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Biphasic 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 tumor type. This tumor closely resembles conventional papillary thyroid carcinoma and exhibits a solid spindle cell component, which is biphasic in appearance. The distinction of this low-grade tumor from other aggressive malignant neoplasms is important for clinical and therapeutic management. Here we present the case of a 19-year-old female who was diagnosed with a biphasic TL-LGNPPA. We also summarize the clinicopathological features, differential diagnosis, and clinical management of TL-LGNPPA with a spindle cell component.

Keywords: Nasopharyngeal cancer, thyroid-like, biphasic, low-grade, spindle, papillary, TTF-1, adenocarcinoma

1. INTRODUCTION

Nasopharyngeal carcinomas (NPCs), specifically the keratinizing and non-keratinizing squamous cell types, are considered by far the most frequent nasopharyngeal malignant tumors. Conversely, primary nasopharyngeal adenocarcinomas (PNPACs) are rare and account for ≤5% of all nasopharyngeal malignancies (El-Naggar et al., 2017). Generally, PNPACs are classified into the following two histologically heterogeneous subtypes: those that originate as of the nasopharyngeal superficial mucosa, such as low-grade nasopharyngeal papillary adenocarcinomas (LGNPPAs), and those that originate from the submucosal seromucous salivary glands, such as polymorphous low-grade adenocarcinomas, mucoepidermoid adenocarcinomas, and adenoid cystic carcinomas (El-Naggar et al., 2017; Wenig et al., 1988). In 1988, LGNPPA was first designated in Wenig et al., (1988) as a primary nasopharyngeal surface epithelial adenocarcinoma with lethargic clinical activities and low-grade histological topographies.

Thyroid-like LGNPPA (TL-LGNPPA) is a rare malignant tumor of the nasopharynx that represents a small proportion of LGNPPAs and shows a

papillary growth pattern and aberrant expression of thyroid transcription factor 1 (TTF-1). Carrizo and Luna (2005) reported the first case of TL-LGNPPA in 2005, and since then, the number of cases published in English medical reports has been very low. Recently, five cases of TL LGNPPA with a spindle cell component were described. Those tumors were referred to as "biphasic low-grade papillary nasopharyngeal papillary adenocarcinomas" (Yokoi et al., 2018; Petersson et al., 2011), (Table 1).

Here we report a sixth case, to the knowledge of the authors, of TL-LGNPPA through biphasic morphology in a teenage female; this tumor showed papillary structures and spindle cells. Furthermore, we reviewed the medical literature of published cases that contained a spindle cell component.

2. CASE REPORT

A 19-year-old Saudi female patient, who was a non-smoker and had no medical history, presented with complaints of bilateral nasal obstruction for 6 months. This symptom was associated with postnasal drip as well as intermittent epistaxis; however, the patient did not experience headache, otitis media, or hearing loss. The patient had no significant family history of cancer. Physical examination revealed non-palpable cervical lymph nodes, and the throat, neck, and ears were unremarkable. Flexible nasopharyngoscope exam discovered a 3 cm exophytic, fragile, and pinkish mass that filled the nasopharynx. Additionally, a pedicle emerging from the superior posterior nasal septal wall primarily on the right side was also observed. The case endured a trans-nasal endoscopic resection of the mass after which the unfixed specimen was sent for histopathological assessment.

Diff-Quik-stained touch imprint cytology smear was also conducted, which revealed bland columnar cells, some of which had formed papillae-like structures (Figure 1). Hematoxylin and eosin staining exhibited a biphasic non-encapsulated tumor that had infiltrated the adjacent stroma. The tumor also exhibited papillary and solid architecture, and less frequently, glandular configurations. This biphasic tumor developed beneath the metaplastic squamous epithelium of the nasopharyngeal surface (Figure 2A). The papillary regions showed hyalinized fibrovascular cores covered by a pseudostratified layer of bland columnar to cuboidal epithelial cells, which on higher magnification demonstrated enlarged and elongated overlapping nuclei with fine chromatin and inconspicuous nucleoli. Occasional tufting of the cells and nuclear grooving were also noted. The spindle cell component comprised the solid part of the lesion. Gland-like spaces containing intraluminal homogenous pink secretory material were seen scattered within the papillary areas (Figure 2B). This material demonstrated a red to rose-red positive reaction to the Periodic Acid–Schiff (PAS) stain (Figure 2C). Psammoma bodies were scattered within the papillae (Figure 2D). Mitotic figures were rare, and necrosis and lymphovascular and neuronal invasion were not identified.

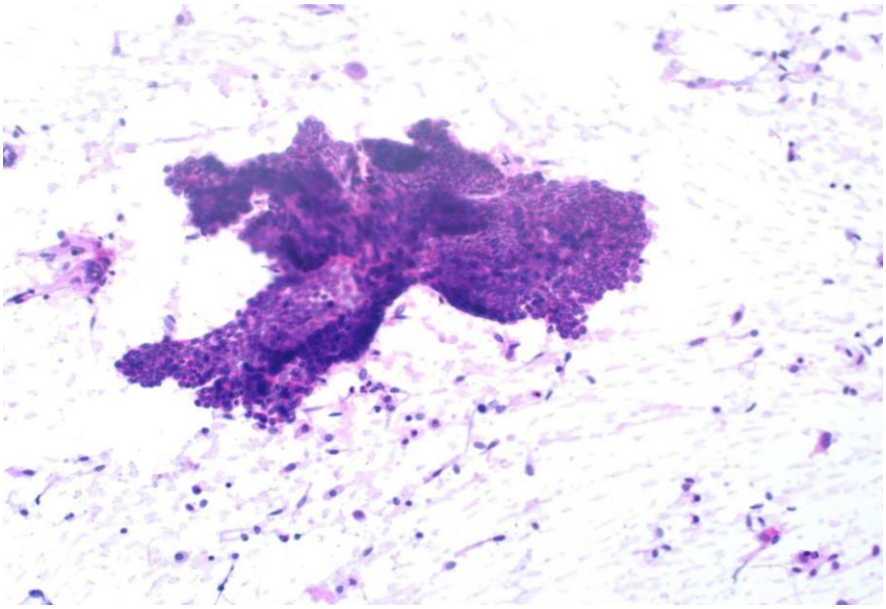

Figure 1 Biphasic Thyroid-Like Low-Grade Nasopharyngeal Papillary Adenocarcinoma with cluster of bland columnar cells forming a papillae-like structure *(arrow)* (Diff-Quik, original magnification x10).

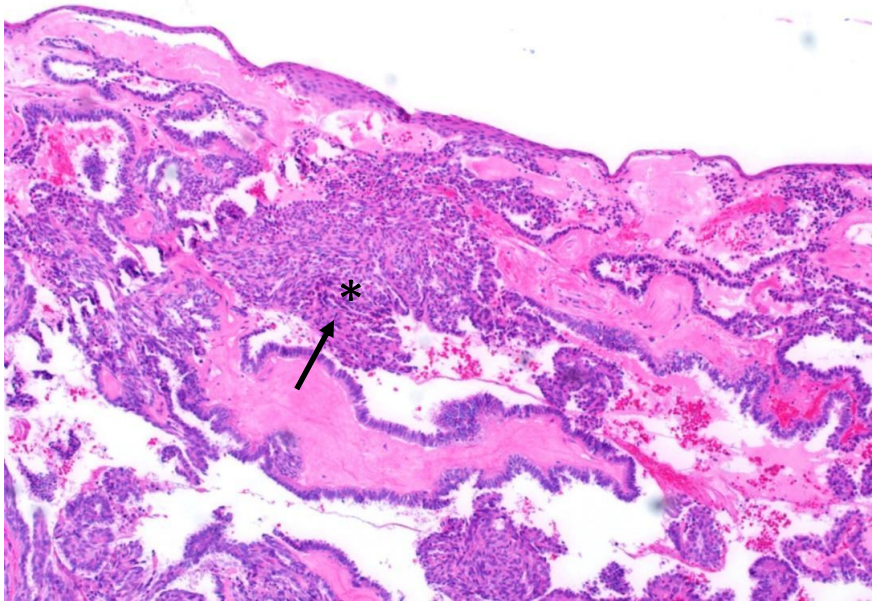

Figure 2A Low power view surface metaplastic squamous epithelium and underlying biphasic tumor with papillary *(arrow)* and solid *(asterisk)* growth (H&E, original magnification x10).

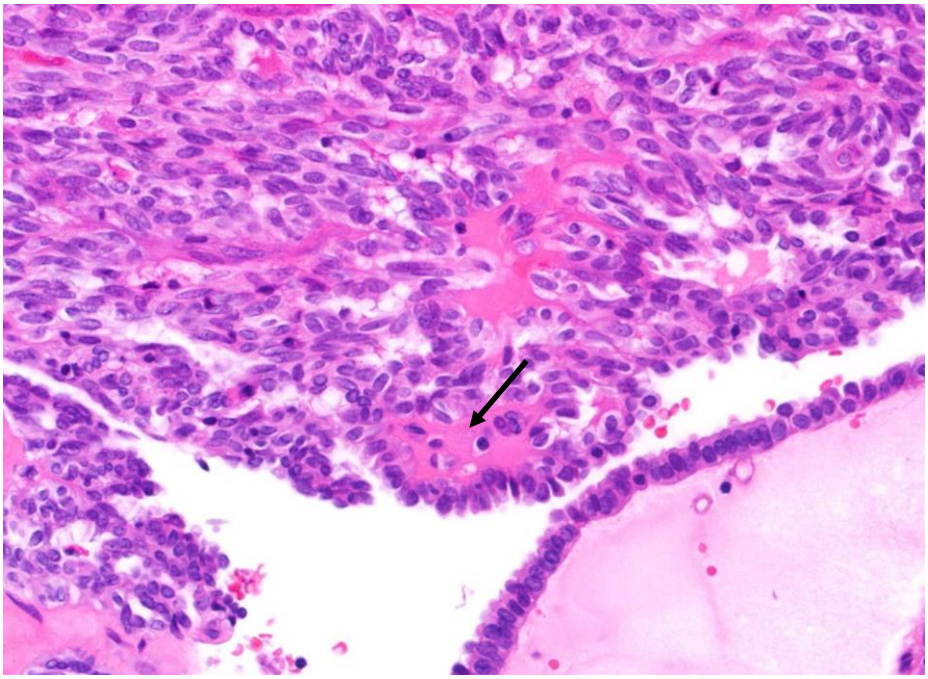

Figure 2B Intermediate power areas of gland-like lumina with homogenous pink secretions *(arrow)* (H&E, original magnification x20).

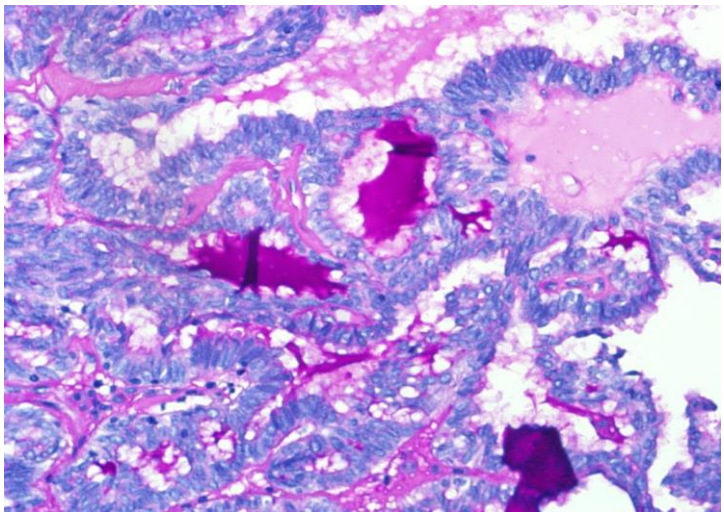

Figure 2C PAS-positive red to rose-red staining in the intraluminal secretions. (Periodic Acid–Schiff (PAS) stain, original magnification x20)

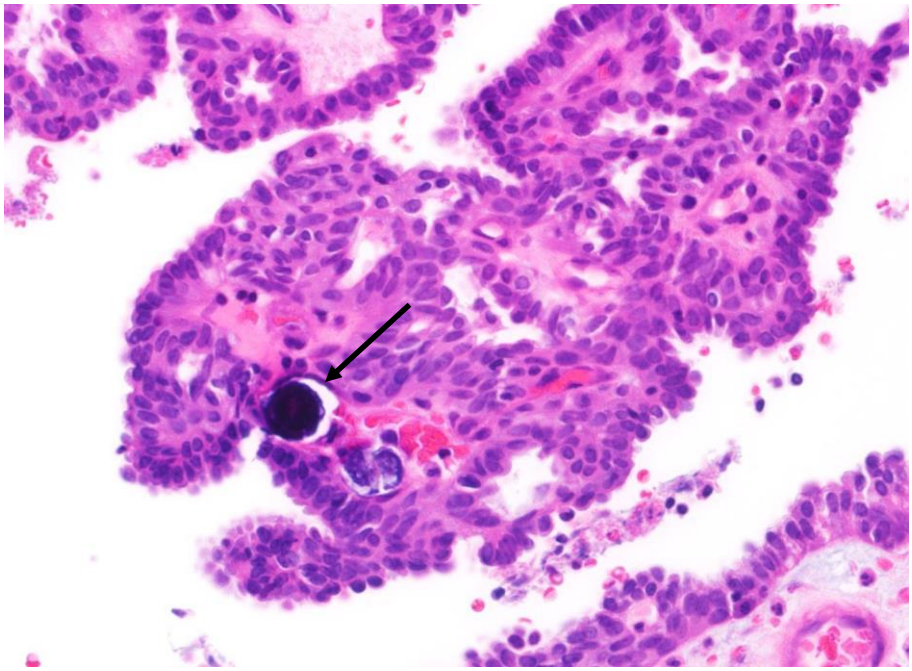

Figure 2D Psammoma body *(arrow)* is situated within the papillae, suggesting papillary thyroid carcinoma (H&E, original magnification x20).

According to an immunohistochemical analysis, the swelling cells in addition to the basal layer were positive for vimentin (Figure 3A). Strong and diffuse positivity for cytokeratin-7 (CK-7) was noted in the growth cells but not in the metaplastic surface epithelium (Figure 3B). Tumor cells were also positive for CK-19 (Figure 3C). All components of the tumor (papillary, glandular, and spindle structures) and the surface of the metaplastic epithelium were positive for TTF-1 (Figure 3D, 3E). This implies that the growth ascended as of the superficial epithelium of the nasopharynx, although squamous metaplasia in the underlying tumor was not observed in this case. Multifocal positivity for P16 was detected in the papillary, glandular, and spindle cell components (Figure 3F, 3G), whereas the growth cells remained negative for P63, thyroglobulin, and PAX-8 (Figure 3H, 3I, 3J). No immunoreactivity was seen for carcinoembryonic antigen (CEA), chromogranin A, calcitonin, or S100. A few weeks later, the patient underwent further endoscopic sphenoidectomy and nasopharyngectomy to ensure tumor- free surgical margins.

Follow-up data revealed no evidence of local recurrence for up to 3 years after complete surgical resection of the mass. Paper knowledgeable agreement was gotten from the parent of the patient regarding writing and publishing all the information mentioned in this case report.

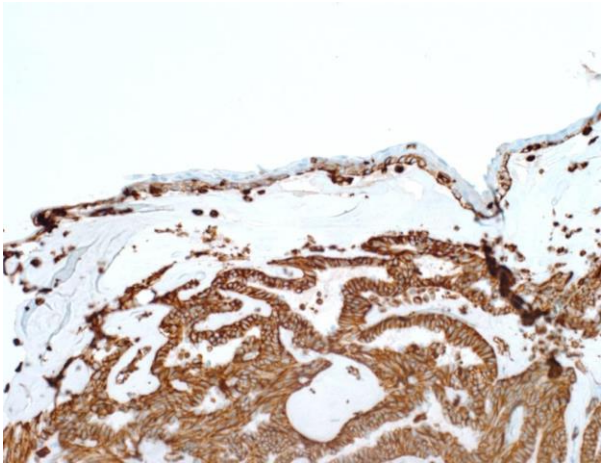

Figure 3A Vimentin positivity in the tumor (arrow) along with the basal layer (arrowhead). (Immunohistochemistry, original magnification 10x).

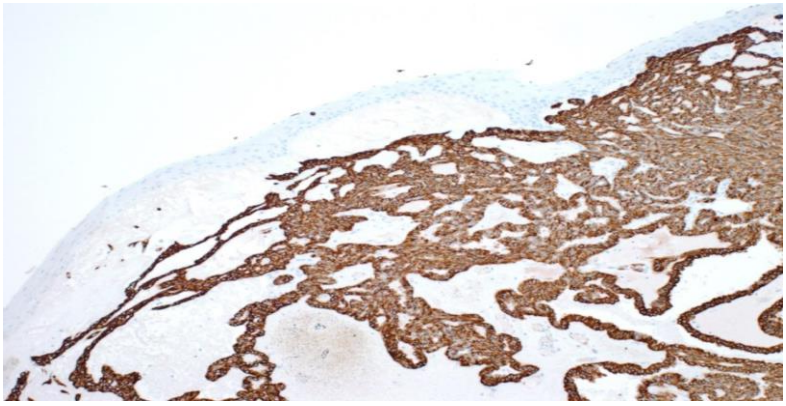

Figure 3B CK7 positivity is noted in the tumor *(arrow)* and not in the squamous metaplastic epithelium. (Immunohistochemistry, original magnification 10x).

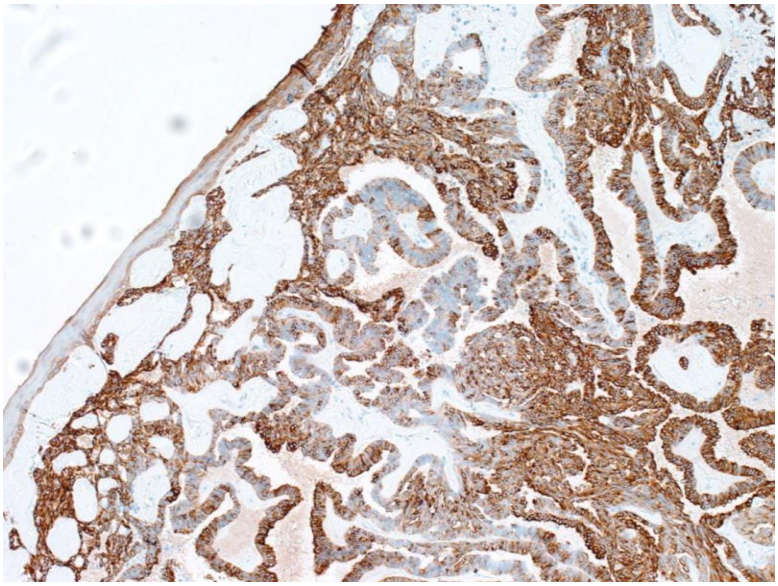

Figure 3C CK19 is positive in the interior the tumor cells besides the basal layer. (Immunohistochemistry, original magnification 10x).

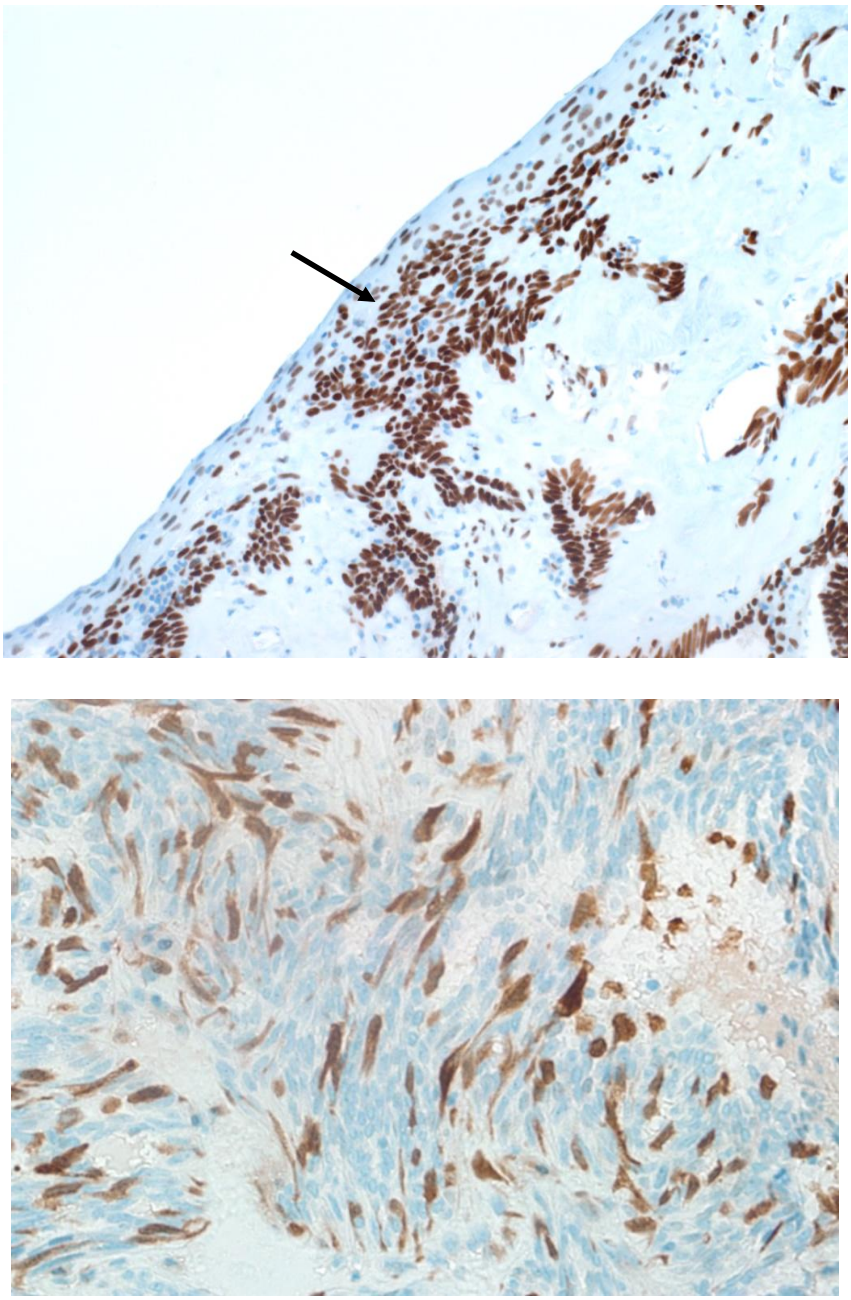

Figure 3D, 3E TTF-1 positive in the nuclei of cancer jail cell located in the surface epithelium (arrow), papillae and the solid component. (Immunohistochemistry, original magnification 10x).

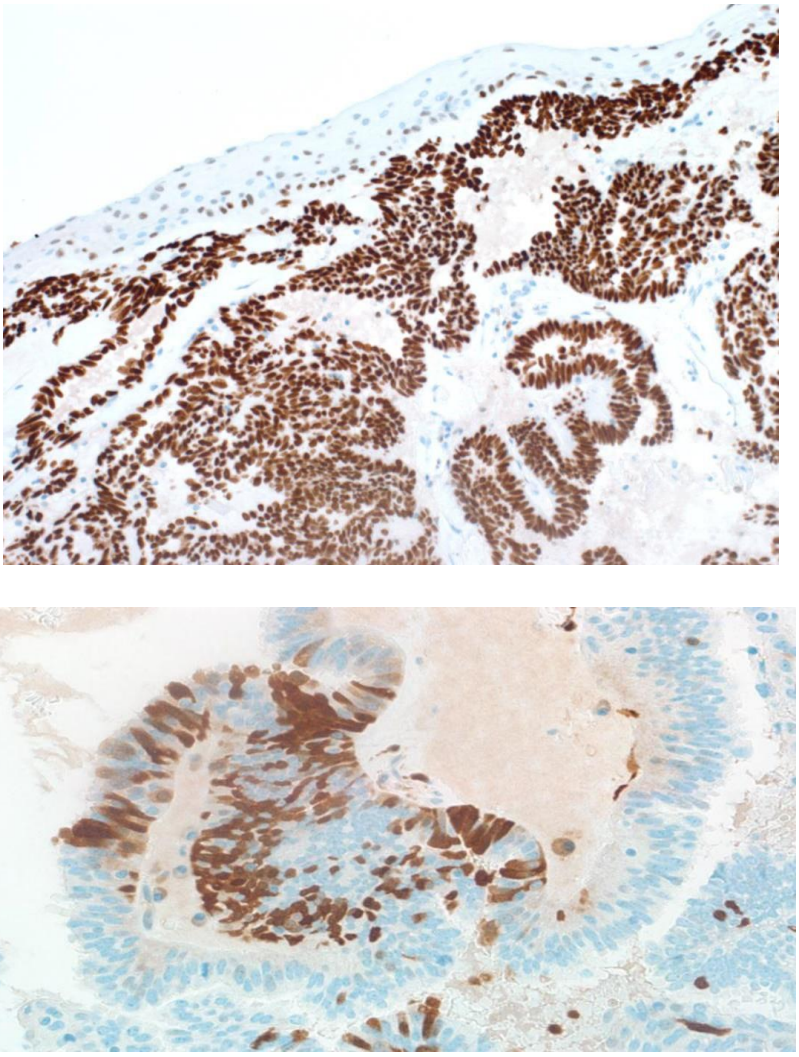

Figure 3F, 3G. P16 multifocal, nuclear and cytoplasmic positivity in the papillary, glandular, and spindle cell components (Immunohistochemistry, original magnification 20x).

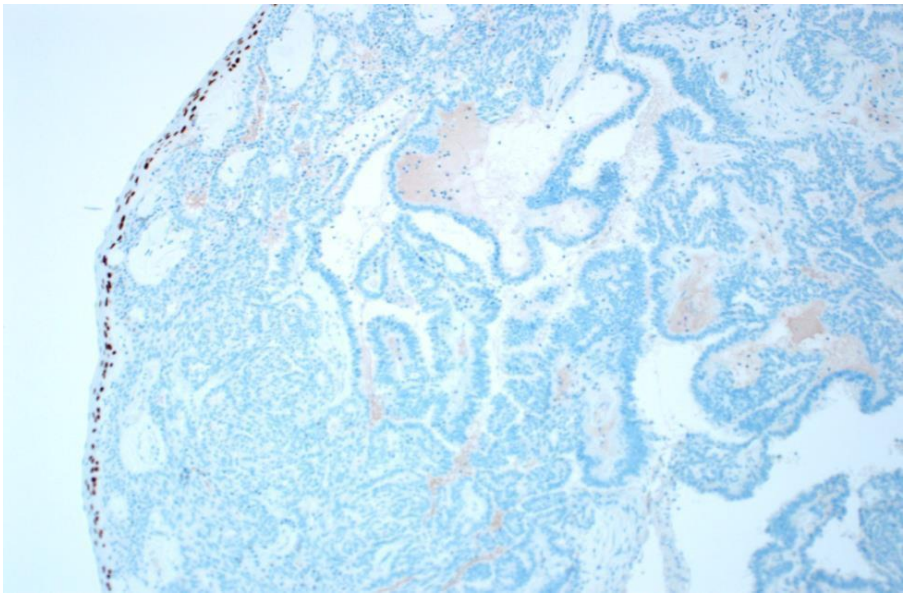

Figure 3H P63 negative in the cancer cells. Positivity is within the basal layer *(arrow)* (Immunohistochemistry, original magnification 10x).

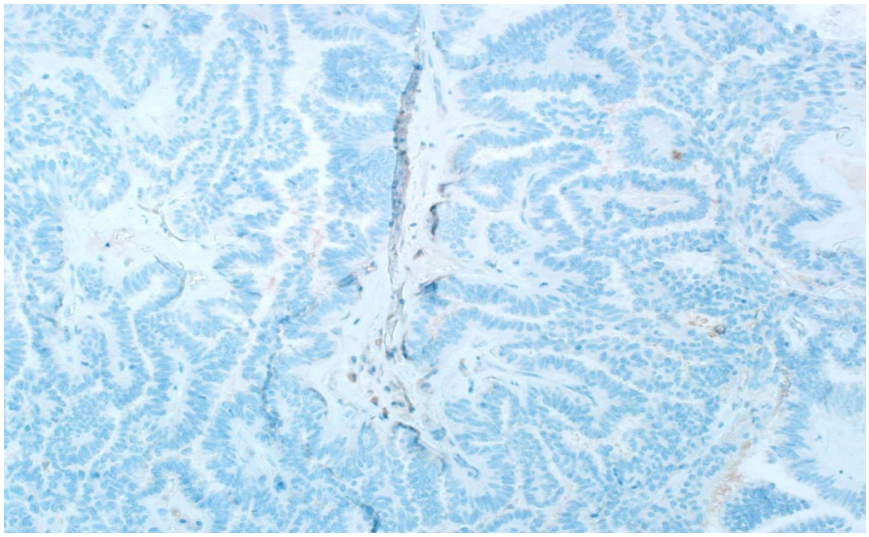

Figure 3I Thyroglobulin negative in the cytoplasm of tumor cells. (Immunohistochemistry, original magnification 20x).

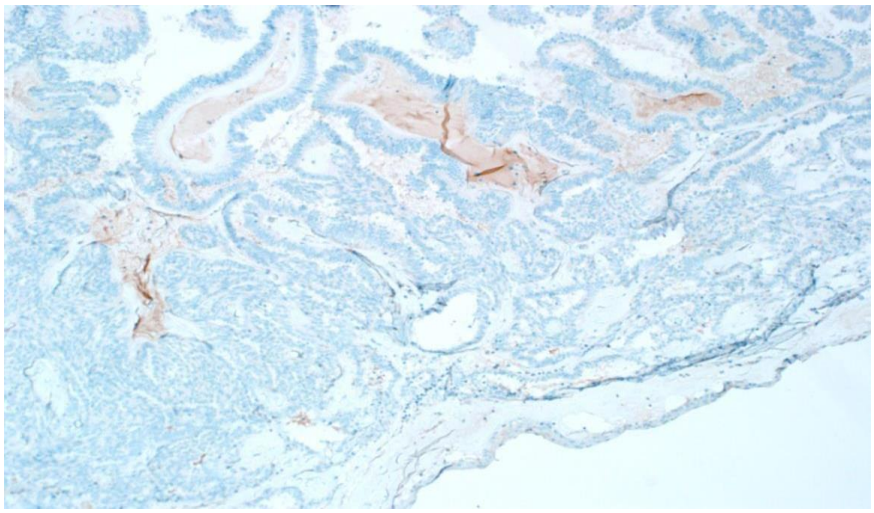

Figure 3J PAX-8 negative in the nuclei of cancer cells (Immunohistochemistry, original magnification 10x).

Table 1 Clinicopathological features of reported cases of Biphasic Thyroid-Like Low-Grade Nasopharyngeal Papillary Adenocarcinoma.

Study	Sex	Age	Ethnicity	Presenting symptom	Tumor location	Microscopic appearance of spindle cells	Immuno-histochemical features of spindle cells	Treatment modality	Disease-free survival
Peterss on et al. [5]	F	39	Asian	Epistaxis, rhinorrhea, and nasal obstruction	Posterior nasal septum	> 50% spindle cell component	Same as columnar cells	Endoscopic resection	NA
Oishi et al. [29]	F	47	NA	Nasal obstruction	Posterior nasal septum	Focal spindle cell component	NA	NA	19 months
Ohe et al. [38]	M	25	Asian	NA	Roof of the nasopharynx	Focal spindle cell component	NA	NA	NA
Ohe et al. [38]	M	41	Asian						
Yokoi et al. [4]	M	65	NA	Asymptomatic; discovered during screening for laryngeal cancer	Posterior nasal septum	> 50% spindle cell component	Same as columnar cells	Endoscopic resection	34 months

Present case	F	19	Asian	Epistaxis, postnasal drip, and nasal obstruction	Posterior nasal septum	> 50% spindle cell component	Same as columnar cells	Endoscopic resection	40 months

Abbreviations: M- Male, F- female, NA- not applicable.

3. DISCUSSION

In 2005, TL-LGNPPA was included in the WHO classification of malignant epithelial growths of the nasopharynx (Thompson, 2006). Since then, rare cases have been pronounced in the medical literature, with a mean overall prevalence of 17.9% among all nasopharyngeal adenocarcinomas (Wenig et al., 1988; Guo et al., 2009; Pineda-Daboin et al., 2006). According to the WHO, LGNPPA is grossly defined as a soft and gritty mass that appears as exophytic, polypoid, or nodular (Carrizo & Luna, 2005). Now, we existing a case of TL-LGNPPA, which is a subset of LGNPPA that displays expression of TTF-1. However, no histological dissimilarities were perceived amid the TTF-1-positive "thyroid-like" neoplasms and the TTF1-negative lesions. Additionally, data of published literature have not confirmed any biological or clinical differences (Yokoi Petersson et al., 2011).

According to currently available literature, this unique tumor has an equal sex distribution and affects individuals of various ages from the first to sixth decades of life (median age: 34 years) (Zhang et al., 2017). This tumor arises anywhere along the nasopharyngeal walls and has a propensity to affect the lateral and posterior walls as well as the rooftop of the nasopharynx (Wenig et al., 1988). The most frequent presentation is nasal obstruction, but other symptoms include rhinorrhea, epistaxis, postnasal drip, and otitis media with or without hearing loss. One case was detected incidentally through a patient workup performed for long-term fever of unidentified cause (Kakkar et al., 2019).

Microscopically, TL-LGNPPA with a spindle cell population has been described in recent and older studies. Table 1 illustrates the clinicopathological characters of the cases with this tumor type. The biphasic appearance of the current case led us to suspect biphasic synovial sarcoma (SS), which can exhibit papillary architecture and TTF-1 positivity according to previous studies (Chan et al., 2003; Lewis et al., 2005). Nevertheless, the low-grade malignancy microscopic morphology and diffuse CK positivity of the spindle cells indicated that a diagnosis of SS was unlikely. Reportedly, the pattern of CK-7 staining in spindle cells of SS is focal (Stacchiotti & Van, 2018). Moreover, the probability of a metastatic papillary thyroid carcinoma had to be excluded because of its morphological resemblance to this tumor type and because of the TTF-1 positivity. However, negative stain for thyroglobulin and PAX-8 in conjunction with positive vimentin staining is not consistent with a PTC diagnosis.

Conversely, Ozer et al., (2013) reported focal thyroglobulin expression in a recent case of TL-LGNPPA and recommended caution to rule out metastatic papillary thyroid malignancy in such circumstances. The identification of medullary thyroid carcinoma (MTC) with metastatis must be considered due to TTF-1 and vimentin positivity in addition to thyroglobulin negativity. MTC may also show spindle cell morphology and a papillary pattern. However, the absence of immunohistochemical positivity for chromogranin A, calcitonin, and CEA in the current patient was inconsistent with such a diagnosis.

Based on the low-grade histological features of the present case and the proximity of salivary gland tissue, salivary gland neoplasms were encompassed in the distinction identification. A papillary variant of polymorphous low-grade adenocarcinoma (PLGA-p) displays bland cuboidal cells in papillary, cribriform, and/or solid arrangements. PLGA-p and the present case share the characteristics of vimentin positivity and P63 negativity. However, S100 positivity, which characterizes PLGA-p, has not up till now been described in TL-LGNPPA (Rooper et al., 2015). Moreover, TTF-1 expression is consistently absent in PLGA-p. The papillary variant of acinic cell carcinoma has been designated as per a papillary cystic mass, in contrast to the present case.

In the papillary variant of acinic cell carcinoma, the neoplastic cells frequently show evidence of serous-acinar differentiation with characteristic PAS-positive, diastase-resistant cytoplasmic zymogen granules. Acinic cell carcinoma reveals S100 and vimentin-positive neoplastic cells by immunostaining (Zarbo et al., 1986; Nakazato et al., 1985; Kahn et al., 1985; Hara et al., 1985; Dardick et al., 1987). Epithelial-myoepithelial carcinoma can display papillary and solid architecture, and the myoepithelial cell constituent can show spindle cell morphology; however, unlike in the present case, these spindle cells are typically optimistic for S100 and smooth muscle actin (Jain et al., 2006).

Papillary neoplasms that arise from the nasopharyngeal surface and posterior sinonasal tract should be added in the discrepancy identification and workup. The first type is the papillary variant (ITAC-p) of the intestine category of adenocarcinoma. This neoplasm displays a high degree of nuclear atypia, exhibits mucinous differentiation, and is commonly positive for CK20 and CDX-2 (Ortiz-Rey et al., 2005). The second Schneiderian papilloma (SP), which have pronounced in the nasopharynx (Sulica et al., 1999; Low et al., 2002) and has the same morphology as SP located in the primary sinonasal tract (i.e., fibrovascular cores lined by non-keratinizing squamous, transitional, or pseudostratified epithelium with oncocytic features). The histological in addition to

immunohistochemical characteristics of the two neoplasms were not observed in this case. The distinction of biphasic TL-LGNPPA from these neoplasms is significant to decide the prognosis and to administer the appropriate therapy. Moreover, the spindle cell constituent in TL-LGNPPA may increase the differential diagnoses and hinder an accurate diagnosis.

The etiology of spindle cell development is still unknown; however, spindle cells were present in a recent case of TL-LGNPPA, which contained scattered foci of squamous cells that exhibited positive TTF-1 immunostaining (Oide et al., 2017). According to the published cases of biphasic TL-LGNPPA (Table 1), spindle cell phenotype may result without squamous differentiation, and it is unclear whether the presence of spindle cells affects the prognosis of TL- LGNPPA because of the small number of cases. Considering the histogenesis of this peculiar neoplasm, several researches have recommended that this tumor type may arise from the superficial epithelial cells of the nasopharynx (Chu & Yue, 2012), whereas others have suggested otherwise (Petersson et al., 2011). This difference in opinion is caused by the great rarity of this tumor. One reason we believe that TL-LGNPPA may originate from the surface epithelium is grounded by the transition of neoplastic cells from the surface, the TTF-1 expression in the surface metaplastic epithelium, and the connection of this positive reaction downward to the tumor cells (Figure 3A). These findings indicate that this tumor originates from the superficial, relatively than arising elsewhere in the nasopharynx and extending to the epithelial surface.

TTF-1 is an important immunohistochemical marker for TL-LGNPPA that is stated in all reported cases to date. This protein is a homeodomain-containing tissue-specific transcription factor encoded by the *NKX2-1* gene and plays an essential role in cellular differentiation both in the lung besides thyroid gland (Holzinger et al., 1996). Nonetheless, positive TTF-1 stain was detected in several other organs including the brain, endometrium, breast, and colon (Ordonez, 2012). The explanation by which LGNPPA expresses TTF-1 is still unclear. A recent case report proposed three theories to explain the pathogenesis. First, TL-LGNPPA may arise from ectopic thyroid tissue that resides in the nasopharynx. Second, the abnormal TTF-1 expression could be produced by a gene rearrangement that affects *NKX2-1*, and ultimately, TTF-1 expression. Lastly, the dysregulation of the NKX2-1 gene may be led by cancer cell reprogramming (Oishi et al., 2012). The highly specific (8G7G3/1) anti- TTF-1 clone for both lung besides thyroid tissue is used in this case (Vidarsdottir et al., 2018).

Epstein–Barr virus (EBV) is concerned in the pathogenesis of NPC, particularly of the WHO types II and III tumors, but less well-established for instance an origin of WHO type I (Guo et al., 2009; Kuo & Tsang, 2001), in which human papillomavirus (HPV) has been suggested to comedy a heroine in addition could be concomitant with the development of such neoplasms (Giannoudis et al., 1995; Punwaney et al., 1999). The results of published *in-situ* hybridization studies of EBV-encoded RNA and HPV DNA have shown that TL-LGNPPAs were all negative for EBV and high-risk (HPV) strains; nevertheless, extra investigation is mandatory to endorse the relationship of this tumor type with EBV and HPV.

The patient presented was not exposed to any non-viral environmental agents, such as cigarette smoke, solvents, or wood fire, and did not partake in the dietary consumption of preserved meat, which have all been shown to be risk factors for the pathogenesis of NPC (Guo et al., 2009). However, the effect of these factors on TL-LGNPPA development has yet to be reported. Few genetic studies have been conducted for TL-LGNPPA. Given its morphological and immunohistochemical resemblance to PTC, Oishi et al., (2014) previously conducted a mutation-specific immunohistochemical study of *BRAF*V600E, which is the greatest communal heritable mutation in PTC. Their study reported the absence of this mutation. Petersson et al., (2011) explored alterations in *BRAF*, *KIT*, and *SSY-SSX1/2*, but no alterations were identified. Ethnicity gives the impression to show a title role in the etiology based on the ethnicity of the cases in the medical literature (Table 1). A family or personal history of cancer or genetic syndromes may not play a role, but interestingly, one case of TL-LGNPPA was reported in association with Turner syndrome (Nojeg et al., 1998).

Although it is considered a malignant tumor, TL-LGNPPA is a low-grade adenocarcinoma with indolent biological behavior, slow growth, and a low recurrence rate. No reports that describe the spread of this tumor to cervical lymph nodes or metastases to distant sites/organs have been published thus far, which suggests a favorable outcome (Carrizo & Luna, 2005; Kakkar et al., 2019). Complete surgical resection for accessible tumors is the primary treatment approach because most patients have localized disease at presentation (He et al., 2003).

An excellent prognosis can be achieved with surgery alone based on the follow-up data of patients who underwent complete surgical resection, as they have not shown any metastatic behavior for as long as 15 years after surgery (Wang et al., 2006). The use of radiotherapy as a therapeutic mainstay is not well-established. In one report, a patient failed primary radiotherapy treatment and subsequently underwent surgical resection and was disease-free for over 10 years (Wenig et al., 1988). Inadequate surgical resection may lead to local recurrence, and in instances such as this one, photodynamic therapy combined with topical 5-aminolevulinic acid have efficaciously used in place of postoperative adjuvant therapy to eradicate residual disease (Ohe et al., 2010).

5. CONCLUSION

TL-LGNPPA is a malignant, yet indolent tumor with a biphasic appearance that may contain a spindle cell component. Both epithelial and spindle cells show almost the same immunohistochemical profile. Whether the physical features of the spindle cells have a function in the prognosis is unclear. The awareness of this primary nasopharyngeal neoplasm is important in distinguishing it from other malignant tumors to avoid potential diagnostic pitfalls and to ensure appropriate therapeutic decisions.

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Author Contributions

All authors contributed equally to manuscript work & production.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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