A primary small cell neuroendocrine carcinoma (SCNC) of the oral cavity (cheek mucosa): description of a case report

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Case Report

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Abstract

Background

Small cell neuroendocrine carcinoma (SCNC) of the oral cavity is a poorly differentiated, high-grade and very aggressive tumor with a poor prognosis.

Case Description

A 64-year-old, Caucasian, smoker man consulted for an ulcero-necrotic, exophytic, lesion of the right retromolar trigone. Head&neck CT scan showed a right tonsillar tumor lesion. The $^{18}$F-PET scan confirmed the presence of a right, highly hypermetabolic tonsillar lesion and two homolateral, cervical lymph nodes. Histology and immunohistochemistry were consisted with the diagnosis of a primary SCNC of the oral cavity. As the tumor was locally advanced and unresectable, the patient underwent a definitive radio-chemotherapy with a cisplatin/etoposide combined regimen (4 cycles). The treatment was well tolerated and led to a complete tumor response.

Conclusion

The particularity of this case relies on the rarity of the oral SCNC, its difficult and challenging diagnosis, and the complexity of its management that is not validated by large clinical trials, data being extrapolated from small cell lung cancer. In our case, the patient presenting a locally advanced tumor was treated by a combined radio-chemotherapy leading to a complete tumor regression. The patient's follow up is too short to assess the real benefit of this treatment on overall survival.

Introduction

Small cell neuroendocrine carcinoma (SCNC) is a poorly differentiated, high-grade and very aggressive tumor most commonly occurring in lung (1–3). Extrapulmonary SCNC accounts for 2.5%-5% of cancers (1–3). Head&neck SCNC contributes to 10%-15% of these cases, the larynx being the most common site, followed by the salivary glands and sinonasal region (4, 5). The oral SCNC seems to originate by the totipotential stem cells of the mucosal epithelium (6–11). The multimodal management of SCNC depends on the tumor stage and patient's comorbidities and performance status (PS) (12) and includes the surgical excision followed by a postoperative chemotherapy or radiation therapy for early stage tumors, a definitive radio-chemotherapy for locally advanced, unresectable tumors and systemic chemotherapy for metastatic patients (12, 13). The prognosis of oral SCNC is poor (12, 13).

In our case, the patient presenting a locally advanced tumor was treated by a combined radio-chemotherapy that led to a complete tumor response. It is difficult to well evaluate the real benefit of this treatment on patient's overall survival as the follow up is too short.

We present the following article in accordance with the CARE reporting checklist.
Case Description

In February 2022, a 64-year-old, Caucasian, smoker man consulted for a painful right submandibular lesion. He presented a type 2 diabetes, an arterial hypertension and a dyslipidaemia as relevant comorbidities. His past clinical history was uneventful. The patient's PS (ECOG) was 0. Clinical examination revealed an ulcer-necrotic, exophytic, tumor lesion of the right retromolar trigone, occupying the intermaxillary commissure, the anterior tonsillar pillar up to the palatoglossal fold and invading the homolateral soft palate (Fig. 1A, green arrow). Biological tests were in the normal ranges. Head&neck CT scan showed a right tonsillar tumor lesion (Fig. 1B, green arrow). The $^{18}$F-PET scan confirmed the presence of a right, highly hypermetabolic tonsillar lesion (Fig. 1C, green arrow) and two homolateral, concomitant cervical lymph nodes (Fig. 1C, red arrow). Histology showed a diffuse infiltration of small, pleomorphic cells with a high proliferating index (Fig. 1D). Immunohistochemically, tumor cells were positive for CD56, synaptophysin and chromogranin-A (Fig. 1E) and negative for cytokeratins AE1/AE3, CK 20 and p40 confirming the diagnosis of a primary SCNC of the oral cavity. The brain Resonance magnetic Image (RMI) was negative. As the tumor was locally advanced and unresectable, the patient started a combined treatment by loco-regional radiotherapy (69 Grays/33 fractions) and concomitant chemotherapy with cisplatin (80 mg/m$^2$) and etoposide (100 mg/m$^2$), administered on days 1–3 of a 21-day cycle (4 cycles). The treatment was well tolerated, the patient presenting an oral radiotherapy-induced mucositis and a cervical dermatitis of grade 2 and a dysgeusia of grade 1. After the first cycle of treatment, the tumor lesion was unchanged (Fig. 1F, green arrow) but, at the end of the treatment, it completely regressed (Fig. 1G, green arrow). At a follow up of 4 months, the patient is alive and free of tumor relapse as documented by clinical examination (Fig. 1H, green arrow), whole body CT scan (Fig. 1L, green arrow) and brain MRI.

Discussion

The primary oral neuroendocrine cancer (NEC) has been classified into typical carcinoid, atypical carcinoid, large cell and small cell NEC (1). SCNC, also called “small-cell carcinoma (SCC),” “oat cell carcinoma” and “anaplastic small cell carcinoma” (1), is a poorly differentiated, high-grade and very aggressive tumor most commonly occurring in lung (1–3). Extrapulmonary SCNC accounts for 2.5%-5% of cancers (1–3). Head&neck SCNC contributes to 10%-15% of these cases, the larynx being the most common site, followed by the salivary glands and sinonasal region (4). Oral SCNC is more frequent in the age group of 40–83 years (average of 67.5 years) and in the males (81.8%) (1–4). As for the squamous cancer, the most common risk factors include smoking and alcohol consumption (1–4). The most commonly involved sites in the oral cavity are tongue (64%), gingiva (9%) and buccal mucosa (18%) (3–4). In a large retrospective study, among the 347,252 patients with head&neck cancer, 1,042 (0.3%) patients presented SCC or poorly differentiated NEC (5). Out of the 853 evaluable patients, 542 (63.5%) showed SCC and 311 (36.5%) poorly differentiated NEC. The median age was 60 years (18–90 years). The majority of patients were male (66%) and classified as white race (86%). Larynx (35%) and nasal cavity/paranasal sinuses (30%) were the most common anatomical sites. The majority of patients had a
locally advanced tumor (stage III-IVB) (61%), the stage I-II and IVC tumors accounting for 17% and 22%, respectively. Overall 55% of patients had lymph node metastases (5).

The pathogenesis of the oral SCNC is unclear, several data supporting the hypothesis that it could originate from the mucosal, totipotential stem cells (6–11).

The multimodal management of SCNC depends on the tumor stage and patient's comorbidities and PS (12). The surgical excision followed by a postoperative chemotherapy or radiation therapy is usually considered as an effective treatment for operable tumors whereas a concomitant radio-chemotherapy is the standard treatment for locally advanced, unresectable tumors. Systemic chemotherapy remains the main treatment for metastatic patients (12, 13).

The prognosis of oral SCNC is poor (12, 13). Baugh et al. showed a median survival of 19 months in patients receiving a chemotherapy as compared to 11 months in those who did not (14). The site of primary tumor may also be prognostically important as reported by Hatoum et al (15), the SCNC arising from salivary glands presenting a better prognosis (14). In a recent retrospective analysis (5), the median and 2-year overall survival (OS) was 20.3 months and 45.2%, respectively. The median OS and 2-year OS by anatomic site was 20.8 months and 44.5% for oral cavity, 23.7 months and 49.4% for oropharynx, 17.9 months and 40.6% for larynx/hypopharynx, 15.1 months and 30.3% for nasopharynx and 36.4 months and 55.4% for nasal cavity primary tumors. Patients with concomitant lymph node metastases showed a median and 2-year OS of 20.8 months and 45.2% compared to 43.9 months and 62.3% for those without a lymph node disease (p < 0.001). For early stage patients, the only prognostic factor was the primary anatomical localization, patients with nasal cavity and paranasal sinuses presenting the best OS. For both early and locally advanced stage patients, the surgery did not add any statistically significant improvement in OS as compared to a definitive chemoradiation or radiation alone (5). The addition of radiotherapy to chemotherapy in metastatic patients did not result in any improved survival attesting for the aggressiveness and very poor prognosis of SCNC as documented by other smaller series (15, 16).

In conclusion, the head&neck SCNC represents a rare, clinically aggressive tumor with a poor prognosis (17). Patients with nasopharyngeal and laryngeal SCNC exhibit the least favorable prognosis, while patients with paranasal and nasal cavity have the best outcomes (1–6). The standard treatment consists of surgery followed by radio-chemotherapy for local, resectable tumors and a definitive radio-chemotherapy for locally advanced, unresectable stage (12). The chemotherapy alone remains the main therapeutical approach for metastatic patients with a modest improved of OS (12).

Conclusions

The particularity of this case relies on the rarity of SCNC, its challenging diagnosis because of the aspecific symptoms and finally on its difficult management due to the absence of prospective and validated data. Our patient presented a locally advanced, unresectable tumor and received a concomitant, definitive radio-chemotherapy leading to a complete tumor response. The patient’s follow up is very short not allowing any accurate evaluation of the efficacy of this treatment on OS.
Abbreviations

SCNC: Small cell neuroendocrine carcinoma
PS: Performance status
RMI: Resonance magnetic Image
NEC: Neuroendocrine cancer
SCC: Small-cell carcinoma
OS: Overall survival

Declarations

Source(s) of financial support: not applicable.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Availability of data and materials

All data and materials are available for review at the Division of Medical Oncology, CHR Metz-Thionville, in an electronic format.

Authors’ contributions

The patient was admitted under the care of RL and underwent systemic chemotherapy by RL, SC, CS, CW, AB, MC, FP, CB, and JE. Radiotherapy was performed by CGB. Radiological imaging was obtained with permission by the Department of Radiology at CHR Metz-Thionville. Histology pictures were courteously done by Dr Claire Bastien (Department of Radiology at CHR Metz-Thionville). All authors substantially
contributed to conception, acquisition, analysis and interpretation of data. All authors have been involved in drafting, revising and approving the final manuscript.

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Not applicable.

References


Figures

**Timeline: Diagnosis, treatment, and follow up**

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**Figure 1**

**Timeline of tumor diagnosis and treatment.**

A: Ulcero-necrotic, exophytic, tumor lesion of the right retromolar trigone (**green arrow**) (baseline clinical examination).

B: Right tonsillar tumor lesion (Haed&neck CT, axial section, **green arrow**).

C: Right, highly hypermetabolic tonsillar lesion (\(^{18}\)F-PET scan, axial section, **green arrow**) with a homolateral, concomitant cervical lymph node (red arrow).

C: Diffuse infiltration of small, pleomorphic cells with a high proliferating index (histology; H&E stain, 100x).

D: Cancer cells are positive for synaptophysin (H&E stain, 200x).
F: Clinical evaluation after the 1st cycle of chemotherapy (green arrow).

G: Clinical evaluation at the of the radio-chemotherapy showing a complete tumor response (green arrow).

H: Clinical evaluation after a follow up of 4 months confirming a complete tumor response (green arrow).

L: Tumor complete response at a follow up of 4 months (Haed&neck CT, axial section, green arrow).

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Carechecklist.pdf