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Case Report

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Mucoepidermoid Carcinoma Metastatic to Cervical Lymph Nodes with an Unknown Primary Site: A Rare Entity

Bouhia H[1*], Benmessaoud H[1], Ahmut H[1], Babouyoub FZ[1], Lachgar A[1], EL Majjaoui S[1], EL Kacemi H[1], Kebdani T[1], Hassouni K[1], Mouna khmou Pr[2], Youssef MAHDI[2] and Basma El Khannoussi[2]

[1]*Department of Radiotherapy, National Institute of Oncology, University Mohammed V of Rabat, Rabat, Morocco.*

[2]*Department of Anatomical Pathology, National Institute of Oncology, University Mohammed V of Rabat, Rabat, Morocco.*

[*]Corresponding Author
Dr. Bouhia hasnae, Department of Radiotherapy, National Institute of Oncology, University Mohammed V of Rabat, Rabat, Morocco.

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1. Introduction

Mucoepidermoid carcinoma (MEC) is a malignant tumour that develops from the salivary glands; most commonly in the parotid gland, but may also involve the accessory salivary glands.

MEC represents both a diagnostic challenge, due to its high morphological variability, and a prognostic challenge due to a histological classification into three entities: high grade, low grade and intermediate grade.High-grade MEC can be very aggressive with a relatively high rate of regional and distant metastases.

Mucoepidermoid carcinoma metastatic to cervical lymph nodes with an unknown primary site is very rare, few cases have been described in the literature.The aim of this article is to describe the clinical and histological aspects and management of a non-primary MEC through a case report.

2.Observation

We report a case of mucoepidermoid carcinoma metastatic to cervical lymph nodes with an unknown primary site in a chronic smoker and alcoholic 62-year-old patient. The initial symptomatology was a left cervical swelling, the cervical CT (computed tomography) scan showed a left sub-angulo-maxillary Lymph node involvement of 25*30*45mm.

The left cervical lymph node curage had revealed several metastatic nodes of a Poorly differentiated squamous cell carcinoma. A PET scan was subsequently performed, showing active lymph node involvement laterocervical (Levels II and III) and left supraclavicular lymph node involvement (Figure 1).

A new work-up was performed with panendoscopy and biopsies, and an oeso-gastroduodenal fibroscopy Revenue all without any particularities.

The patient subsequently underwent a left radical curage involving the left jugular vein, which revealed lymph node metastases from a high-grade mucoepidermoid carcinoma with capsular rupture infiltrating the adventitia of the left jugular vein (Figure 2).

The patient received adjuvant radiotherapy at a dose of 66Gy to the left ganglionic areas (from the skull base down to the clavicle) and prophylactic radiotherapy to the homolateral parotid and submaxillary glands at a dose of 60Gy using the VMAT technique (Figure 3).

For planning radiation treatment, we use CT simulator (Siemens, Erlangen, Germany).

High-risk Clinical Target Volume (CTV-HR), include the anatomic sites at the highest risk of tumour invasion corresponding to the left ganglionic areas, and it was expanded by isotropic 5 mm margin to generate planning target volume (PTV). Organs at risk (cord, brainstem, optic chiasma, right eye, right lens, right retina, right optic nerve, temporal lobes, cochleae, right parotid gland, oral cavity, larynx,) were contoured.

Planning goals for the PTV based on ICRU 83 were the following: at least 90% and 95% of the prescribed total do (PTD) encompassing at least 98% and 95% of PTV, respectively (V≥98% and V≥ 95%, respectively); and no more than 2% of PTV received more than 107% of the PTV (V≤ 2%).

The following constraints were set for some OARs: for cord, the

maximum dose received by 2% of its volume less than 45 Gy (D2%<45 Gy); for brainstem, D2%<55 Gy; for optic chiasm, D2%<60 Gy; for temporal lobes, D2%<65 Gy;for oral cavity Dmean<30-40Gy, and lastly, the mean dose received by right cochleae and left cochleae was respectively Dmean 25Gy and 23Gy (Figure 4).

Afterwards, the patient received external loco-regional radiotherapy at a dose of 50 Gy in 25 fractions, using the volumetric modulated arc therapy (VMAT) technique (Figure 3) plan with 6-MV photon beams was set by the medical physicist. VMAT plan was done with Elekta Versa HD. Patient position was verified weekly by kV cone beam CT imaging prior to treatment.

The patient tolerated the treatment and was seen weekly during treatment by our doctors.

No significant side effects were observed except mucite grade 1.

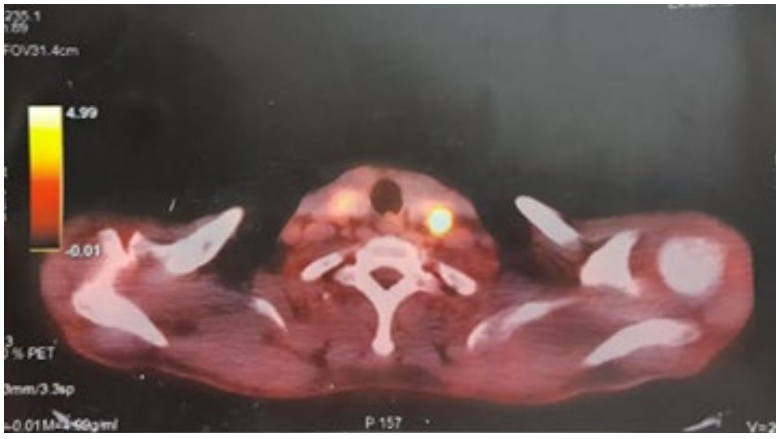


Figure 1: Axial positron emissiontomography (PET)/CT showing active lymph node involvement laterocervical (II and III) and left supraclavicular.

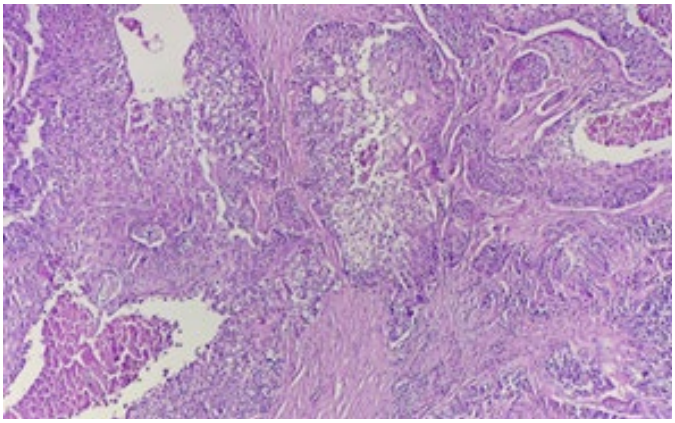


Figure 2: Solid and cystic areas of the tumor formed by different proportions of epidermoid (squamous) cells, mucus cells and intermediate cells (H&E stain, 10x).

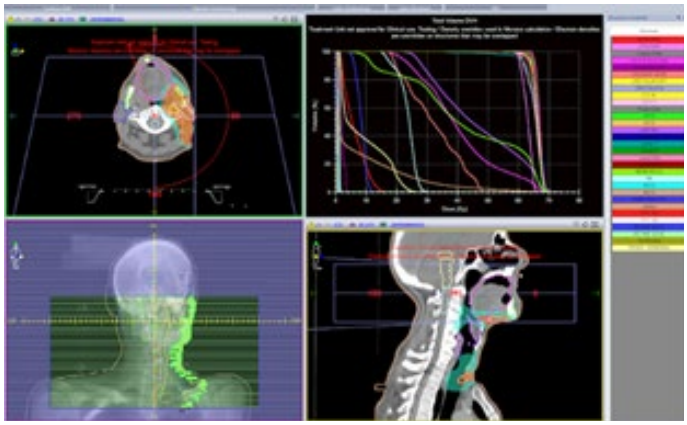
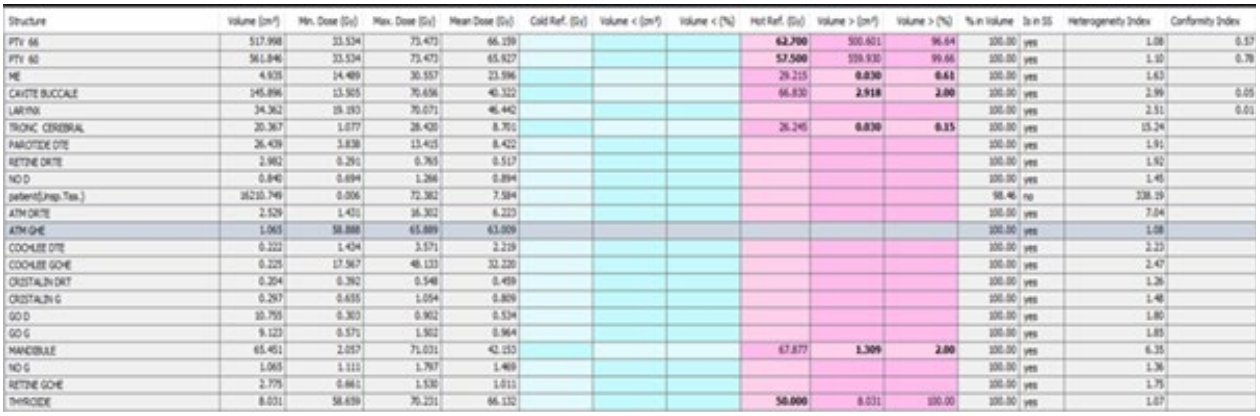


Figure 3: Computed tomography scan showing the target volumes: PTV-HR high risk in Red, PTH-IR intermediate risk in White. Volumetric modulated arc therapy was delivered to the region of high risk, to doses of 66 Gy.



Structure	Volume [cm³]	Min. Dose [Gy]	Max. Dose [Gy]	Mean Dose [Gy]	Cold Ref. [Gy]	Volume < [cm³]	Volume < [%]	Hot Ref. [Gy]	Volume > [cm³]	Volume > [%]	% in Volume	In in SS	Heterogeneity Index	Conformity Index
PTV 66	517.998	33.534	73.473	66.159				**62.700**	500.601	96.64	100.00	yes	1.08	0.57
PTV 60	561.846	33.534	73.473	65.927				**57.500**	559.930	99.66	100.00	yes	1.10	0.78
ME	4.928	14.489	30.557	23.596				29.215	**0.030**	**0.61**	100.00	yes	1.63	
CAVITE BUCCALE	145.896	13.505	70.656	40.322				66.830	**2.918**	**2.00**	100.00	yes	2.99	0.05
LARYNX	34.362	19.193	70.071	46.442							100.00	yes	2.51	0.01
TRONC CEREBRAL	20.367	1.077	28.420	8.701				26.245	**0.030**	**0.15**	100.00	yes	15.24	
PAROTIDE DTE	26.439	3.838	13.415	8.422							100.00	yes	1.91	
RETINE DRTE	2.982	0.291	0.765	0.517							100.00	yes	1.92	
NO D	0.840	0.694	1.266	0.894							100.00	yes	1.45	
patient(Unsp.Tiss.)	16210.749	0.006	72.382	7.584							98.46	no	338.19	
ATM DRTE	2.529	1.431	16.302	6.223							100.00	yes	7.04	
ATM GHE	1.065	58.888	65.889	63.009							100.00	yes	1.08	
COCHLEE DTE	0.222	1.434	3.571	2.219							100.00	yes	2.23	
COCHLEE GCHE	0.225	17.567	48.133	32.220							100.00	yes	2.47	
CRISTALIN DRT	0.204	0.392	0.548	0.459							100.00	yes	1.26	
CRISTALIN G	0.297	0.655	1.054	0.809							100.00	yes	1.48	
GO D	10.755	0.303	0.902	0.534							100.00	yes	1.80	
GO G	9.123	0.571	1.302	0.964							100.00	yes	1.85	
MANDIBULE	65.451	2.057	71.031	42.153				67.877	**1.309**	**2.00**	100.00	yes	6.35	
NO G	1.063	1.111	1.797	1.469							100.00	yes	1.36	
RETINE GCHE	2.775	0.661	1.530	1.011							100.00	yes	1.75	
THYROIDE	8.031	58.639	70.231	66.132				**50.000**	8.031	100.00	100.00	yes	1.07	

Figure 4: Dose-volume histogram distribution of the following structures: planning target volumes, spinal cord ; Oral cavity; larynx; brain stem; parotid glands (right); Right optic nerve; left optic nerve temporomandibular joints (right and left), right lens and left lens; ocular globes (right and left) cochleae(right and left); mandibular; thyroid gland.

3.Discussion

Salivary gland MEC is a rare malignancy. It accounts for 1-3% of malignant tumours of the head and neck and only 0.3% of all malignant tumours. It is characterised by epithelial proliferation of mucinous, intermediate and squamous cells [1].

The preferred site is, in decreasing order, the parotid gland (48%), the palate (20%) and the submandibular gland (7%) [2]. There is a slight female predominance. The average age of discovery varies between 40 and 60 years according to the authors [3]. Older age and the presence of lymph node metastasis with extra-glandular invasion are factors of poor prognosis [4].

Its etiopathogenesis is not well understood and the clinical signs are generally not very suggestive, especially in the initial stages. To our knowledge, there has been 2 case report of MEC metastatic to the cervical lymph nodes in which the primary site was not identified [5].

MEC metastatic to the cervical lymph nodes in which the primary site typing is based on several histological criteria. Furthermore, according to Seethala, the histological grade is a significant indicator of the prognosis of MEC as it defines the degree of aggressiveness of the tumour and determines the management [6].

Poorer prognosis factors of MEC metastatic to the cervical lymph nodes in which the primary site are: age >40, male sex, high histologic grade; advanced stage, regional lymph node metastatic (rate of 72%); distant metastatic rate of 13% [7-10].
The management of MEC metastatic to the cervical lymph nodes in which the primary site depends on the pathological diagnosis. Surgical treatment remains the treatment of choice [6,17]. Lymph node dissection is indicated in high-grade tumours where the risk of lymph node metastases is greater than 50% [3-11].

Low-grade MEC are treated by surgery alone with good outcome and an estimated 5-year OS of >92%. Unlike high-grade MEC; which are at risk of local and distant recurrence with an estimated OS of 60% [9-10].

For inoperable patients or who refused surgery; 2 long-term studies on primary radiation therapy for salivary gland malignancies (patients receiving over 66 Gray (Gy).) showed 10-year local control rates of 57%14 and 75%,15 respectively, with a significant local control. Even if MEC has traditionally been considered radioresistant [12,13].

Adjuvant radiation increased locoregional control and improve overall survival for patients with positive Margins and advanced-stage disease as well as for all high-grade tumors, where the risk of local recurrence and metastasis is high[10,11,14,16-19].

The toxicities of postoperative adjuvant radiation include facial dysfunction (epiphora and ectropion); osteoradionecrosis of the temporal bone and the jaw [20-21]. To our knowledge, there has been 2 case report of MEC metastatic to the cervical lymph nodes in which the primary site was not identified [28].

The first patient underwent a panendoscopy and incisional biopsy of a 6 cm neck mass that was positive for MEC. He was treated with an ipsilateral radical neck dissection and postoperative radiation from the skull base down to the clavicle [1].

The second patient was biopsied extensively at many common minor salivary gland sites, and underwent complete excision of the ipsilateral sublingual gland.

Parotid and submandibular glands were clinically and radiographically negative. Furthermore, PET scan was negative in identifying the primary site he underwent complete excision and adjuvant radiotherapy was recommended by a multidisciplinary tumor board. Our patient has not only had an unknown primary site but multiple risk factors for progression of disease (age, sex, stage, grade), thus adjuvant radiotherapy was recommended by a multidisciplinary tumor board.

Concomitant radiochemotherapy was not recommended for our patient.

Indeed, several series have evaluated the use of chemotherapy

without salivary gland tumours with response rates ranging from 18% to 44% [23-25].

A Case control study based on retrospective medical record review comparing 2 arms of adjuvant therapy concomitant chemoradiotherapy and radiotherapy alone) in patients treated for locally advanced salivary tumours showed an improvement in overall survival with no difference in progression-free survival in favour of the concomitant chemoradiotherapy arm. However, the overall survival advantage was observed in patients with adenocarcinoma and salivary carcinoma; no difference was observed in the MEC subgroup.

Also high toxicity (grade 3) was observed in the concomitant chemoradiotherapy arm [21].

Retrospective studies evaluating the efficacy of PET/CT in detecting the extent of malignancy at the primary site show overall sensitivities ranging from 85.7% to 100% [26,27].

Our patient was treated with postoperative radiotherapy to the tumor bed, ipsilateral neck, and likely sites of an occult primary, such as the parotid and submandibular glands. The minor salivary glands were not included in the field given the negative examination under anesthesia. The patient completed radiation therapy and, on follow-up PET/CT 3months later, there was no uptake.

The long-term prognosis of mucoepidermoid carcinoma depends on healthy surgical margins and histological grade. Low-grade tumours have a 5-year survival of 90-100%, whereas this percentage falls to 20-40% for high-grade tumours [2,3].

4. Conclusion

The radiosensitivity of MEC is questionable, but in the case of MEC metastatic to cervical lymph nodes with an unknown primary site, irradiation of lymph node areas and suspected primary sites has shown significant benefit in controlling locoregional recurrence. However, the lack of randomised studies, particularly in regional lymph node metastases, does not allow its real effectiveness to be evaluated.

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