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About A Rare Case of Small Neuroendocrine Carcinoma of the Mandible at the University Hospital of Casablanca in Morocco

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Abstract :- Neuroendocrine tumors (NETs) arise from neuroendocrine cells and are mostly observed in the gastrointestinal tract, pancreas, and lungs. NETs in the oral and maxillofacial region are extremely rare. We report a case of a 67-year-old man with an NET in the mandible. The patient did not show any symptoms except for remarkable jugular swelling. The lesion appeared as a radiolucent honeycomb abnormality with bone destruction on panoramic radiography. The histopathologic diagnosis following a biopsy was NET. Contrast-enhanced computed tomography (CT), 18F-fluorodeoxyglucose positron emission computed tomography (18F-FDG PET/CT), showed tumor mass of the soft parts of the right mandible with bone lysis without lymph node, visceral or bone hypermetabolism . He had three chemotherapy cures with good clinical and radiological response followed by concomitant radio chemotherapy 60Gy.The evolution was marked by a febrile grade IV aplasia leading to the death of the patient. Neuroendocrine carcinomas of mandible are unusual. Their prognosis is overall bleak. The morphological characteristics, the clinical aspects and the therapeutic management of these tumors are comparable to the neuroendocrine tumors of the lung.

***Keywords* :-** *Neuroendocrine Small Cell Carcinoma, Mandible, Radiotherapy, Chemotherapy, Surgery.*

I. INTRODUCTION

Neuroendocrine tumors arise from neuroendocrine cells and are mainly seen in the gastrointestinal tract, pancreas and lungs [1]. Neuroendocrine cells of the oral mucosa are an underestimated component of the neuroendocrine system whose biological roles are elusive in the oral cavity [2]. Neuroendocrine carcinoma is a tumor that occurs in different places, especially the lungs and the larynx. The oral cavity is a very rare location for primary neuroendocrine carcinomas [3]. These tumors also have a very unfavorable prognosis. The diagnosis is often made at an advanced stage which further darkens its prognosis. Due to their rarity, there is no standard of care. The treatment is generally based on the data already known in the management of pulmonary localization. However, it is necessary to be familiar with the different therapeutic modalities for better management. We report a case of neuroendocrine carcinoma of the gum.

II. CLINICAL CASE

A 67-year-old Moroccan man, chronic smoker at 15 pack-years, weaned 10 years ago. He is known hypertensive with cardiac arrhythmia controlled under treatment. He has a history of eye surgery for cataract in 2009. This patient was seen in consultation for a swelling of the right cheek evolving for 08 months and gradually increasing in size becoming painful, the starting point of which would be the right mandibular angle. On clinical examination, the patient was in good general condition with a WHO Performance Status of 1. There was a voluminous swelling on the right cheek of about 20 cm in long axis, painful, taking the ascending branch of the mandible with infiltration in endo - buccal (Picture 1). Mouth opening was limited and there was no peripheral clinical lymphadenopathy.

A cervico-facial scan was performed showing tumor mass under and latero mandibular right coming into contact with the right parotid and encompassing the submaxillary responsible for mandibular lysis (Image 3)

A biopsy of the mass was performed. The histological study shows a malignant proliferation of undifferentiated round cells of medium size with an indistinct scanty cytoplasm and a hyperchromic, irregular, sometimes strongly nucleolated nucleus. Immunohistochemical study showed tumor cells with intense and diffuse synaptophysin positivity, but negative for chromogranin A, cytokeratin, CD 20, CD 3, CD 99, desmin and myogenin with a Ki 67 at 60%.

Positron emission tomography with 18 FDG coupled with CT scan showed a hyper metabolic process of the soft tissues encompassing the right mandible with bone lysis extending submandibularly and ascending along the ascending branch of the mandible with a max SUV at 10.22 for a max liver SUV at 2.2 (Image 5). There was no lymph node, visceral or bone hypermetabolism.

Based on these findings, a diagnosis of poorly differentiated small cell neuroendocrine carcinoma of the right locally advanced gingiva was made. The patient received 3 courses of neoadjuvant chemotherapy based on Etoposide + Cisplatin. He developed non-febrile Grade 2 neutropenia after the second course. Post-chemotherapy evaluation by cervico-facial CT scan noted a 90% regression in size of the mass (Image 4). For surgeons, a surgical

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intervention would be very dilapidating with a mandibulectomy. We therefore decided on concomitant radio-chemotherapy with dose reduction: association of homolateral locoregional irradiation at a dose of 60 Gray in classic fractionation of 30 sessions and two sessions of etoposide 100 mg and cisplatin 20 mg chemotherapy on D1 and at D21. After 15 radiotherapy sessions, the patient presented with grade 3 mucositis plus non-febrile grade 4 neutropenia, which led us to stop radiotherapy and hospitalize him. The patient unfortunately died in an array of multi-visceral failure.

III. DISCUSSION

A neuroendocrine tumor is an epithelial tumor whose cells present structural, phenotypic and functional characteristics reminiscent of those of normal endocrine cells secreting peptide hormones [2]. They constitute a heterogeneous group of tumors arising from cells of the diffuse neuroendocrine system [4]. They differ in their location, embryological origin, degree of differentiation, biological behavior, functional activity and size but share common morphological, immunohistochemical and structural characteristics [5]. These are rare tumors but can be found in most locations. There are several classifications of neuroendocrine tumors depending on the primary location. On the head and neck, they are classified as typical carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma which can be well, moderately or poorly differentiated [6; 7].

The predilection site of neuroendocrine carcinomas is the lung and the digestive tract. But other rare locations are encountered in the literature, in this case gynecological [8; 9; 10], head and neck [11; 12], bladder [13] and breast [14; 15]. In terms of ENT and stomatology, the frequent location is the larynx, gingival neuroendocrine carcinoma is exceptional [2]. In an analysis of the National Cancer Center database in 2017 in the United States, out of 1042 patients with small cell carcinoma of the head and neck, only 9% had an oral location [12]. Small cell neuroendocrine carcinoma is frequently encountered in the elderly with a history of smoking, as is the case in our patient [16]. ENT and dental neuroendocrine carcinomas are very aggressive and have an unfavorable prognosis with lymph node, locoregional and distant involvement [12; 17]. Small cell forms are rare in the oral cavity and very few are localized to the gumline. HAS To our knowledge, we find in the literature a case localized at the level of the retromolar trigone described by Benning et al [18], a case reported by Mochizuki Y et al [17] on the upper gum but combined with squamous cell carcinoma. Zeng M et al [19] reported a case on the lower gingiva and a case on the lower anterior gingiva was reported by Wu Zhang B. et al in 2014 in a 25-year-old woman [3].Epidemiologically, the sex ratio is 6/1 for neuroendocrine carcinomas of the oral cavity and 11/1 for localizations of the oral mucosa. Most patients are over 50 years old [2].

Diagnosis is based on pathological examination. On histological examination, the diagnosis of the neuroendocrine nature of these tumors is suggested by morphology and confirmed after an immunohistochemistry study. The morphological aspect is similar to what is observed in the lung: neuroendocrine morphology with a high mitotic and necrotic power. The cells are large, with moderate to abundant cytoplasm [20]. In terms of immunohistochemistry, neuroendocrine carcinomas are defined by the presence of neuroendocrine markers, essentially chromogranin A, synaptophysin, neuron-specific enolase (NSE) and CD56 [20]. However, the expression of neuroendocrine markers is inconstant and the absence of expression of one of these markers does not exclude the diagnosis of neuroendocrine carcinoma. In the 04 cases of neuroendocrine carcinoma of the gingiva published in the literature that we reported, synaptophysin was always expressed whereas chromogranin was positive in only 3 patients [3; 17; 18; 19]. In our observation, only synaptophysin is expressed. However, to retain the diagnosis of a neuroendocrine carcinoma of the gum with certainty, the presence of another primary site must be excluded. In the literature, the clinical manifestations are not always described, but in most localizations of the oral cavity, we find a painful swelling as a reason for consultation [3], as in our case. The general condition is most often preserved at the time of diagnosis.

Computed tomography has been used in the arsenal of the paraclinical assessment in several studies. The place of PET-FDG is not clearly defined, it is mainly used to search for clinically non-noisy secondary localizations

Therapeutically, there is no therapeutic standard given the rarity of neuroendocrine carcinomas of the gums. Radical surgery and adjuvant chemotherapy using cisplatin and etoposide seem to be good options for localized forms [21]. The rechemoth dieterapie for carcinomaatsmall cells of lung origin, which includes genotecisplatin andetoposide is most often used [11]. In case of non-metastatic disease, chemotherapy can be used in neoadjuvant or adjuvant treatment to reduce tumor burden and reduce the risk of distant metastasis. In a series published by Pointer et al in 2017, 61% of patients had received chemotherapy and radiotherapy combined. Concomitant radiochemotherapy was the most frequent treatment in patients with early and locally advanced disease [12]. Although surgery has an important role in local control, the Pointer et al series showed that adding surgery to radiotherapy and chemotherapy in patients with locally advanced disease does not did not result in improved survival compared to patients treated with combined radiotherapy and chemotherapy [12]. The case reported by Benning et al [18] had been treated with chemotherapy only and the evolution was marked by a locoregional recurrence and the patient died of his disease 30 months after diagnosis. Overall survival for all patients with small cell carcinoma of the head and neck was 20.3 months in the National Cancer study [12]. In light of these data from the literature which highlight the role of systemic treatment in this disease, neoadjuvant chemotherapy is recommended before any local treatment in locally

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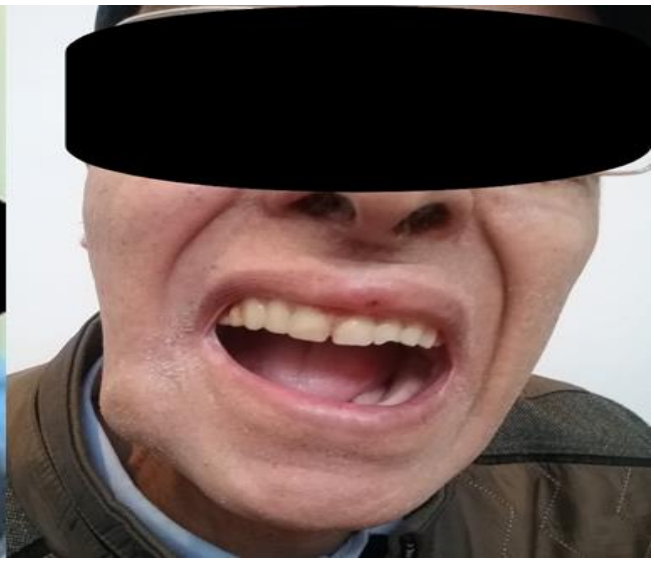
advanced disease. Faced with a locally advanced disease, the prognosis is poor from the outset, the trimodal treatment consisting of chemotherapy, surgery and radiotherapy, which is the ideal combination, hardly improves survival [12]. In our case the patient responded well to neoadjuvant chemotherapy, the observed toxicity could be related to the concomitant chemotherapy.

IV. CONCLUSION

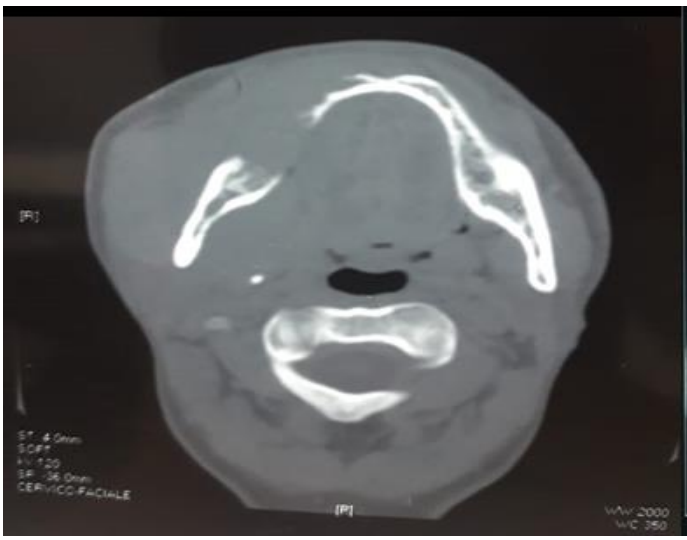
Although neuroendocrine carcinomas are well described in certain locations, particularly the lungs, they remain a poorly understood entity, especially in the oral location. Due to the lack of knowledge about this type of tumor coupled with their non-specific clinical behavior, the disease often reaches an advanced stage before the diagnosis is made, making cure impossible. We have reported a case of rare neuroendocrine carcinoma occurring in the gingiva. He had a reserved prognosis from the outset with local invasion. We consider that for locally advanced forms that cannot be resected from the outset:

APPENDICES

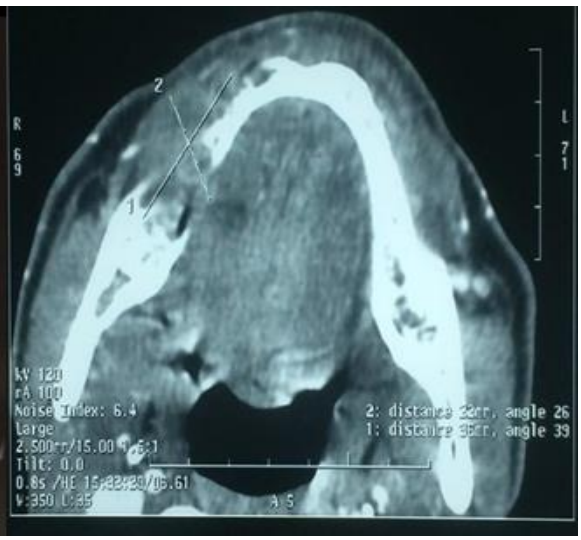
Picture 1 Photo at the First Day in Consult.



Picture 2 Photo After 3 Courses of Chemotherapy



Picture 3 Axial Slice on Diagnostic CT



Picture 4 CT Slice After Chemo

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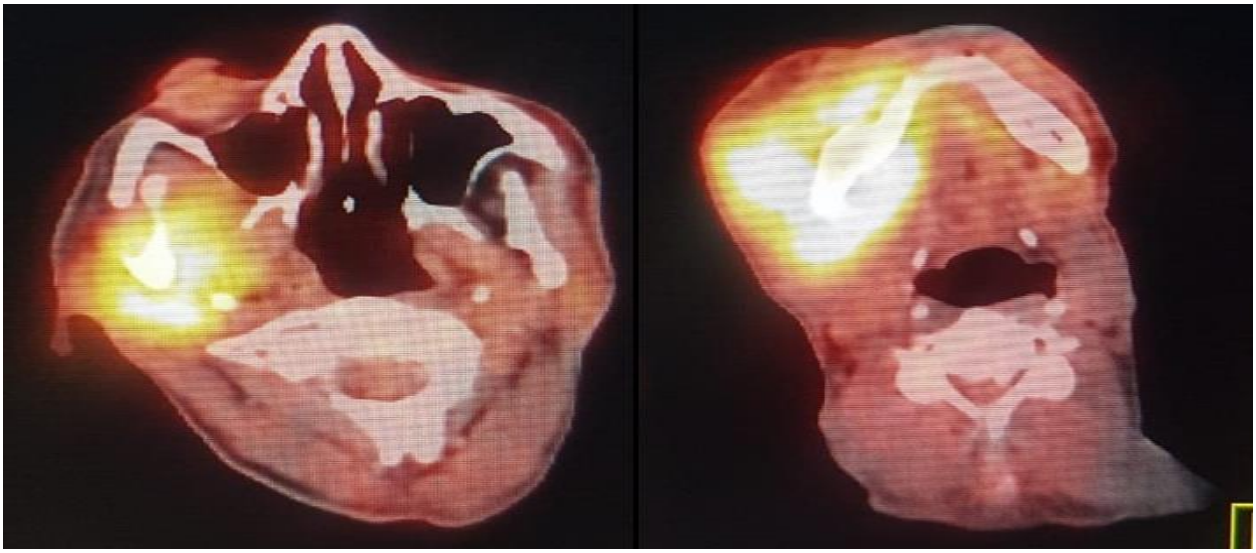

Picture 5 PET Image of Diagnostic

Table 1 Distribution Of Cases Reported In The Literature

Authors	Age/Sex	Size (Cm)	Extension	Treatment	Survival In Months
Wu Zhang B et al	25/F	1.5x2	localized	Wide surgery only	13 months progression-free survival
	38/F	2x3	localized	Surgery + Radiotherapy	08 months progression-free survival
Mochizuki Y et al [17]	62/F	2x0.8x0.6	localized	Surgery with maxillectomy only	23 months progression-free survival
Benning et al [18]	63/M	Unspecified	localized	Chemotherapy + Radiotherapy 60 Gray	Local recurrence at 08 months Distant metastasis at 20 months Death at 24 months
Zeng M et al [19]	73/M	2.8x2x1.4	localized	Large surgery and partial mandibulectomy + chemo	14 months progression-free survival

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