Teaching Case

Microcystic Adnexal Carcinoma of the Face Treated With Definitive Chemoradiation: A Case Report and Review of the Literature

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Received 22 July 2019; revised 29 October 2019; accepted 14 November 2019

Introduction

Microcystic adnexal carcinoma (MAC) is a rare, indolent, low-grade, malignant cutaneous neoplasm believed to arise from the sweat glands most commonly seen in the head and neck area.1,2 Since MAC was first described as a distinct histologic entity in 1982,3 less than 700 cases have been reported worldwide. MAC typically affects middle aged to elderly whites. MAC lesions usually present as a solitary, slow-growing 1- to 3-cm white yellowish papule or plaque located primarily over the face.1,4,6 Patients are generally asymptomatic and may present years after initial development of the skin lesion.7,8 Some develop ulceration or paresthesia if there is perineural invasion (PNI).5,9 Despite its subtle clinical appearance, MAC is a locally aggressive and infiltrative tumor and commonly presents with extensive subclinical involvement and PNI,4,6,10 although lymph node involvement and distant metastasis are rare.2 Given its rarity, research on MAC management is limited to case reports and small retrospective studies. MAC is routinely treated surgically by wide local excision and Mohs micrographic surgery.11 However, owing to its deeply invasive nature, MAC often requires extensive surgical resection resulting in large anatomic defects in the head and neck region.12,13 For patients with large lesions, PNI, and extension to muscle and bone, obtaining clear margins may not be technically feasible or patients may not want to undergo the poor cosmetic and functional consequences. In these cases, there are reports outlining a potential role for radiation (RT) in the adjuvant and definitive setting.1,5,7,8,10,12,14-30

Sources of support: No external funding was received for this manuscript.

Disclosures: Dr Tishler has received personal fees from Regeneron (Advisory Board), PSI Oragenics (Data Safety Monitoring Board), and EMD Serrono (Advisory Board). All other authors have indicated they have no financial relationships relevant to this article to disclose. All authors have indicated they have no potential conflicts of interest to disclose.

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https://doi.org/10.1016/j.adro.2019.11.008
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is necessary. To our knowledge, the use of definitive concurrent chemoradiation (chemoRT) as the initial treatment has not been reported. In this case report, we will share our experience treating one patient with an extensive MAC lesion using weekly chemotherapy with concomitant RT.

Case Presentation

A 73-year-old man with a 12-year history of a biopsy-proven MAC nodule on his philtrum presented with worsening upper lip numbness, midfacial swelling, and nose firmness over 1 year. He had previously declined surgical resection at his local hospital for this nodule. On our initial examination, he was noted to have a 1 cm exophytic smooth nodule on the philtrum with induration and deformity of upper lip and anterior dorsal nose extending to bilateral cheeks (Fig. 1 A). Biopsy of the upper lip lesion confirmed MAC without any PNI or lymphovascular invasion. Positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) demonstrated 2 fluorodeoxyglucose- (FDG) avid lesions: a 5.5-cm soft tissue thickening extending from the upper frenulum to the nose and a 2.5-cm submandibular mass (Fig. 2A). There was no bony involvement or distant metastasis. Biopsy of the submandibular mass revealed a low-grade oncocytic neoplasm with hyalinization. The patient declined surgery and his multidisciplinary care team agreed that surgery would result in significant cosmetic and functional deficits given his extensive MAC involvement. Given the long untreated history of this nodule, we recommended definitive RT to the primary site and nodal area with concurrent chemotherapy as a potential radiosensitizer to enhance the efficacy of the treatment in the setting of a 12-year history of an untreated MAC. Throughout 7 weeks of treatment, he received 70 Gy of intensity modulated RT over 35 fractions to the primary site and 4 cycles of concomitant weekly carboplatin (area under the curve 1.5) and paclitaxel (30 mg/m²; Fig. 3). Carboplatin/paclitaxel have activity in the metastatic setting and also act as a radiosensitizer in head and neck cancers. In addition, the patient was not a good candidate for cisplatin given his history of bilateral sensorineural hearing loss requiring hearing aids. The facial lymphatic regions were treated to 63 Gy, and bilateral levels I to II lymph nodes were treated to 56 Gy. Taxol was withheld during the last 2 weeks of treatment owing to severe mucositis and pain. There were no radiation treatment breaks.

Clinical response of MAC was observed as early as the second week of chemoRT where he was noted to have reduced facial firmness and deformity. At his 3-month visit, PET/CT showed interval decrease in the FDG-avidity and size of the nasal and upper lip lesion, with a focal intense uptake in upper lip correlating with superficial ulceration noted on physical examination likely representing treatment effect (Fig. 2 B). MRI showed a slight reduction in tumor thickness. Follow-up scans 6 months after treatment demonstrated a continued decrease in FDG-avidity (Fig. 2 C). One year after chemoRT, firmness in his philtrum was confined to 1 × 1 cm at midline (Fig. 1 B), and PET/CT did not demonstrate any FDG avidity or lesions at the site of the primary (Fig. 2 D). MRI showed stable soft tissue thickening of the upper frenulum and nose. The patient remains asymptomatic and progression-free 6 years from the completion of his treatment.

Discussion

MAC is typically treated surgically by wide local excision or Mohs micrographic surgery. However, definitive surgery is not an option for patients who refuse it or are poor surgical candidates for reasons including competing comorbidities, large expected surgical defects, and inability to achieve negative margins owing to tumor location, PNI, and deep infiltration. In such cases, adjuvant or definitive RT have been used and demonstrated

Figure 1  Microcystic adnexal carcinoma: (A) Before chemoradiotherapy. One cm nodule on the philtrum with midfacial induration of the lower two-thirds of the nose, philtrum, entire upper lip, and lateral cheeks secondary to microcystic adnexal carcinoma infiltration. (B) One-year after chemoradiotherapy. Excellent tumor response with reduction of previously extensive midfacial induration to 1 × 1 cm area of the philtrum.
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cacy (Table 1).5,7,8,10,12,14,15,17-25,27,29,30 Chemo-
therapy has been used in only 4 reported cases showing
mixed outcomes.17,21,25,30 Here, we report a case of an
extensive, locally advanced MAC treated by de-
finitive chemoradiotherapy resulting in an excellent tumor response and
durable disease control.

Our experience builds on previous data showing the
efficacy of RT in MAC. In Table 1,1,5,7,8,10,12,14-30 we
summarize cases of MAC treated by definitive or adjuvant
RT. Although interpretation of these studies is limited by
the varying clinical situations and heterogeneous RT
regimens used, most suggest that RT is effective among
cases with high-risk features and may be beneficial even
in the definitive setting as a surgical alternative. In a
retrospective study by Baxi et al.10 14 cases treated with
local excision and adjuvant RT (median 55 Gy) achieved

Figure 2  Fluorodeoxyglucose-positron emission tomography (PET), computed tomography (CT), and fused PET/CT scans showing
microcystic adnexal carcinoma lesion of the nose and philtrum at (A) 1 month before chemoradiotherapy and response to treatment at
(B) 3 months, (C) 6 months, and (D) 1 year after chemoradiotherapy. A fused PET-CT image was not available for the pretreatment
scan.

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local excision and adjuvant RT (median 55 Gy) achieved
a 93% crude local control rate despite 56% and 69% having had positive margins and PNI, respectively. Among 5 case reports\(^8,14,15\) using upfront definitive RT as a surgical alternative, 3 described positive clinical outcomes.\(^8,14,15\) Pugh et al\(^8\) used RT (63.6 Gy) as an initial monotherapy for an upper lip MAC lesion and achieved complete remission lasting at least 40 months. At 48 months post-RT, there was recurrence in the treatment area which was reirradiated, resulting in remission. Another case by Gulmen and Pullon\(^14\) using RT (60 Gy) to a lower lip lesion and one suspicious submental lymph node (50 Gy) demonstrated a complete response, although follow-up was only 6 months. Schipper et al\(^15\) reported a case of a tongue tumor in a patient who declined surgery which was treated with RT and resulted in no clinical progression at 21 months. Poor outcomes were observed in 2 cases using upfront RT. Chen et al\(^17\) reported a case of a left thumb nodule initially treated by RT but the patient developed distant metastases involving the lymph nodes, liver, spleen, and lung 36 months later. Stein et al\(^16\) observed recurrence within 6 months after RT (58 Gy) to the nasal dorsum, with a clinically more extensive and aggressive tumor notable for histopathologic dedifferentiation. The paucity and heterogeneity of cases using RT in MAC make the exact role of RT in treating MAC challenging to interpret.

The role of chemotherapy in MAC is even less clear as there are only 4 reported cases\(^17,21,25,30\) of chemotherapy used to treat it (Table 2). Bier-Laning et al\(^25\) used a single course of cisplatin and 5-fluorouracil for a recurrent metastatic disease which was resistant to multiple surgical resections and RT. Chemotherapy failed to eradicate the tumor and the patient required salvage surgery and RT within 8 months. Chaudhari et al\(^21\) reported a case of MAC in a 14-year-old adolescent who received chemoRT for lymph node involvement after undergoing surgical resection of the primary lip lesion; details regarding chemoRT and clinical outcomes were not reported. For the first time, Chen et al\(^17\) reported a case of an objective partial response confirmed by PET/CT 1 month after 4 cycles of paclitaxel/carboplatin in a widely metastatic MAC which had relapsed 36 months after initial RT to a thumb nodule. Unfortunately, progression was noted 2 months later with new metastases in the bone and liver.

**Figure 3**  Radiation plan for treatment of microcystic adnexal carcinoma primary tumor and elective regional nodes in (A) axial, (B) sagittal, and (C) coronal view. **Abbreviation:** PTV = planning target volume, defined as 5 mm expansion of clinical target volume (CTV). Computed tomography simulation performed with tongue immobilizer. Daily cone beam computed tomography used for imaging guidance; 0.5 cm bolus used daily.
| Location                      | Planning objectives | Achieved objectives |
|-------------------------------|---------------------|---------------------|
| Brachial plexus, left         | Max                 | <60 Gy              | Max                 | 35.2 Gy |
| Brachial plexus, right        | Max                 | <60 Gy              | Max                 | 40.3 Gy |
| Brain stem                    | Max                 | <54 Gy              | Max                 | 25.8 Gy |
| Chiasm                        | Max                 | <54 Gy              | Max                 | 29.7 Gy |
| Cochlea, left                 | Max                 | <30 Gy              | Max                 | 21.5 Gy |
| Cochlea, right                | Max                 | <30 Gy              | Max                 | 20.7 Gy |
| Constrictors                  | Mean                | <40 Gy              | Mean                | 32.1 Gy |
| Cord                          | Max                 | <45 Gy              | Max                 | 32.8 Gy |
| Esophagus                     | Mean                | <30 Gy              | Mean                | 1.1 Gy  |
| Eye, left                     | Max                 | <45 Gy              | Max                 | 41.6 Gy |
| Eye, right                    | Max                 | <45 Gy              | Max                 | 39.8 Gy |
| Lacrimal, left                | Max                 | <30 Gy              | Max                 | 17.9 Gy |
| Lacrimal, right               | Max                 | <30 Gy              | Max                 | 18.8 Gy |
| Larynx                        | Mean                | <40 Gy              | Mean                | 20.1 Gy |
| Optic nerve, left             | Max                 | <54 Gy              | Max                 | 27.8 Gy |
| Optic nerve, right            | Max                 | <54 Gy              | Max                 | 35 Gy   |
| Mandible                      | Max                 | <50 Gy              | Max                 | 72.7 Gy |
| Parotid, left                 | V30                 | <50%                | V30                 | 13.10%  |
|                               | Mean                | <26 Gy              | Mean                | 17.3 Gy |
| Parotid, right                | V30                 | <50%                | V30                 | 23.40%  |
|                               | Mean                | <26 Gy              | Mean                | 23.4 Gy |
| Post cricoid                  | Mean                | <40 Gy              | Mean                | 5 Gy    |
| PTV 56 Gy                     | Min                 | V54.9               | 97.30%              |
|                               | V100% prescription dose | V56 | 95.20% |
|                               | >95%                |                     |                     |
| PTV 63 Gy                     | Min                 | V61.7               | 96.40%              |
|                               | V100% prescription dose | V63 | 93.20% |
|                               | >95%                |                     |                     |
| PTV 70 Gy                     | Min                 | V68.6               | 98.20%              |
|                               | V100% prescription dose | V70 | 93%    |
|                               | >95%                |                     |                     |
| Submandibular gland, left     | Mean                | <39 Gy              | Mean                | 61.7 Gy |
| Submandibular gland, right    | Mean                | <39 Gy              | Mean                | 61.5 Gy |

*Figure 3 (continued)*
| Author                  | Age/sex | Primary tumor site | Initial treatment | TTR (mo) | Site of recurrence | Salvage treatment | Outcome                          |
|-------------------------|---------|--------------------|-------------------|----------|--------------------|------------------|----------------------------------|
| **Definitive RT**       |         |                    |                   |          |                    |                  |                                  |
| Gulmen and Pullon (1976) | 35/F    | Left lower lip + palpable submental LN | RT to primary (60 Gy) + LN (50 Gy) | n/a      | n/a                | n/a              | NED at 6 mo                      |
| Schipper et al (1995)   | 65/M    | Tongue             | RT (NS); declined surgery | n/a      | n/a                | n/a              | No change in tumor size. No tumor progression at 21 mo |
| Stein et al (2003)      | 76/F    | Right nasal dorsum | RT (58 Gy)        | 6        | Primary site + left nasal dorsum + right medial cheek | SE              | Recurrent tumor notable for dedifferentiation. NED at 14 mo |
| Pugh et al (2012)       | 53/F    | Upper lip          | RT (63.6 Gy)      | 48       | Primary site       | RT (64 Gy)       | NED at 15 mo                     |
| Chen et al (2017)       | 68/M    | Left thumb nodule  | RT (NS)           | 36       | Left axillary/ supraclavicular LNs + liver, spleen, and lung | Chemo           | Objective partial response after 1 mo of chemo followed by new bony and hepatic lesions at 3 mo. |
| **Adjuvant RT**         |         |                    |                   |          |                    |                  |                                  |
| Birkby et al (1989)     | 51/M    | Left lower lip     | SE with positive margins + RT (57.5 Gy) | 36       | Primary site + left mandible invasion | MMS + SE + RT (61.2 Gy) | NED at 18 mo                     |
| Yuh et al (1991)        | 51/M    | Left lower lip     | SE with positive margins + RT (57.5 Gy) | 36       | Primary site with invasion of mandible | SE + RT          | NED at 18 mo                     |
| Kirkland et al (1997)   | 55/F    | Nasal septum       | SE with positive margins + RT (55 Gy) | n/a      | n/a                | n/a              | NED at 6 mo                      |
| Ong et al (2004)        | 89/F    | Right eyebrow      | SE + RT           | n/a      | n/a                | n/a              | NED at 6 mo                      |
| Baxi et al (2010)       | 14 pts, median age 71 y | Head and neck region | SE (with 56% PNI + 69% positive margins) + RT (median 55 Gy) | Median follow up of 5.4 y. Crude local control rate of 93%. One pt with local recurrence involving CN V salvaged with RT but progressed after 2 y. One pt with ipsilateral cervical nodal recurrence 18 months after RT. Both salvaged with SE followed by RT with NED. | n/a      | n/a                | n/a              | NED at 26 mo                      |

(continued on next page)
| Author            | Age/sex | Primary tumor site | Initial treatment                                                                 | TTR (mo) | Site of recurrence | Salvage treatment | Outcome                  |
|-------------------|---------|--------------------|-------------------------------------------------------------------------------------|----------|--------------------|--------------------|--------------------------|
| Pugh et al (2012) | 60/F    | Chin               | MMS with muscle and PNI → SE + RT (66 Gy)                                            | n/a      | n/a                | n/a                | NED at 30 mo             |
| Kim et al (2014)  | 56/F    | Scalp              | SE with positive margins, PNI, and perioisteal involvement → SE + RT (NS)            | n/a      | n/a                | n/a                | NED at 3 y               |
| Chaudhari et al (2015) | 14/M    | Right medial upper lip + submandibular LN | SE + SLNB with LN involvement → RT + chemo (NS)                                      | n/a      | n/a                | n/a                | NED                      |
| Waqas et al (2017) | 59/F    | Scalp              | SE with positive margins + RT (45 Gy)                                              | n/a      | n/a                | n/a                | NED at 36 mo             |
| Waqas et al (2017) | 53/M    | Left temporal scalp | SE with positive margins + RT (45 Gy)                                              | n/a      | n/a                | n/a                | NED at 36 mo             |
| Wong et al (2018)  | 15/F    | Right nipple       | SE with positive margin and PNI + RT SE with positive margin + RT                   | n/a      | n/a                | n/a                | NED at 17 mo             |
| Brent et al (2018) | NS      | Orbit              |                                                                                   |          |                    |                    | NED                      |
| Bier-Laning et al (1995) | 46      | Right cheek        | SE                                                                                  | 96       | Primary site       | RT (60 Gy)         | Field edge recurrence at 18 mo treated with reirradiation (45 Gy). Recurrence at 19 mo requiring multiple reirradiation + resections + chemo. Remained with suspicious lesion on lip. |
| Bier-Laning et al (1995) | 85      | Right cheek        | Several SEs                                                                         | NS       | Primary site + right CN Vb | MMS with positive margin → SE | Right lower eyelid involvement at 13 mo salvaged with RT (60 Gy). NED at 7 mo. |
| Bier-Laning et al (1995) | 55      | Left posterior scalp | Several SEs                                                                         | 10       | Primary site extending to dura | MMS + SE | Progression at 46 mo. Debulking only + RT (54 Gy). NED at 10 mo. |
| Carroll et al (2000) | 86/M    | Left upper forehead | MMS                                                                                 | 5        | 3 new distant nodules in scalp | MMS | 3 months later developed 5 more small nodules on scalp. Received RT |
| Author                  | Age/sex | Primary tumor site | Initial treatment | TTR (mo) | Site of recurrence | Salvage treatment | Outcome                                                                 |
|------------------------|---------|--------------------|-------------------|----------|--------------------|-------------------|-------------------------------------------------------------------------|
| Sebastien et al (1993) | 57/F    | Chin               | MMS               | 60       | Primary site       | MMS               | (60 Gy, 6 megavolt scalp) but developed nodal recurrence 3 mo later. Underwent MMS but found to have LN infiltration. Expired shortly after from metastatic small cell lymphoma. MMS + adjuvant RT (55 Gy) for local recurrence 48 mo later. NED at 16 mo. Controlled at 47 mo. |
| Clement et al (2005)  | 83/M    | Right canthus      | SE                | 7        | Upper eye lid      | SEs with positive margin + RT (60 Gy) | Recurrence at 4 mo → MMS, SEs + RT (57.6 Gy). Third recurrence in left cheek treated with RT (45 Gy). Controlled at 71 mo. Exenteration for local recurrence 24 mo after RT. Developed brain stem and cavernous sinus metastases 21 mo later. Managed with supportive care. SE + RT (58 Gy). NED at 18 mo |
| Clement et al (2005)  | 59/M    | Left temporal      | SE with positive margin and PNI | 8        | Primary site       | MMS               | Recurrence at 4 mo → MMS, SEs + RT (57.6 Gy). Third recurrence in left cheek treated with RT (45 Gy). Controlled at 71 mo. Exenteration for local recurrence 24 mo after RT. Developed brain stem and cavernous sinus metastases 21 mo later. Managed with supportive care. SE + RT (58 Gy). NED at 18 mo |
| Gomez-Maestra (2009)  | 75/F    | Right eyebrow      | MMS               | 24       | Right supraorbital nerve | SE + RT (61.2 Gy) | Recurrence at 4 mo → MMS, SEs + RT (57.6 Gy). Third recurrence in left cheek treated with RT (45 Gy). Controlled at 71 mo. Exenteration for local recurrence 24 mo after RT. Developed brain stem and cavernous sinus metastases 21 mo later. Managed with supportive care. SE + RT (58 Gy). NED at 18 mo |
| Mamic et al (2018)    | 74/F    | Left upper lip     | SE                | 36       | Primary site       | SE with positive margin | SE + RT (58 Gy). NED at 18 mo |
| King et al (2018)     | 3 pts   | NS                 | SE                | NS       | NS                 | SE + RT           | 2 had progressive disease with 1 developing fatal metastases to skin, LN, and lung. |
| Haga et al (2019)     | 78/F    | Philtrum           | SE                | Unknown Primary site | RT (60 Gy) | Recurrence at primary site and ala of the nose < 2 y after RT. Chemo at 6 y for recurrence. Under control at 15 mo. |

**Abbreviations:** CN = cranial nerve; F = female; LN = lymph node; M = male; MMS = Mohs micrographic surgery; n/a = not applicable; NED = no evidence of disease; NS = not specified; PNI = perineural invasion; pt = patient; RT = radiation therapy; SE = surgical excision; TTR = time to recurrence.
S-1 is a combination drug including tegafur/gimeracil/oteracil. Chaudhari et al (2015) recently reported a case using a combination chemotherapy S-1 (tegafur/gimeracil/oteracil) for a locally invasive recurrent tumor of the philtrum previously treated by resection and RT (60 Gy). Objective partial response of the tumor was seen at 8 weeks and the tumor was controlled at 15-month follow-up.

To our knowledge, this is the first case of a patient with MAC treated without surgery with definitive chemorT. Although prophylactic regional nodal irradiation is not standard treatment given its toxicity and rare nodal metastasis of MAC, regional nodes were irradiated in this case to maximize locoregional control given the unresectable disease and that chemotherapy could potentially act as a radiosensitizer to improve local control. Using RT with 70 Gy and concomitant paclitaxel/carboplatin, clinical improvement, and radiographic partial response was achieved within 2 weeks and 3 months of chemorT, respectively. The patient remains asymptomatic and progression free for about 6 years, which is the longest follow-up reported on MAC tumor control achieved with either RT or chemotherapy. Although our patient did experience significant mucositis and was transiently G-tube dependent, he recovered within 1 month after completion of his treatment and the toxicities are consistent with those expected for a patient treated with chemorT for a head and neck cancer. Overall, he had an excellent cosmetic result and was able to avoid surgery. Given the retrospective review of our case, it is uncertain whether his tumor would have responded to monotherapy with RT or chemotherapy alone. However, our experience suggests that chemorT is a tolerable and potentially effective therapeutic modality for locally advanced MAC. ChemorT in the definitive setting could be considered for patients with inoperable MAC lesions.

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