

Original Article

Thyroid-like low-grade nasopharyngeal papillary carcinoma with a “biphasic” morphology: report of 3 cases and literature review

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Abstract: Objectives: Thyroid-like low grade nasopharyngeal papillary adenocarcinoma (LNPPA) is a very rare tumor occurred in nasopharyngeal area. Here we presented 3 cases, with one demonstrating biphasic differentiation which was even rarely encountered. Methods: Tumor's gross appearance, histology, immunohistochemistry and in situ hybridization were described. Their clinic-pathological features, as well as other cases in literature were also comprehensively reviewed. Results: All three tumors showed an exophytic mass grossly. Histologically, all consisted of papillary structure lined with cuboidal or columnar epithelium. A second population of spindle cell component was identified in one case which showed quite different morphology feature compared with the epithelial counterpart while demonstrating the same immunohistochemical phenotype. Strong and diffuse positivity of thyroid transcription factor 1 (TTF-1), CK19 and CK7 in both components, while negative expression in thyroidglublin (TG), CK5/6 and CK20 were observed. In situ hybridization (ISH) EBER showed no evidence of EBV infection. In a follow up of up to 2 years, no local recurrence or distant metastasis was identified. Conclusion: Thyroid-like LGNPPA is a rare carcinoma of low malignancy, with indolent bio-behavior and favorable outcome. Spindle cell component in it does not mean high grade transformation. Differentiation diagnosis should include other papillary mimickers, metastatic disease and ectopic lesion.

Keywords: Low grade nasopharyngeal papillary adenocarcinoma, nasopharyngeal adenocarcinoma, thyroid transcription factor 1

Introduction

Primary nasopharyngeal adenocarcinoma is a group of heterogeneous malignancies that comprise only 0.11%~6.2% of all nasopharyngeal carcinoma [1-3]. According to WHO 2004 [4], it was categorized into nasopharyngeal papillary adenocarcinoma and salivary gland-type carcinoma. Low grade nasopharyngeal papillary adenocarcinoma (LGNPPA) is a rare entity of nasopharyngeal papillary adenocarcinoma, with favorable outcome and indolent bio-behavior [5]. Among them, it lays a subgroup of tumor that additionally expressed TTF-1, and hence nominated as “thyroid-like” LGNPPA [6]. Morphologically, this rare tumor mimics thyroid papillary carcinoma, and no more than 40 cases were reported in literature.

In addition to its typical papillary growing pattern, an unusual spindle component or “biphasic” appearance was also noticed in 4 reports [7-10]. Here, we present three cases of thyroid-like-LGNPPAs, one of them also showing spindle cell component. The clinic-pathological features and the previous cases are also summarized.

Case report

The first case was a non-smoking 27-year-old Chinese female who had no family history of cancer. She complained a 2 years history of frequent blocked nose rhinorrhea accompanied with a mild headache. Nasendoscopy showed a 1.8 cm mass in the pharyngonasal cavity (**Figure 1A**). MR examination revealed an irregu-

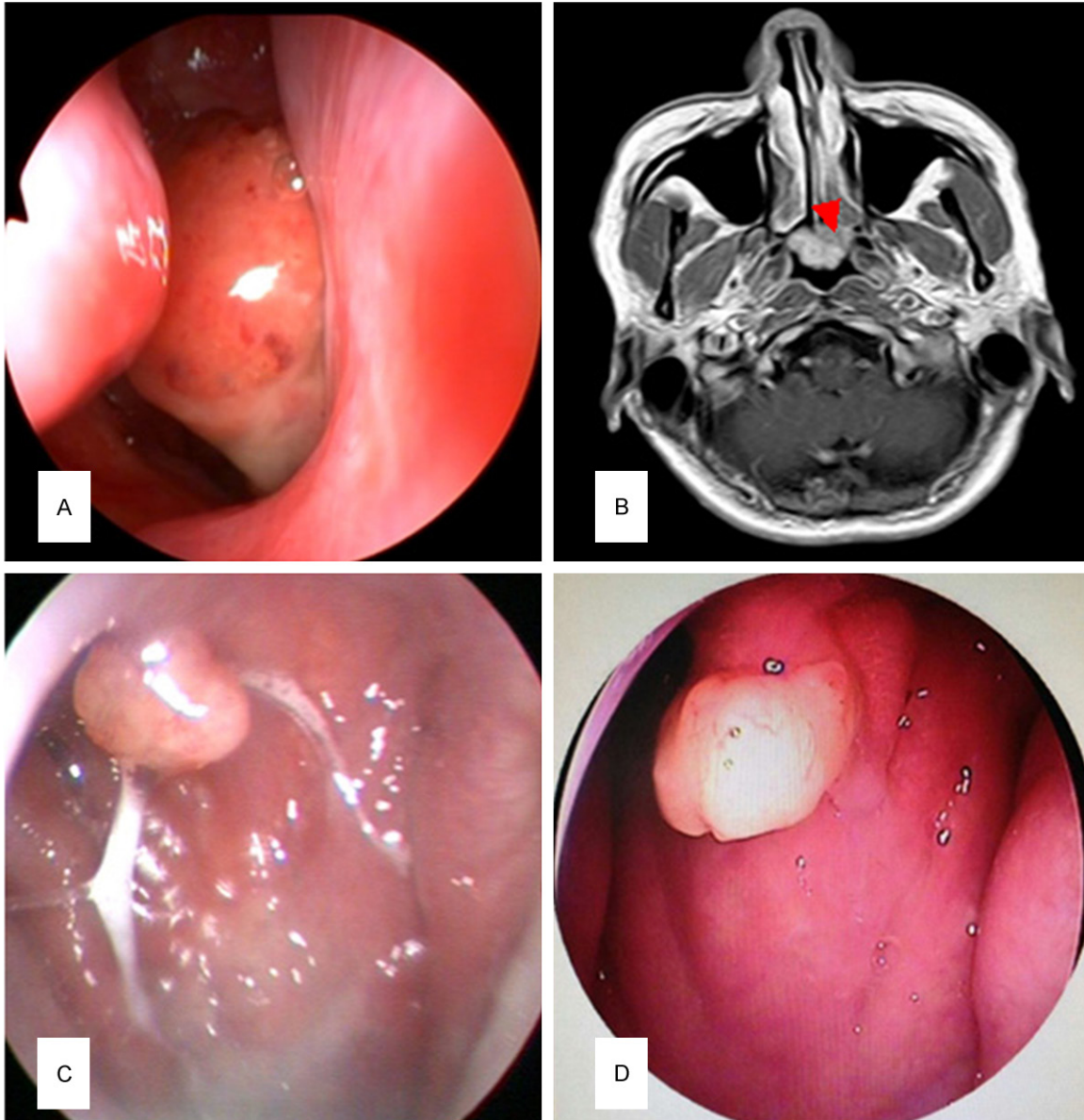


Figure 1. Gross appearance of LGNPPA. A. On nasoendoscopy, a mass was seen located in the pharyngonasal cavity. B. MR revealed the mass surrounded the posterior edge of the nasal septum leading to obstruction of the pharyngonasal cavity (arrow). C. A nodular mass was detected on top of nasopharynx. D. A polypoidal tumor was seen located on the back end of nasopharyngeal roof.

lar 2.1*1.8 cm mass surrounding the posterior edge of the nasal septum (**Figure 1B**). Both pharyngeal recess and pharyngeal opening of auditory tube are normal. No thyroid tumor or cervical lymphadenopathy was found with ultrasound examination. Breast ultrasound was negative. The mass was then sampled and sent for pathologic evaluation. Thyroid like LGNPPA was diagnosed and then the patient got an operation for the removal of the whole mass.

The second case was a 34-year-old woman, who presented with tinnitus and loss of hearing for 4 days and was referred to our hospital. No significant medical history was found. She did not complain other symptoms such as obstruction, epistaxis or headache. Thyroid function test showed normal thyroxine and thyrotropin level. Cervical ultrasound did not reveal thyroid nodules or lymphadenopathy. On nasopharyngoscopy, a nodular mass measuring 0.5 cm

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Table 1. Antibodies used for Immunohistochemical staining with source and lot numbers

Antibody	Vendor	Clone
Thyroglobulin	NovoPro	Monoclonal, 2H11
TTF-1	DAKO	Monoclonal, 8G7G3/1;
CK7	DAKO	Monoclonal, OV-TL 12/30;
CK19	DAKO	Monoclonal, RCK 108;
EMA	DAKO	Monoclonal, E29;
PR	DAKO	Monoclonal, PgR 636;
S-100	DAKO	Polyclonal Rabbit;
M-CEA	DAKO	Monoclonal, IL-7;
Calponin	ZSGB-BIO	Monoclonal, EP63;
Actin	DAKO	Monoclonal, 1A4

was detected on top of nasopharynx (**Figure 1C**). The nodule was then completely removed via nasal endoscope surgery.

The third case was a 23-year-old male, who complained nasal discomfort for 3 days and was referred to the sixth Affiliated Hospital of Sun Yat-sen University. He had no significant family history of cancer. He did not complain other symptoms such as obstruction, epistaxis or headache. No abnormality was found in thyroid and cervical area with ultrasound examination. Nasopharyngoscopy revealed a neoplasm on the back end of nasopharyngeal roof, measuring 0.5 cm. The nodule was then removed and sent for pathologic evaluation.

Materials and methods

The entire tumor tissue removed by nasal endoscope surgery was submitted for microscopic examination. Formalin-fixed, paraffin-embedded tissue samples were obtained. The 4-um sections were stained with H&E and examined. Immunohistochemical analysis was performed using the DAKO Autostainer Link 48 (DAKO, Glostrup, Denmark) using a panel of primary antibodies (**Table 1**) according to established protocols. In situ hybridization of EBV was performed according to the manufacture's protocol (Leica, Bond™ Ready-to-Use ISH EBER Probe, Catalog No. PB0589).

Results

Morphological features

Grossly, all three cases showed polypoid growth, with or without stalk, measuring from

0.5 cm to 1.8 cm located in pharyngonasal cavity or on top of nasopharynx (**Figure 1**). The tumors were soft, with a smooth surface (1 case showing hemorrhagic surface). No necrosis or calcification was observed on cut section. Incisional biopsies were performed in two of them (cases 2 and 3).

Histologically, all three cases were composed of papillae with fibro-vascular cores. The papillae were delicate or complex. The surrounding epitheliums were stratified, cuboidal or columnar, with abundant and eosinophilic cytoplasm showing only minor degrees of pleomorphism and hyperchromatism. The nuclei were round or oval, with vesicular chromatin and indistinctive nucleoli (**Figure 2**). Occasionally, the nuclei might tightly packed or overlap with each other, forming nuclear grooves. The cells showed mild atypia and mitosis were uncommon. The blood vessels of the fibro-vascular core were hyalinized in all three cases. In one of the three cases, small foci of psammoma bodies were found. All histological features referred to a “thyroid like” appearance. Continuity of tumor cells with the normal ciliated columnar epithelium was identified in all three cases. In addition, we also found spindle component in one case (Case 2), as mentioned in some reports [7, 8]. The spindle cells grew in sheet-like pattern, underlying or intermingling with the papillae. The cytoplasm was bland, with only mild atypia and rare mitosis. No necrosis was identified in all cases.

Immunohistochemical features

Immunohistochemistry (IHC) and in situ hybridization (ISH) were performed to aid the diagnosis, (**Figure 3A-D**). Both epithelial and spindle cells showed the same IHC profile, with strong nuclear expression of TTF-1, and cytoplasmic immune-reactivity of CK, CK7, CK19, EMA and vimentin. PR was variably expressed in both cell types. Thyroglobulin (TG) was negative. The myoepithelial marker like S-100, calponin, and actin were negative and hence ruled out the possibility of pleomorphic adenoma. M-CEA was also negative. All three cases showed negative result in ISH EBER examination.

Follow-up

All three patients recovered soon after the tumors were removed. The follow-up time of case 1 was 3 year and case 2 and 3 was 1 year,

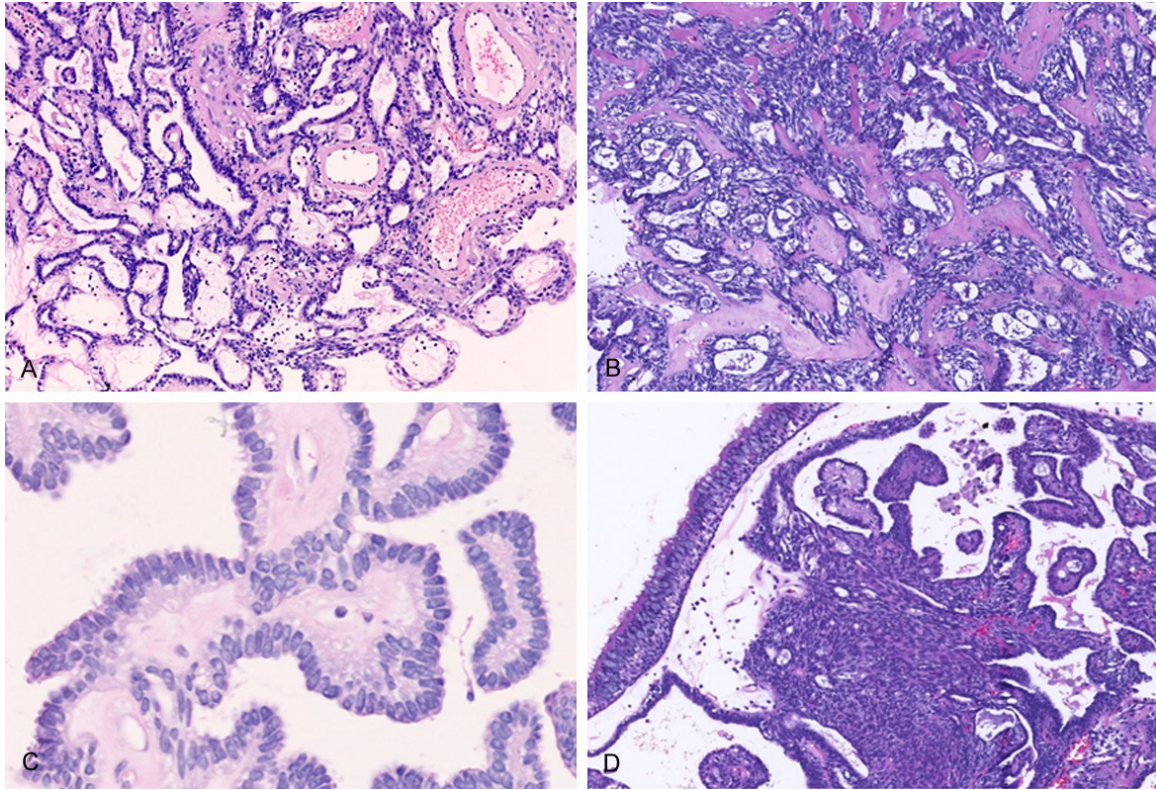


Figure 2. Histological features of LGNPPA. A, B. The tumor displayed papillary and gland like structures with hyalinized fibrovascular cores. H&E 10×. C. The papillae were lined by bland columnar or cubical epithelial cells which display crowded nuclei and inconspicuous nucleoli. H&E 40×. D. A prominent intervening spindle cell component was found. Normal ciliated columnar epithelium was identified overlying the tumor. H&E 10×.

no local recurrence or metastasis was reported.

Discussion

In nasopharynx, the most common malignancy is nasopharyngeal carcinoma, which had a close correlation with Epstein-Barr virus (EBV) infection [4]. Primary nasopharyngeal adenocarcinoma, however, only compose a minority of primary nasopharyngeal malignancy. Nasopharyngeal papillary adenocarcinoma includes LGNPPA and its rare thyroid-like variant. LGNPPA was first described by Wenig et al [5] as a distinct entity of adenocarcinoma arising from nasopharynx, with rather indolent behavior and good prognosis. Afterwards, Ma et al [6] identified TTF-1 expression in two cases of LGNPPA and separated a thyroid-like subtype. As very few cases were reported in literature, we summarized the clinical and biological features of all these cases and compared with our present cases (**Table 2**) [5-21]. Patients' age ranged from 9 to 68 years old, with a rather

equal gender distribution (Male to female: 1.27:1). Due to its location (septum, roof, lateral wall of nasopharynx, less often choanal vault and pharyngeal recess), the main symptoms included nasal obstruction, pharyngeal paraesthesia, epistaxis or blood in nasal discharge if hemorrhage was present. Other symptoms might include hearing loss, globus sensation or headache or symptomless in those accidentally encountered during routine body check. Nasopharyngoscopy often revealed a pink, exophytic or polypoid mass, with or without stalk, measuring from 0.3 cm to 4.0 cm. Except in one case [12], the tumor grew as a localized mass and rarely invaded into the peripheral tissue. Cervical ultrasonography and/or Computer Tomography showed negative findings of the thyroid and no cervical lymph nodes metastasis, indicating its nasopharyngeal origination and low progressiveness.

Microscopically, in addition to the typical papillary pattern mentioned above, an extra spindle cell component could occasionally be identi-

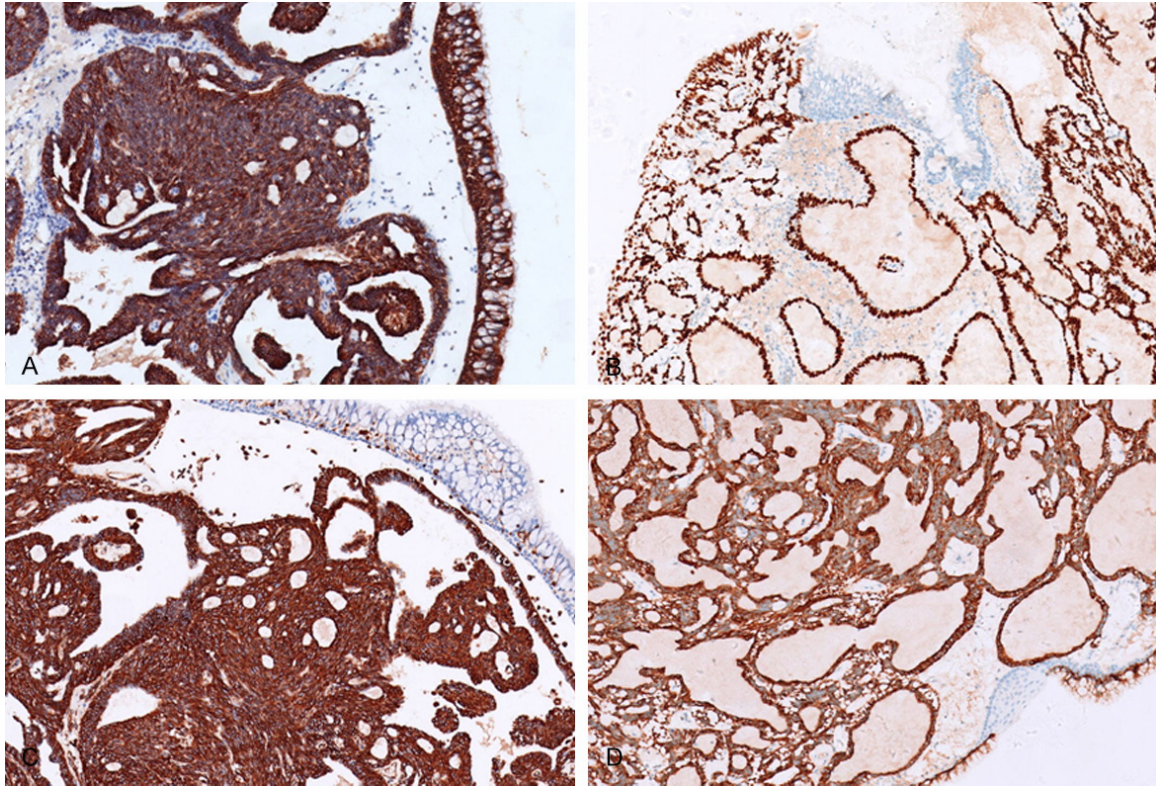


Figure 3. Immunohistochemical staining of LGNPPA. Tumors showed diffuse positive of CK (A), TTF-1 (B), Vimentin (C), and CK7 (D). Normal ciliated columnar epithelium which was TTF-1 negative was found to be continuous with tumor cells which were TTF-1 positive (B). Both the epithelial cells and the spindle cells showed diffuse positive of Vimentin (C). IHC10 \times .

fied, even in major predominance [7-10]. The spindle cells showed similar nuclear feature and IHC profile with their epithelioid counterpart. In our cases, we also identified spindle cells underlying the epithelium in one case, with similar IHC features. These findings might indicate that spindle component is not an uncommon phenomenon in this tumor. Based on their similar IHC pattern, the spindle cell might be a variation of the epithelium or merely spindle cell changes. The biphasic morphology of thyroid like-LGNPPA, together with its unique immuno-expression, should help make distinct differentiate with other primary or second tumors.

In literature, both the epithelial and spindle component showed strong positivity in CK, CK7, CK19 and vimentin, the same as in our cases [5-20]. EMA was also positive in a diffuse or focal pattern. There were varied expression of S-100, PR and P53. ISH EBER, as well as HPV detection revealed no evidence of viral

infection in this tumor [7, 10, 13, 14]. Except for only one case [17], all cases were negative in TG, the main distinguishing tool of thyroid papillary carcinoma. No BRAF-gene mutation was found, which was common in thyroid papillary carcinoma [8, 18]. In addition, thyroid-like LGNPPA showed strong and stable reaction with TTF-1, a useful marker for demonstrating thyroid and lung originating tumor, with high specificity and sensitivity [22]. Possible mechanism might include genomic amplification or aberrant expression as showed in other tumors e.g. malignant mixed Müllerian tumors, ovarian carcinoma, uroepithelial carcinoma and colorectal adenocarcinoma [23-26]. However, further studies are needed to provide sufficient evidence for the above hypothesis.

Differentiation diagnosis of adenocarcinoma in nasopharyngeal area should include the followings: first and foremost, a metastatic or ectopic thyroid papillary carcinoma (PTC) should be excluded. Given the same TTF-1 expression in

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Table 2. Clinical features of thyroid like LGNPPA

Reference	Year	No. of case	Age	Gender		Clinical presentation	Location	Size	Gross morphology	Follow up	Status
				M	F						
Wenig BM [5]	1988	9	37 (11~64)	5	4	airway obstruction	roof of nasopharynx, lateral nasopharynx, choanal vault	0.3- 4.0 cm	polypoid, nodular, papillary, granular, gritty or friable mass	1-15 year	no recurrence or distant metastasis
Nojeg MM [11]	1997	1	29		1	nasal blockage and discharge, ipsilateral hearing loss and facial weakness	/	/	/	15 m	no recurrence or distant metastasis
Luna MA [6]	2005	2	11 (9~13)	2		nasal fullness/obstruction, blood in his saliva	nasopharyngeal wall,	2 cm, 1.5 cm	exophytic with a papillary appearance	2 yr 15 yr	no recurrence or distant metastasis
Luna MA [12]	2006	13	/	/	/	/	/	/	/	5-20 yr	alive at 5-20 year
Chien CY [13]	2007	1	35		1	no associated symptoms	left nasopharynx	1 cm	yellowish pedunculated polypoid mass	3 yr	no recurrence or distant metastasis
Chang KP [14]	2008	1	68	1		globus sensation	roof of the nasopharynx	/	pedunculated mass with stalk	1 yr	no recurrence or distant metastasis
Sillings CN [15]	2010	1	19	1		epistaxis	free edge of the nasal septum	1.5 cm	pink, freely mobile, pedunculated	/	/
Uemura Y [7]	2010	2	33 (25, 41)	2		bloody sputum, or no associated symptom	junction of the nasal septum and the vault; roof of the nasopharynx	0.5-0.8 cm		9-13 m	no recurrence or distant metastasis
Li JF [16]	2011	1	26		1	nasal obstruction ,blood in nasal discharge	nasopharynx	1.5 cm	polypoidal mass	8m	no recurrence or distant metastasis
Fredrik Petersson [8]	2011	1	39		1	epistaxi, blocked nose and rhinorrhoea	the posterior edge of the bony septum	1 cm	polypoidal mass	/	/
Zhang RY [9]	2013	1	40		1	nasal obstruction	roof of nasopharyngeal	2 cm*1 cm	polypoidal mass	12 m	no recurrence or distant metastasis
Kosemehmetoglu K [17]	2013	1	17		1	nasal obstruction ,bloody nasal discharge	choanae	2.7*2.2 cm	bilobulated mass	1 yr	no recurrence or distant metastasis
Naoki Oishi [18]	2014	1	47		1	nasal obstruction	posterior edge of the left nasal septum	2 cm	Pedunculated and hemorrhagic mass	19 m	no recurrence or distant metastasis
Wu R [10]	2014	9	45.3 (23-62)	8	1	headache, nasal obstruction, blood in nasal discharge	posterior pharyngeal wall, pharyngeal recess, back end of Nasal septum,	0.3 cm-1 cm	polypoidal or pedunculated mass	1 m to 9 yr 8 m	no recurrence or distant metastasis
Chen ZZ [19]	2014	1	42		1	pharyngeal paraesthesia	nasal septum, near nasopharyngeal wall	0.5 cm	round protrusion	1 yr	no recurrence or distant metastasis
Jiang XJ [20]	2015	1	42		1	pharyngeal paraesthesia, nasal obstruction, bloody nasal discharge	back-end of nasal septum	2.8*3.5 cm	fragile and hemorrhagic mass, with suspicious stalk	2 yr	no recurrence or distant metastasis
Wu HP [21]	2015	1	36		1	epistaxis and nasal obstruction	roof of the nasopharynx	/	pedunculated tumor	31 m	no recurrence or distant metastasis
Present cases	2016	3	28	1	2	Blocked nose, headache, tinnitus and loss of hearing	nasal septum, nasopharyngeal roof, top of nasopharynx	0.5cm-2.1cm	Irregular or polypoid	12 m-36 m	no recurrence or distant metastasis

both PTC and thyroid like LGNPPA, TG would help exclude thyroid origin tumors, which did not react with thyroid like LGNPPAs. With different covering epithelium, Schneiderian papilloma and squamous papillomas were easy to rule out. Papillary variant of polymorphous low-grade adenocarcinoma (PLGA) showed diffuse S-100 and Galectin-3 positivity and other myoepithelial expression, which were lack or focal expressed in thyroid like LGNPPAs [4]. In biphasic cases, an extra exclusion should be made among pleomorphic adenoma (PA) and synovial sarcoma (SS). The latter displayed more cellular atypia and higher cellularity. A panel of IHC and FISH were reliable in helping distinguish these two entities. Useful markers include myoepithelial markers (positive in PLGA and PA) and t(X;18) in the FISH study or SYT-SSX1/SSX2 fusions transcripts in PCR (SS). Since the spindle component of thyroid like LGNPPA did not react with CEA, calcitonin and chromogranin, an ectopic medullary thyroid carcinoma (MTC) was easy to be excluded. To sum up, the application of IHC panel, or ISH EBER and FISH when necessary, could help differentiate with most of primary or secondary tumors at this site.

The exact origination of thyroid like-LGNPPA remains unknown. Generally, it was considered to originate from nasopharyngeal surface mucosa [8]. In many reports, as well as our present cases, continuity of the tumor cells with the normal epithelial lining was found, but it is not sure whether this means the origin of the tumor or just an involvement of the surface epithelial by the tumor. It was still under debate whether it was an ectopic thyroid origin as its IHC profile lacked TG expression. With only one exception in 2011 [16] (no detailed data could be achieved), there was no evidence of EBV or HPV infection in thyroid like LGNPPA. Pineda DK reported one case with turner syndrome [11], a clinical syndrome associated with many gynecologic malignancies, but whether LGNPPA in turner syndrome was an incidental event or with innate correlation still need prudent inspection.

Radical removal of the tumor was the major treatment. Given its complex anatomic location, surgical modality might include transpalatal pathway, transoral approach, facial translocation approach or simply endoscopic excision [7, 8, 12, 27, 28]. Radiotherapy or photodynamic therapy with topical 5-aminolevulinic acid

was applied in rare invasive cases, or to avoid local recurrence after incomplete resection [5, 12, 29]. As there were still limited experience, whether adjuvant therapy should apply or not still need to be further investigated. In the follow up periods of up to 15 years, there was no event of local recurrence or distant metastasis, including those with adjuvant therapy.

Conclusion

In conclusion, we presented three cases of thyroid like LGNPPAs and summarized the clinic-pathological features in literature. It was a rare subtype of primary nasopharyngeal carcinoma with TTF-1 expression. In addition with its typical papillary pattern, spindle component could be identified occasionally. As this entity presented with very good prognosis, a panel of IHC needed to be applied in order to distinguish with its mimickers such as thyroid papillary carcinoma. The biphasic appearance of this tumor, positive expression in TTF-1 while negative in TG, might help make reliable differentiation.

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Disclosure of conflict of interest

None.

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