 cm × 2 cm × 1 cm	Surgery	6 years
Le *et al.* (14)	50	F	Vietnam	Facial pain	4 cm	Surgery	NA
Oide *et al.* (15)	68	M	Japan	Sore throat, hemosputum	0.8 cm × 0.4 cm	Surgery	NA
Ozer *et al.* (16)	17	F	Turkey	Nasal obstruction	2.7 cm × 2.6 cm	Surgery	12 months
Present study	42	F	China	Pharyngeal foreign body sensation	0.5 cm × 0.5 cm × 0.5 cm	Surgery	7.7 years
References in the supplementary material							
Pineda-Daboin *et al.* (25)	9	M	United States	Nasal obstruction	NA	Surgery	5 years
	13	M	United States	Nasal obstruction	NA	Surgery	20 years
Ohe *et al.* (26)	25	M	Japan	Bloody sputum	0.8 cm	Surgery	13 months
	41	M	Japan	No associated symptoms	0.5 cm	Surgery	9 months
Li *et al.* (27)	26	F	China	Nasal obstruction, bloody sputum	1.5 cm × 1.3 cm × 1.4 cm	Surgery	8 months
Wu *et al.* (28)	36	F	China	No associated symptoms	NA	Surgery	3 years
Du *et al.* (29)	47	F	China	Bloody sputum, nasal foreign body sensation	1 cm × 0.8 cm × 0.6 cm	Surgery	3 years
Horino *et al.* (30)	25	F	Japan	Fever of unknown origin	1.7 cm × 1.2 cm	Surgery	3 years
Zhou *et al.* (31)	49	M	China	Nasal obstruction, bloody sputum	2.5 cm × 1.5 cm × 1.5 cm	Surgery	3 months
Oishi *et al.* (32)	47	F	Japan	Nasal obstruction	2 cm	Surgery	19 months
Niu *et al.* (33)	43	F	China	Neck discomfort	1.2 cm × 1.2 cm × 1.2 cm	Surgery	8 months
Fu *et al.* (34)	68	M	China	Pharyngeal foreign body sensation	NA	Surgery	12 months
Sillings *et al.* (35)	19	M	United States	Epistaxis, nasal congestion	1.5 cm	Surgery	NA
Appukutty *et al.* (36)	49	M	Britain	Snoring	0.6 cm × 0.6 cm × 0.5 cm	Surgery	9 months
Ozturk *et al.* (37)	24	F	Turkey	Nasal congestion	3 cm × 2.5 cm	Surgery	4 years
Petersson *et al.* (38)	39	F	China	Epistaxis, blocked nose, rhinorrhea	1 cm	Surgery	NA
Liu *et al.* (39)	38	F	China	Nasal foreign body sensation	1 cm × 0.7 cm × 0.5 cm	Surgery	15 months
Yao *et al.* (40)	44	F	China	Nasal obstruction, blood in the sputum	1.2 cm × 1 cm × 0.4 cm	Surgery	14 months
	67	M	China	Hoarseness, pharyngeal foreign body sensation	0.8 cm × 0.4 cm × 0.2 cm	Surgery	NA
Zhang *et al.* (41)	16	F	China	Nasal obstruction, rhinorrhea	1.5 cm × 1 cm × 0.5 cm	Surgery	NA
Dai *et al.* (42)	31	F	China	Bloody sputum	1.5 cm × 1 cm × 0.5 cm	Surgery	16 months
Liu *et al.* (43)	25	M	China	Nasal congestion	1 cm × 1 cm	Surgery	19 months
	57	M	China	Nasal congestion, dizziness	1.2 cm × 0.8 cm × 0.8 cm	Surgery	4 months
Tang *et al.* (44)	22	M	China	Epistaxis, nasal congestion, bloody sputum	1.5 cm × 0.9 cm × 0.9 cm	Surgery	1 year
García-Gómez *et al.* (45)	40	F	Spain	Right ear serous otitis media	2 cm × 2 cm × 1.7 cm	Surgery	1 year
Chen *et al.* (46)	34	F	China	Detection in physical examination	0.5 cm × 0.3 cm	Surgery	3.5 years

F, female; M, male; NA, not available.

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