Oral Oncology 97 (2019) 151–152

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Letter to the editor

Successful tri-modality treatment of atypical carcinoma ex-pleomorphic adenoma with more than 50 nodal metastases☆

ARTICLE INFO

Keywords:
Carcinoma ex-pleomorphic adenoma
Nodal metastases
Composite resection
Radiotherapy
Chemotherapy

ABSTRACT

Carcinoma ex-pleomorphic adenoma (CEPA), an extremely aggressive malignant tumor, bears a significant potential for locoregional recurrence and distant metastases. Management of the disease usually involves definitive surgery with postoperative radiotherapy administered for identified nodal metastases. Two cases of CEPA with many (> 50) cervical lymph node metastases and other histopathological features were managed by tri-modality treatment scheme. No evidence of disease occurred during follow-up of at least 2 years. These cases may eventually establish the value of surgery with adjuvant radiochemotherapy in patients with CEPA and supernumerary nodal metastases.

Introduction

Carcinoma ex-pleomorphic adenoma (CEPA), an epithelial malignancy arising from a pleomorphic adenoma, is a relatively uncommon neoplasm representing 3–5% of all salivary gland neoplasms, and 5–15% of all salivary gland cancers (SGC) [1]. In a recent clinical investigation of the risk of pleomorphic adenoma progression to CEPA, an increased chance for the occurrence of the phenomenon was found in older patients and individuals presenting with larger tumor volumes/sizes [2]. The optimal treatment strategy in cases of CEPA and supernumerary nodal metastases (SNM) remains unclear. Herein, we present two cases diagnosed at our institution wherein the tri-modality treatment scheme was found beneficial.

Cases reports

This study was approved by the institution's local review board, and pertinent patient information was collected after the approval was obtained. These individuals with CEPA and more than 50 nodal metastases (NM) were identified from a review of the lists of presented cases at the weekly/monthly multidisciplinary oncology conferences of the Departments of Otolaryngology-Head Neck Surgery and Oral Maxillofacial Surgery.

Patient 1

A 62-year-old man presented with a 12-month history of a progressively enlarging, fixed mass in the right submandibular region. A biopsy specimen in April 2017 confirmed the presence of CEPA. Positron emission tomography-computed tomography (PET-CT) showed lymphadenopathy in the right side of the neck. Given the high-risk histopathologic features observed after composite resection (Table 1), adjuvant radiochemotherapy was administered. Only three cycles of cisplatin chemotherapy were applied due to the Grade 3 neutropenia that developed. Ipsilateral conventional fractionated megavoltage locoregional postoperative radiotherapy (PORT) meant the delivery of 66 Gy to the primary tumor bed and upper neck with 60 Gy to the lower neck. In September 2017, post-treatment PET-CT did not show any residual tumor. At follow-up in March 2019, the patient was asymptomatic and disease-free.

Patient 2

A 70-year-old man sought medical attention because of a left-sided subauricular mass that had increased in size over the last 6 months. A diagnosis of carcinoma with large pleomorphic cells was made after needle aspiration of the tumor in June 2016. PET-CT at the time revealed intraparotid gland nodules and multiple cervical lymph nodes. Histopathology (Table 1) from the total parotidectomy and modified neck dissection (of levels I - V) indicated the need for adjunctive radiochemotherapy. Postoperative cisplatin chemotherapy was limited only to 4 cycles (and entailed the use of a reduced dose in the last week of therapy) because of severe nausea and vomiting. The applied dose-fractionation scheme for unilateral conventional external beam locoregional PORT of the parotid area and neck was 68.4 Gy/38 fractions. Adjuvant combined therapy was completed in October 2016. A PET-CT in March 2018 found no evidence of CEPA. Follow-up a year later documented the patient's tumor-free status.

Discussion

Any modification of the radical neck dissection represents only sampling of the nodes present because there are approximately 300 lymph nodes in the neck (150 nodes per side) [3]. The maximum amounts of declared NM in individuals with head and neck cancer (HNC) were 68 in a review of 87 patients with high-grade SGCs [4], and

Abbreviations: CEPA, carcinoma ex-pleomorphic adenoma; SGC, salivary gland cancer; SNM, supernumerary nodal metastases; NM, nodal metastases; PET-CT, positron emission tomography/computed tomography; PORT, postoperative radiotherapy; HNC, head and neck cancer

☆ This research did not receive any specific grant from funding agencies in the public, commercial, and not-for-profit sectors.

https://doi.org/10.1016/j.oraloncology.2019.07.025
Received 15 July 2019; Received in revised form 23 July 2019; Accepted 25 July 2019
Available online 08 August 2019
1368-8375/

Table 1
Two cases of carcinoma ex-pleomorphic adenoma (CEPA) with supernumerary (> 50) nodal metastases.

Features	Case 1	Case 2
Age (in years)/Gender	62/Male	70/Male
CEPA location	Submandibular gland	Intraparotid lymph nodes
Tumor histopathology		
Size (in cm)	3.9 × 2.6 × 2.5	2.4 × 1.9 × 1.7
Grade	III	III
Resection margins	–	+
Perineural invasion	+	+
Lymphovascular invasion	+	+
Extracapsular spread	+	+
Number of metastatic nodes/		
Number of examined nodes	62/87	52/71
Pathologic stage	pT2N2b	pT2N2b
Follow-up PET-CT*	NED	NED
Disease-free follow-up (in months)	24	34

* Imaging obtained more than three months after the application of tri-modality therapy; NED (No evidence of disease).

130 in a sample of 309 people with oral cavity cancers [5]; however, treatment and outcomes of these patients were not discussed in the reports. Recently, the important association between the increased number of positive nodes and an adverse prognosis in the population with SGC was asserted [6]. A review of our 2-year experience of 370 patients diagnosed with HNC yielded two individuals (0.5%) with CEPA-SNM. To our knowledge, there are no previous reports about CEPA and more than 50 NM. In the characterized classification of CEPA [7] (non-invasive, minimally invasive and widely invasive groups), the last category is more commonly encountered [8]. Moreover, we think this degree of invasiveness could occasionally express its aggressive potential in the manner of SNM. For the proper design of therapeutic intervention, a thorough knowledge of the known risks of locoregional recurrence and distant tumor spread is essential. Although a level 1 evidence-based management algorithm does not exist for CEPA, definitive surgery is the accepted mainstay of treatment, and postoperative radiotherapy (PORT) has often been administered [4,9] for documented metastatic disease in the regional lymph nodes. To date it is not clear that adjuvant chemotherapy is useful in these individuals especially in the presence of an excessive number of positive nodes. Two salient points are noteworthy in the management of CEPA: The recorded incidence of locoregional recurrence in patients with NM from CEPA has ranged from 38% to 65% [1,10] and a recognized correlation between advanced nodal stage and the development of systemic disease was reported in an experience of 51 individuals with CEPA {1]; Zhao et al. [1] found the risk for development of distant metastasis was approximately 6-fold more frequent in patients with pathological NM versus patients without pathological NM (65% and 9%, respectively, $p < .001$). Mindful of the axiom that adjunctive therapy is appropriate when the risk of tumor relapse is ≥20% [11], we believe the preceding observations formed the support for the prudent use of postoperative concurrent radiochemotherapy in our subjects.

The present findings suggest tri-modality therapy directed at CEPA-SNM can be associated with acceptable prognosis. Indeed, the observation period of tumor-free status may not be long enough. However, such duration appears to be in line with the observed median time of development of locoregional recurrences or distant metastases in patients with CEPA; these events have been demonstrated within 24 months following therapy [8,10].

Conclusion

The correct determination of the risks and selection of multimodal therapy in the 2 presented cases of CEPA-SNM led to an acceptable, intermediate-term outcome. This may assist in the ultimate establishment of postoperative radiochemotherapy as standard of care.

Declaration of Competing Interest

None.

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Federico L. Ampil[a,*], Nestor de la Cruz[b]
[a] *Department of Radiology, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA, USA*
[b] *Department of Pathology, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA, USA*
E-mail address: fampil@lsuhsc.edu (F.L. Ampil).

* Corresponding author.