

## Up-to date review and case report

# Rare oral metastasis from a probable large-cell neuroendocrine carcinoma of the lung

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**Abstract – Introduction:** The prevalence of neuroendocrine tumors is 1/100 000 worldwide. Lung locations account for 25% and the oral cavity is very rarely involved. **Observation:** We reported the case of gingival hyperplasia around an upper molar in a patient with a medical history of lung adenocarcinoma treated by targeted chemotherapy. Incisional biopsy of the intraoral lesion revealed a large-cell neuroendocrine carcinoma (LCNEC). New imaging assessment revealed multiple metastasis locations of the lung disease. This case made us question the link between gingival LCNEC and the lung adenocarcinoma diagnosed through pleural cytology. Review of cytology findings did not make it possible to identify a neuroendocrine component among adenocarcinoma cells. Immunohistochemical tools sometimes help to differentiate primary from secondary lesions, but this was inconclusive here. **Discussion:** The literature shows that in cases of lung composite carcinoma, one component may be absent on small histology samples, and therefore on cytology. It was not possible either to rule out neuroendocrine carcinoma development under the effect of targeted chemotherapy. We considered the diagnosis of intraoral metastasis of a composite lung carcinoma which metastasized to its neuroendocrine component in the oral cavity. **Conclusion:** To our knowledge, this is the first case of LCNEC gingival hyperplasia revealing metastatic progression of lung adenocarcinoma.

**Mots clés :**  
tumeur  
neuroendocrine /  
carcinome pulmonaire  
non à petites cellules /  
métastase gingivale

**Résumé – Rare métastase buccale d'un probable carcinome neuroendocrine pulmonaire à grandes cellules.**  
**Introduction :** La prévalence des tumeurs neuroendocrines est de 1/100 000 à travers le monde parmi lesquelles 25 % sont de localisation pulmonaire. Mais la localisation buccale est extrêmement rare. **Observation :** Il s'agissait d'une lésion gingivale hyperplasique autour d'une molaire maxillaire chez un patient présentant un antécédent d'adénocarcinome pulmonaire suivi et traité par chimiothérapie ciblée. L'analyse anatomopathologique de la lésion intra-orale montrait un carcinome neuroendocrine à large cellules (LCNEC). Un bilan d'imagerie révélait de multiples métastases de la tumeur pulmonaire. Ce cas nous interpelle sur le lien entre un LCNEC gingival et l'adénocarcinome pulmonaire diagnostiqué initialement à partir d'une cytologie pleurale. Le nouvel examen de cette cytologie n'a pas permis d'identifier une composante neuroendocrine parmi les cellules prélevées.

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L'immunohistochimie aide parfois à distinguer les lésions primaires des lésions secondaires, mais cette approche n'a pas été concluante dans ce cas. **Discussion :** La littérature montre que dans les cas de carcinomes pulmonaires composites, l'une des composantes peut être absente sur des échantillons de petite taille et donc *a fortiori* sur des cytologies. L'apparition d'un carcinome neuroendocrine sous les effets de la chimiothérapie ciblée n'est pas non plus exclue. Nous retenons le diagnostic de métastase buccale d'un carcinome pulmonaire composite qui a métastasé dans sa composante neuroendocrine. **Conclusion :** Il s'agit, à notre connaissance, du premier cas de LCNEC gingival révélant l'évolution métastatique d'un cancer pulmonaire.

## Introduction

Neuroendocrine cells express markers of neuronal and endocrine differentiation. They are either grouped in clusters forming the endocrine glands, or isolated forming the diffuse neuroendocrine system. Neuroendocrine tumors are rare, with a prevalence of 1/100 000 worldwide. The lung accounts for more than 25% of them. LCNEC is very rare in the head and neck area and even more so in the oral cavity.

The 2015 World Health Organization (WHO) classification of lung diseases subdivided pulmonary neuroendocrine tumors into four groups: low-grade typical carcinoid, intermediate low-grade atypical carcinoid, and two high-grades, small-cell neuroendocrine carcinoma and large-cell neuroendocrine carcinoma (LCNEC) [1]. The diagnosis can be made in various ways: tumor mass syndrome, paraneoplastic syndrome or incidental discovery through medical imaging. In metastatic cases, the identification of the primary lesion can sometimes constitute a challenging diagnosis. We report and discuss a unique case with a gingival location of LCNEC in a patient with a pleural metastatic lung adenocarcinoma.

## Case-report

A 70-year-old patient was referred by his general practitioner for a gingival hyperplastic lesion around tooth 27 (Fig. 1).

His medical history revealed tobacco use at 60 pack-years and a lung adenocarcinoma diagnosed 18 months earlier after a pleural metastatic effusion. The diagnosis of lung adenocarcinoma was initially based on the cytological analysis of the pleural fluid and additional immunohistochemical analysis showing a TTF-1+/CK7+/CK20- phenotype. Bronchoscopy and lavage cytology were not contributive. Chemotherapy (carboplatin and pemetrexed) was administered the first year. The patient was subsequently treated with erlotinib, an EGFR-tyrosine kinase inhibitor (EGFR-TKI).

An incisional biopsy of the oral lesion and tooth extraction were performed under local anesthesia. Histopathology showed the presence of a large-cell neuroendocrine carcinoma (Fig. 2). Immunohistochemical studies revealed positivity for synaptophysin, chromogranin A, CD56 and CK7 (Fig. 3). Negative staining was found with TTF-1 and CK20. Orthopantomogramme and cone beam computed tomography did not show

any bone extension in the upper jaw (Fig. 4). Staging of cancer was made by an 18-fluorodeoxyglucose (18-FDG) positron emission tomography (PET). A marked accumulation of 18-FDG was found in the left lung, left pleural cavity, mediastinal, cervical and retroperitoneal lymph nodes, liver, bone and left adrenal gland (Fig. 5). Review of the initial pleural cytological specimen did not show any neuroendocrine component after complementary immunohistochemical analyses with chromogranin A, synaptophysin and CD56. Nevertheless, clinical and paraclinical arguments led to the diagnosis of an intraoral metastasis of the large neuroendocrine carcinoma component of a primary composite non-small cell lung carcinoma.

## Discussion

The WHO classification of lung diseases constantly changes, reflecting the complexity of pulmonary tumors. The diagnosis of large-cell neuroendocrine carcinoma is based on morphological and immunohistochemical findings [1]. It is characterized by a specific architecture with formation of rosettes, trabeculae and palisades. Tumor cells are large with a nuclear-cytoplasmic ratio between 5 and 7 and a high mitotic index. Large areas of necrosis are frequent. The differential diagnosis with small-cell lung carcinoma (SCLC) is based on several criteria, notably larger size of the cells, with abundant cytoplasm, and prominent nucleoli. The atypical carcinoids have a lower mitotic index. There are three neuroendocrine markers: chromogranin A, synaptophysin and CD56. At least one of them must be expressed.

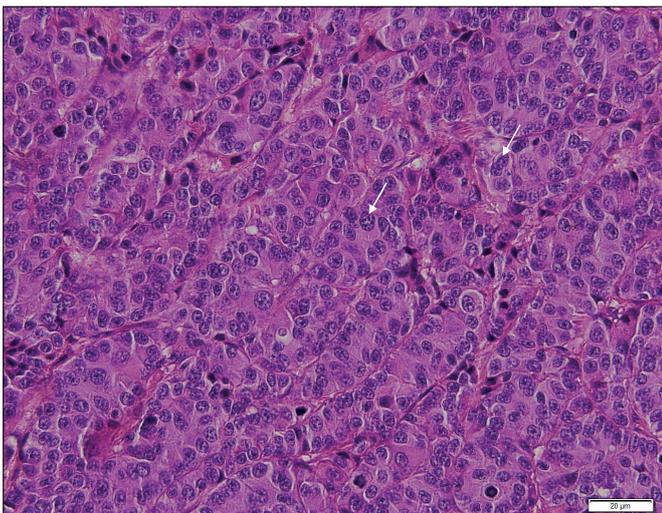
Neuroendocrine tumors occur very rarely in the head and neck. Reported primary large-cell neuroendocrine carcinomas have been observed exceptionally in the oral cavity: only one case located in the retromolar trigone [2]. Other peri-oral locations have been described: larynx and salivary glands, the two most frequent locations in the head and neck area; oropharynx and hypopharynx (Tab. 1) [3]-[14]. Secondary lesions are also uncommon. Only one case of an intraoral metastasis in the lower jaw of a large-cell neuroendocrine carcinoma has been reported in the English-language literature [15]. Standard histological analysis alone does not enable differentiation between primary and secondary lesions in the case of a high-grade neuroendocrine tumor.

Immunohistochemical studies can be used for this purpose. TTF-1 is a protein that regulates the transcription of specific



**Fig. 1.** Initial intraoral photograph. The hyperplastic and inflammatory tumor was localized around the left maxillary second molar region.

*Fig. 1. Photographie endobuccale initiale. La tumeur, d'aspect hyperplasique et inflammatoire, était localisée autour de la seconde molaire maxillaire gauche.*

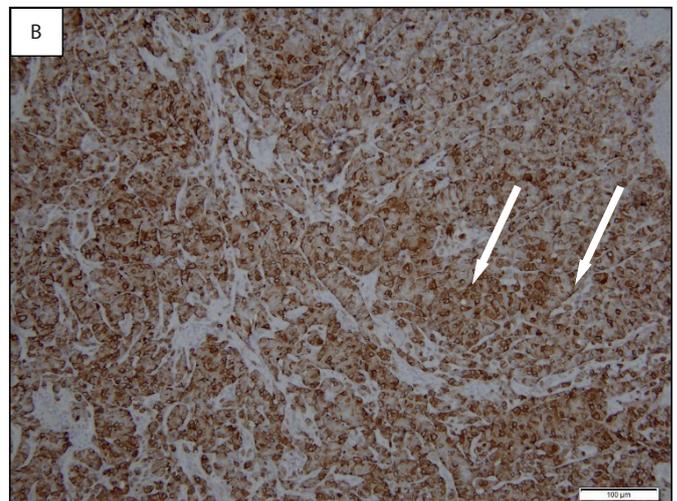
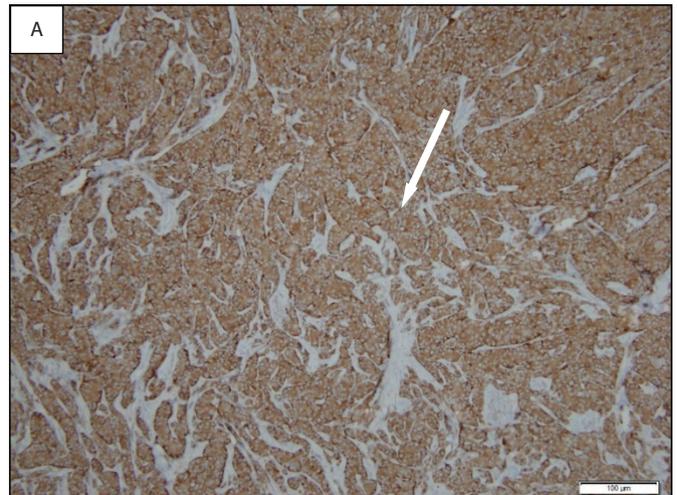


**Fig. 2.** Optical microscopy. HE, magnification  $\times 40$ . Large carcinoma cells in the chorion. The arrows show mitosis.

*Fig. 2. Microscopie optique. HE, grossissement  $\times 40$ . Grandes cellules carcinomateuses dans le chorion. Les flèches montrent des mitoses.*

genes in the thyroid, lung and diencephalon. Its expression has been shown in 50% of large-cell neuroendocrine lung carcinomas [16]. Cytokeratins (CKs) are found in epithelial tissues. The phenotype CK7+/CK20- is not specific and is found in the majority of carcinomas of the lung, breast, thyroid, biliary tract, pancreas and ovary [17].

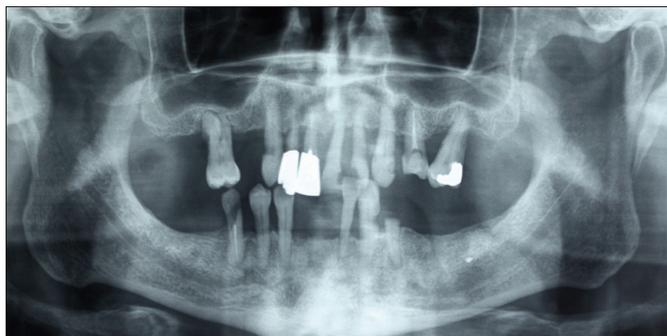
As immunohistochemistry cannot solve all the cases, correlation with clinical and radiologic findings is important in



**Fig. 3.** Immunohistochemistry. Diffuse intracytoplasmic immunoreactivity for synaptophysin (A, magnification  $\times 10$ ) and chromogranin A (B, magnification  $\times 10$ ) are observed (white arrows) on a majority of cells by brown-orange (image A) and brown (image B) labeling.

*Fig. 3. Immunohistochimie. On observe (flèches blanches) un immunomarquage diffus intracytoplasmique pour la synaptophysine (A, grossissement  $\times 10$ ), et la chromogranine A (B, grossissement  $\times 10$ ) sur la plupart des cellules par un marquage brun-orange sur l'image A et brun sur l'image B.*

order to determine the primary or secondary nature of a neuroendocrine tumor. In this case, the intraoral lesion appeared 18 months after the discovery of the lung adenocarcinoma. Among pulmonary neuroendocrine tumors, large-cell neuroendocrine carcinoma is the most difficult to diagnose in preoperative biopsy specimens. The concordance between preoperative biopsy and final diagnosis after surgical resection of large-cell neuroendocrine lung carcinoma has been evaluated in two studies: none of the cases was accurately diagnosed

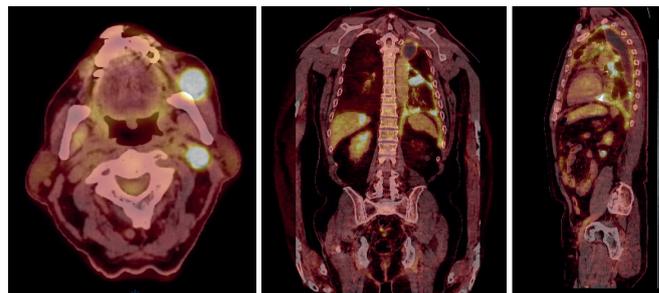


**Fig. 4.** Panoramic radiography. No osseous defect around tooth 27 is observed.

*Fig. 4. Panoramique dentaire. Aucune lyse osseuse autour de 27 n'est observée.*

[18]. Furthermore, 20% to 50% of the cases were misdiagnosed as adenocarcinoma at preoperative biopsy. Concerning our case, the cytological reanalysis of the pleural liquid specimen did not change the diagnosis of lung adenocarcinoma and the patient did not undergo lung surgery.

Thus, the lung cancer in this patient may be a combined non-small cell lung carcinoma that contains a large-cell neuroendocrine carcinoma component and an adenocarcinoma component. Yamada, K et al. report that in cases of combined high-grade neuroendocrine carcinoma (HGNEC), adenocarcinoma is the most frequent non-HGNEC component, followed by squamous cell carcinoma [16]. The large-cell neuroendocrine carcinoma component could be absent in the initial pleural cytological sample. Moreover, the neuroendocrine phenotype could have appeared after treatment with EGFR-TKI. Resistance to this treatment could be explained by sequential mutation [19]. This neuroendocrine differentiation seems to be correlated with a poorer prognosis.



**Fig. 5.** PET-CT: left to right: head horizontal slide, frontal slide and sagittal slide of the body. This PET-CT fusion picture shows an abnormal accumulation of 18-FDG in multiple locations of the body: maxilla, left lung and pleural cavity, left adrenal gland, liver, vertebrae; cervical, mediastinal, retroperitoneal lymph nodes.

*Fig. 5. TEP-TDM : de gauche à droite: coupe axiale de la tête, coupes frontale et sagittale du tronc. Cette image de fusion en TEP-TDM montre un hypermétabolisme glucidique pathologique au niveau du maxillaire, du poumon gauche, de la cavité pleurale gauche, de la glande surrénale gauche, du foie, de vertèbres, de ganglions cervicaux, médiastinaux, rétropéritonéaux.*

There is no consensus on treatment of large-cell neuroendocrine lung carcinoma because of the very low number of cases [20]. Platinum-based chemotherapy provides some short-term results in the treatment of advanced pulmonary large-cell neuroendocrine carcinoma. Targeted molecular therapies are currently being tested [20]. In this case, surgical treatment was not indicated. The patient received ten courses of carboplatin and etoposide over six months. This treatment was followed by paclitaxel (Taxol). Nevertheless, the intraoral lesion slowly progressed 9 months after its removal (Fig. 6). The visceral locations were stable according to regular CT assessment, but the patient died one year after the discovery of the intraoral lesion.

**Table I.** Reported primary and secondary LCNEC of the head and neck in the English-language literature.

*Tableau 1. LCNEC primaires et secondaires de la tête et du cou rapportés dans la littérature anglophone.*

References	Topography	Nature	Number of cases (n=29)
	oral cavity		
[2]	retromolar trigone	primary	1
[15]	mandible	secondary	1
	oropharynx		
[3], [4]	tongue base	primary	3
[4]	lateral wall	primary	1
[4]	hypopharynx	primary	1
[4], [5],[6], [7], [8], [9]	larynx	primary	16
	salivary glands		
[10], [11], [12], [13]	parotid gland	primary	5
[14]	submandibular gland	primary	1



**Fig. 6.** Follow-up. Intraoral (A) and extraoral (B) views. Recurrence of the intraoral tumor extending to the cheek after 8 months of chemotherapy.  
*Fig. 6. Suivi. Photographies endobuccale (A) et exobuccale de profil (B). Récidive de la tumeur intra-orale s'étendant à la joue après 8 mois de cures de chimiothérapie.*

To our knowledge, this is the second description of an intraoral metastatic large-cell neuroendocrine carcinoma in the English-language literature. However, in this case, the diagnosis was challenging and required further clinical, pathology and radiological analyses to conclude on probable metastatic progression of an association of two different primary non-small cell lung carcinomas. Any suspicion of LCNEC in the oral cavity requires, firstly, advanced pathology investigations and secondly, clinical and radiological assessment to detect or rule out hypothetical, occult metastatic disease.

**Conflicts of interests:** none declared

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