Case report

The rare combination of low-grade thyroid-like nasopharyngeal papillary adenocarcinoma and squamous cell carcinoma: a case report and literature review

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Thyroid-like low-grade nasopharyngeal papillary adenocarcinoma (TL-LGNPA) is an extremely rare neoplasm that generally originates from the nasopharynx surface epithelium. The case presented herein is of a 70-year-old male patient referred from another centre, who was observed to have this tumour together with squamous cell carcinoma. The clinicopathological findings of this combination are presented, which has very rarely been mentioned in the literature.
Although the prognosis of TL-LGNPA is generally excellent, it may sometimes be combined with other tumours, and therefore it must be kept in mind that it could have a clinically more aggressive course.

Key words: low-grade nasopharyngeal papillary adenocarcinoma, squamous cell carcinoma, sinonasal region.

Introduction

Thyroid-like low-grade nasopharyngeal papillary adenocarcinoma (TL-LGNPA) is a rarely observed adenocarcinoma, showing a papillary growth pattern and abnormal expression of thyroid transcription factor 1 (TTF-1), generally in the nasopharyngeal area [1]. These adenocarcinomas are accepted as a separate entity from other adenocarcinomas, including papillary adenocarcinomas in the sinonasal region [2]. This tumour, which is seen extremely rarely, is presented herein for the first time in the literature in combination with squamous cell carcinoma.

Case report

A 70-year-old male presented at another centre with the complaint of throat pain ongoing for one month. In the examination at that centre, an ulcerovegetating mass was determined involving the left tonsil and extending to the anterior plica. The patient had a 10-year history of hypertension and coronary artery disease, and he had undergone bypass surgery. The incisional biopsy taken in the Ear, Nose, and Throat Clinic was reported as malignant epithelial tumour. On positron emission tomography, a lesion in the left pharyngeal area was observed, 35 × 26 mm in size, showing an increase in fluoro-2-deoxyglucose (FDG) metabolism (SUV max: 22.2) at the level of malignancy. In the bilateral cervical lymphatic chain, lymph nodes were seen showing increased FDG metabolism at the level of malignancy in the left supraclavicular area, left upper and lower paratracheal areas, bilateral hilar regions, and lumbar and bilateral inguinal regions. In light of these imaging findings, biopsy material was taken, 0.3 ×

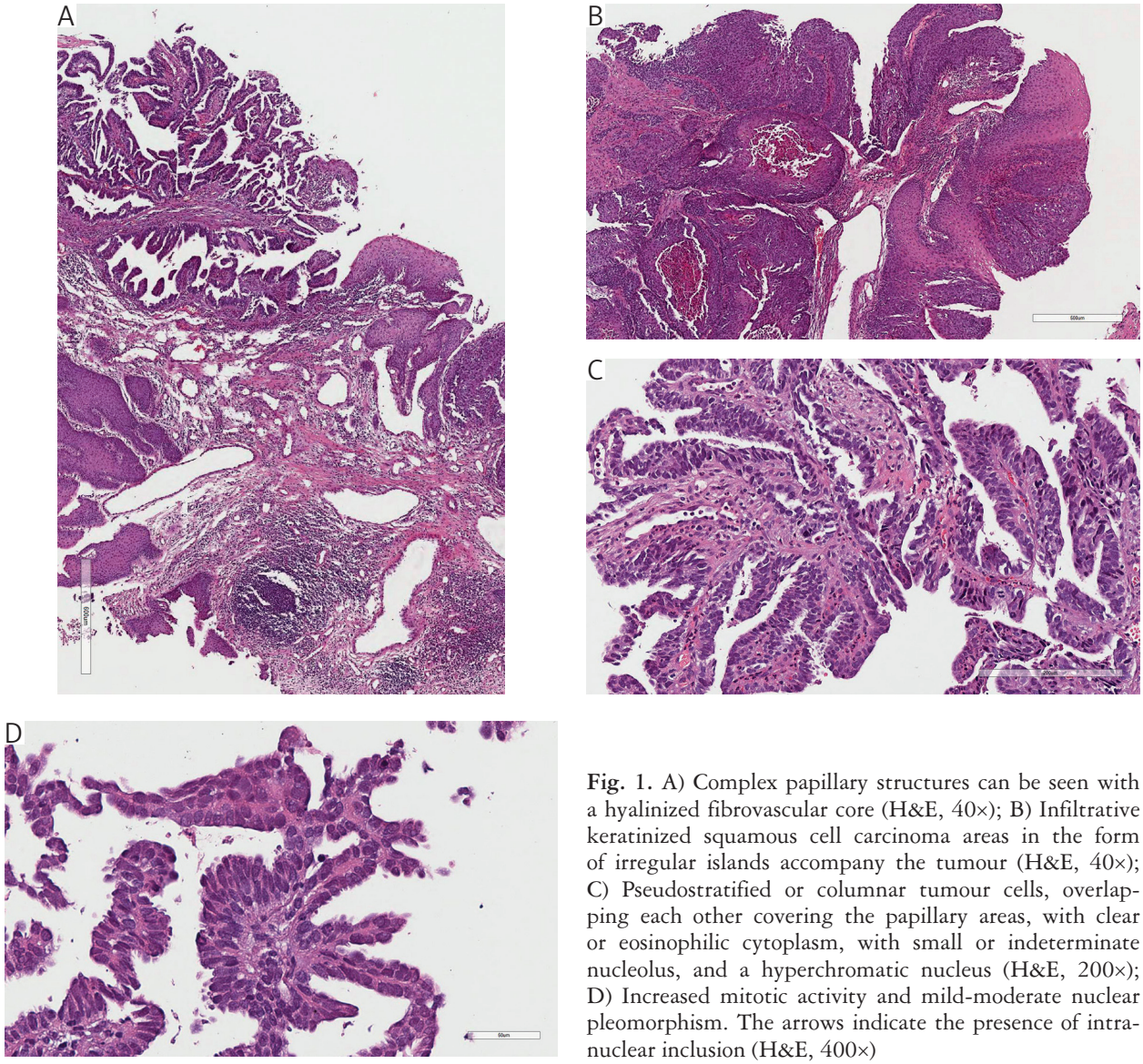

Fig. 1. A) Complex papillary structures can be seen with a hyalinized fibrovascular core (H&E, 40×); B) Infiltrative keratinized squamous cell carcinoma areas in the form of irregular islands accompany the tumour (H&E, 40×); C) Pseudostratified or columnar tumour cells, overlapping each other covering the papillary areas, with clear or eosinophilic cytoplasm, with small or indeterminate nucleolus, and a hyperchromatic nucleus (H&E, 200×); D) Increased mitotic activity and mild-moderate nuclear pleomorphism. The arrows indicate the presence of intranuclear inclusion (H&E, 400×)

0.3 × 0.2 cm in size, and dirty white-brown in colour. In the histopathological examination, a tumour was determined showing complex papillary structures and a glandular growth pattern, with a hyalinized fibrovascular core, similar to thyroid papillary carcinoma. At high magnification, there were seen to be pseudostratified or columnar tumour cells, which were eosinophilic, partially clear cytoplasm with small or indeterminate nucleolus, a hyperchromatic nucleus, partially clear cytoplasm, and nuclear overlapping. A mild-moderate increase in nuclear pleomorphism and mitotic activity was noticeable in these cells. The presence of intranuclear inclusion in focal areas was observed (Fig. 1D). Next to this area, there was also squamous cell carcinoma containing significant nuclear atypia and mitosis showing keratinization (Figs. 1A–C). In both areas, necrosis and lymphovascular or perineural invasion were not observed. In the neoplastic cells showing papillary structures, the immunohistochemical application of TTF-1, EMA, CEA, and CDX2 showed positive results, and P53, thyroglobulin, S100, actin, and p16 were negative. The proliferation index was determined as 60% with Ki-67 (Figs. 2A–D). The case was reported histopathologically as combined tumour of TL-LGNPA and squamous cell carcinoma.

Discussion

The combination of TL-LGNPA and squamous cell carcinoma, as seen in this case, has not been previously reported in literature.

Nasopharyngeal papillary adenocarcinoma (NPA) was first described by Wenig *et al.* in 1988 [2]. It has been suggested that these should be evaluated as a separate entity from traditional adenocarcinomas because of the histologically low-grade nuclear characteristics and the insidious clinical course compared to conventional adenocarcinomas [2]. In 2005, the World Health Organisation included these

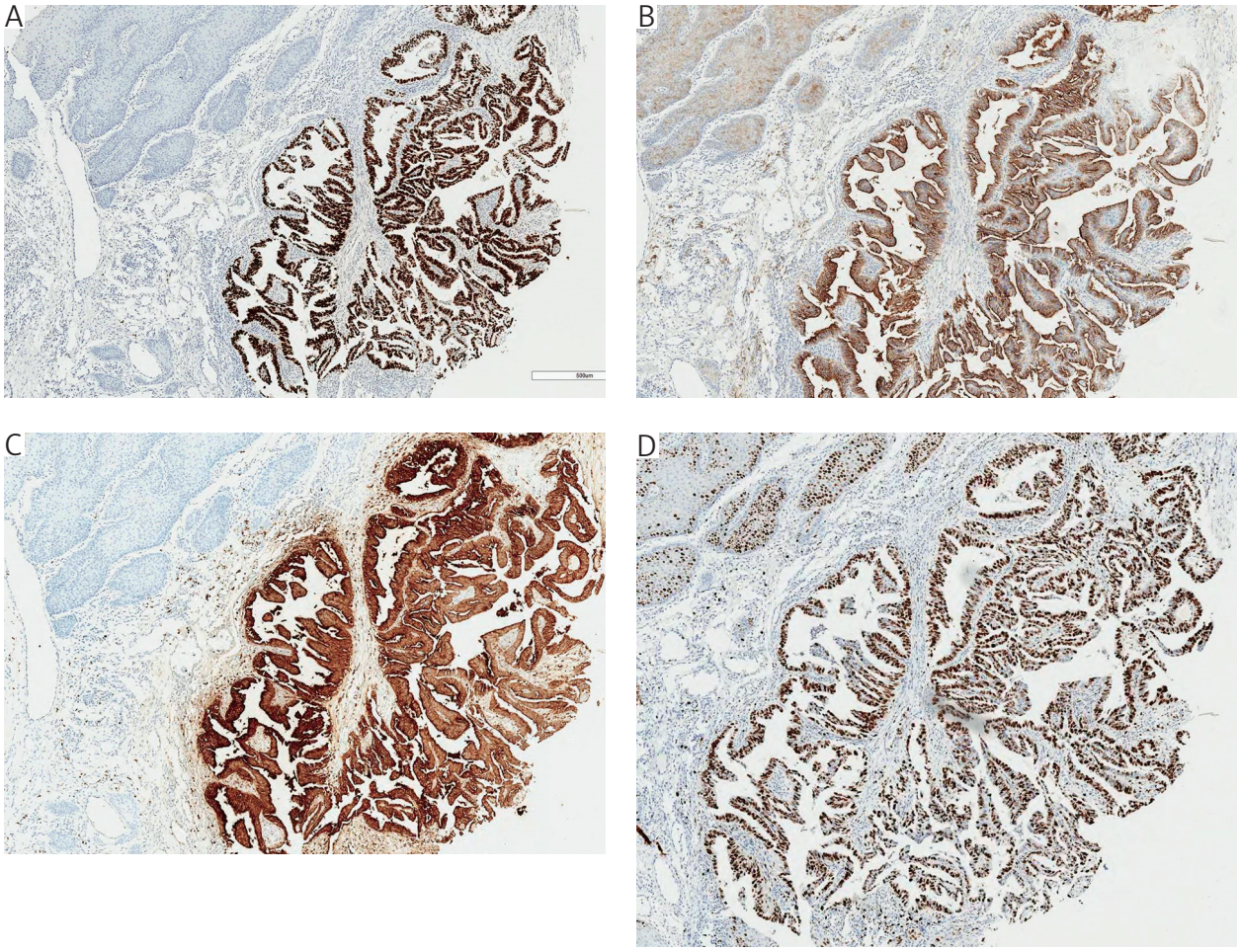

Fig. 2. A) Immunohistochemical application of TTF-1 showed diffuse nuclear positive staining in tumour cells showing papillary structure (40×); B) Membranous positive staining in tumour cells with EMA (50×); C) Cytoplasmic positive staining in tumour cells with CEA (50×); D) The proliferation index was determined as 60% with Ki-67 (50×)

in the classification of malignant epithelial tumours of the nasopharynx [3].

Carrizo and Luna discovered TTF-1 expression for the first time in 2005 and identified these cases as thyroid-like NPA [4]. This papillary configuration mimics papillary thyroid carcinoma (PTC) and abnormal TTF-1 expression is the differentiating characteristic for TL-LGNPA. This is an extremely rarely seen neoplasm, and few cases have been reported in the literature [4–19]. In the reported cases, the mean age is 35 years, ranging from 9 to 72 years. The current case was a 70-year-old male. TL-LGNPA are generally localised in the roof of the nasopharynx and on the posterior edge of the nasal septum. The localisation of the tumour in the current case was in the left oropharyngeal region.

Thyroid-like low-grade nasopharyngeal papillary adenocarcinoma are observed macroscopically as a peduncled or polypoid mass, with a mean diameter of 2 cm [20]. In the current case, an ulcero-vegetating mass was observed reaching 3.5 cm in the widest area. Histologically, these malignant neoplasms often show papillary and glandular structure formed from moderate-level pleomorphic, columnar epithelial cells arranged around a fibrovascular core, as in PTC. Nuclear characteristics such as nuclear clarity, overlapping, and groove and psammoma bodies may be observed. In addition, 3 different cases of TL-LGNPA containing spindle cell components have been reported in the literature (Table I) [7, 17, 19]. In the current case, no spindle cell component was observed, but squamous cell carcinoma was determined adjacent to the tumour.

In the literature to date, the combination of TL-LGNPA and squamous cell carcinoma has not been reported. Squamous differentiation has been stated in only one case [5]. In that case, reported by Oide *et al*., no nuclear atypia or proliferation activity was seen in the squamous cells (unlike the current case), TTF-1 positivity was determined with IHK, and these squamous cells showed morphology similar to the squamous metaplasia of PTC [5]. Squamous cell carcinoma and squamous metaplasia must be differentiated in terms of prognosis. In the current case,

Table I. The biphasic components and clinical findings defined in thyroid-like low-grade nasopharyngeal papillary adenocarcinoma

Case	Age (years), gender	Biphasic component	Localisation	Treatment	Recurrence	Follow-up period
Petersson *et al*. [19]	39, female	Spindle cell	Posterior Nasal Septum	Surgery	Unknown	None
Ohe *et al*. [17]	41, male	Spindle cell	Nasopharynx posterior wall	Surgery	No recurrence or metastasis	9 months
Oishi *et al*. [7]	47, female	Spindle cell	Left nasal septum posterior wall	Surgery	No recurrence or metastasis	19 months
Oide *et al*. [5]	68, male	Squamous differentiation	Nasopharynx	Surgery	Unknown	None
Current case	70, male	Squamous cell carcinoma	Left oropharynx	Surgery + chemotherapy +radiotherapy	Lymph node metastasis was determined on PET at the time of diagnosis. Recurrence developed	19 months

PET – positron emission tomography

this area was evaluated as squamous cell carcinoma because of significant atypia, atypical mitosis, and invasion observed in the squamous cells, and TTF-1 marker was negative in this focus (Fig. 2A).

TTF-1 is a transcription factor containing homeodomain encoded by NK homeobox 1 (NKX2-1) in the development of lung and thyroid epithelial cells, and it is widely used in the diagnosis of lung and thyroid cancers [21]. Immunohistochemically, TL-LGNPA shows TTF-1 expression. This can be explained by 3 different mechanisms. The first is that this tumour could have developed from ectopic thyroid tissue, the second is that re-regulation of a gene affecting TTF-1/NKX2-1 could cause abnormal expression of TTF-1, and the third is that genetic instability and re-programming of cancer cells could cause differentiation and deregulation of TTF-1/NKX2-1 [7].

In the differential diagnosis of TL-LGNPA, because it shows similarity to PTC in particular, differentiation from PTC metastasis is important for definitive diagnosis, treatment, and prognosis of the patient. For the differentiation of these 2 entities, thyroglobulin and CD15 markers are recommended immunohistochemically. These 2 markers are positive for PTC and negative for TL-LGNPA in immunohistochemical examinations [22]. In the current case, thyroglobulin was negative. In the differentiation of low-grade nasopharyngeal adenocarcinoma (LGNA) and TL-LGNPA, negativity of TTF-1 and S100 markers in LGNA is helpful [18]. In polymorphous low-grade papillary adenocarcinoma, vimentin and S100 markers are positive immunohistochemically, and there is no TTF-1 expression [7]. Another entity that must be considered in the differential diagnosis is intestinal type papillary adenocarcinoma. In these cases, nuclear atypia is evident, cells generally do not show mucinous differentiation, and immunohistochemically CK20 and CDX2 markers are positive [23]. In the current case, there was focal staining in CDX2, but morphologically no evident nuclear atypia or mucinous differentiation was seen. Carcinomas with acinic cells showing a papillary component are often cystic, and immunohistochemically, variable S100, and vimentin-positive staining is seen [19].

In the cases reported in the literature, the proliferation index with Ki-67 has been determined as a mean of approximately 5%, and maximum 20% [11]. In the current case, this rate was determined as 60%. This high rate was thought to be due to the combined tumour. In all the cases reported to date, lymph node metastasis and local recurrence or metastasis following total excision have not been reported for patients diagnosed with TL-LGNPA [11, 20].

Surgical excision is generally sufficient for the treatment of TL-LGNPA [2]. When surgical excision is not possible or positive surgical margins are observed, radiotherapy can be used as adjuvant therapy [24]. In the current case, following radical surgery that included the tonsil, hard and soft palate, lower lateral pharyngeal area, pterygoid muscle, tongue-uvula, skull base, and bilateral neck dissection, chemotherapy and radiotherapy were applied because several ($n = 9$) metastatic lymph nodes were determined. During follow-up, no recurrence developed in the retroauricular region. The treatment and follow-up of the patient are ongoing.

Conclusions

This is the first reported case of TL-LGNPA combined with squamous cell carcinoma. These tumours are rarely seen. Although the prognosis is generally

good, it must be kept in mind that it can be more aggressive in combined form.

The authors declare no conflict of interest.

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