CASE REPORT

Primary cutaneous mucoepidermoid carcinoma

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Abstract

Primary cutaneous mucoepidermoid carcinoma (MEC) is a rare disease entity. Only around 20 cases have been reported so far. Herein, we present two cases for better understanding of the condition: A 74-year-old lady with a low-grade primary cutaneous MEC at her right external auditory ear canal was treated with surgical resection and adjuvant radiotherapy. The patient developed recurrence five months later and succumbed. Another 81-year-old lady with a high-grade primary cutaneous MEC carcinoma on her left parietal scalp treated by excisional biopsy remained disease free for 10 years. Their histological slides were discussed in details. Current evidence in the literature was also reviewed and summarized.

Key words

Cutaneous mucoepidermoid carcinoma, Salivary gland tumour, Metastatic MEC

1 Introduction

Mucoepidermoid carcinomas (MEC) was first established as a unique entity, which diagnostic features include squamous or epidermoid cells, basal or intermediate cells, and mucin-secreting cells, in 1945 by Steward et al. by reviewing a series of 45 salivary gland tumour [1]. It most commonly arises from the salivary glands and accounts for 10%-30% of salivary gland tumour [1-4]. Apart from the major salivary glands, MEC is also relatively commonly found in the oral cavity, especially the palate, presumably arising from minor salivary glands [5]. In 1958, Gallager et al. reported the first case of primary cutaneous mucoepidermoid carcinoma, reviewing a lady who died of widespread metastasis of cutaneous MEC on the dorsum of her foot [6]. MEC used to be regarded as interchangeable with adenosquamous carcinoma (ACS) in skin, until it was suggested by Riedlinger et al. in early 2000s that MEC and ACS are discrete in histopathology and clinical behaviour. Low-grade MEC is indolent with limited metastatic potential, contrasting high local recurrence rate and metastasis of high-grade ACS [4]. At about the same time, the first case of primary cutaneous MEC in child was reported by Berk et al. and the case of MEC arising from nevus sebaceous of Jadassohn was first reported by Diwan et al. [7, 8]. Berk et al. has demonstrated to us primary MEC does not only affect the group of patients at their 70s, and ACS of skin is actually less well circumscribed, not demonstrating peritumoural fibrosis, variability in the epithelial lining, mucinous, or papillary features; MEC is dermal-based and ACS is likely intraepidermal in origin [7]. Only after 55 years Gallager et al. discovering cutaneous MEC was the use of immunostaining of p63 gene to differentiate cutaneous MEC from MEC metastatic to skin suggested [3, 9].
Primary cutaneous MEC is extremely rare. The biology of this tumour can be better understood if more cases are reported. Much more effort is needed to have more advances in the diagnosis of the disease. It is important to rule out cutaneous metastasis from distant sources of MEC, as suggested to have an entire different behaviour and prognosis [2]. Immunohistochemical staining for p63 has been suggested to use for differentiation of primary from metastatic MEC [2, 3, 9, 10]. Unlike MEC originating from salivary gland, primary cutaneous MEC is more common in males [2, 3].

To the best of our knowledge, there are only several papers documenting treatment outcomes of 19 patients having primary cutaneous MEC [2, 3]. Here, we described two cases of primary cutaneous MEC and reviewed current evidence in the literature.

2 Case reports

2.1 Case report 1

A 74-year-old Chinese woman presented with right otorrhoea. Physical examination revealed a fleshy tissue in the external auditory canal. Her facial nerve was intact. She had a history of nasopharyngeal carcinoma treated with radiotherapy in 35 years ago and was in remission since then. Incisional biopsy of the fleshy mass revealed a salivary gland-type neoplasm.

Magnetic resonance imaging (MRI) showed a tumour at the right posterior external auditory canal obstructing right mastoid air cells. There was labyrinth infiltration and the mass was in close proximity to right cervical internal carotid artery. No intracranial extension was observed. Radical mastoidectomy with lateral temporal bone resection was performed. Intraoperatively, the tumour was found to fill up the entire external auditory canal, and eroded all the ossicles. Histological examination confirmed a mucoepidermoid carcinoma. She completed a course of adjuvant radiotherapy (60 Gy in 30 fractions). Unfortunately, the tumour recurred at the skull base five months after completion of radiotherapy. MRI showed intracranial infiltration into the temporal lobe. The tumour was deemed inoperable. Further radiotherapy was also impossible due to two previous courses of treatment. She was treated conservatively and eventually succumbed one year after the initial surgery.

Pathological findings

The excised specimen showed fragments of a firm white and tan-coloured tumour which measure 4.5 cm in altogether. The tumour was composed of cystic and papillary projections of basaloid epithelioid cells arranged in broad sheets (see Figure 1a). Squamoid areas are noted. Occasional vacuolated cells were noted within the central aspect of the cyst-like spaces (see Figure 1b). A small amount of PASD and mucicarmine material is present in some of the vacuoles (see Figure 1c). No epidermal connection was noted. No lymphovascular or perineural invasion was seen. Immunohistochemical staining for p63 was diffuse and strong (see Figure 1d).

Figure 1. Histological slides of the first patient. (1a, H&E 20×) Cystic and papillary projections of tumour. (1b, H&E 400×) Mixture of squamoid and mucin-filled goblet cells. (1c) There is a more limited population of mucous cells as seen with dPAS stain. (1d) Immunohistochemical staining for p63 is more diffuse and strong.
2.2 Case report 2
A 81-year-old Chinese woman presented with a left parietal scalp nodule. She enjoyed good past health all along. Physical examination revealed a pink and firm nodule. There was no palpable cervical lymph node. Excisional biopsy was performed and the histological examination showed a mucoepidermoid carcinoma with clear resection margins (see Figure 2). A thorough physical examination and investigations showed no other primary site of tumour. The patient refused adjuvant radiotherapy. She was seen up to 120 months after the surgery and remained disease-free.

Pathological findings
Gross examination revealed a well-circumscribed 13 mm × 8mm white nodule in an ellipse of hair-bearing skin. The nodule was composed of sheets of polygonal squamous cells with histiocytes in between. The squamous cells were moderately pleomorphic with vesicular nuclei and prominent nucleoli (see Figure 2a-c). Mitotic figures were occasionally identified. Some tumour cells formed squamous eddies with vague keratin pearl formation. Numerous mucin-filled foamy goblet cells, which stained positive for PAS and mucicarmine, were seen (see Figure 2d). These lesions were infiltrated by a brisk of lymphoplasmacytic infiltrate. Tumour infiltration into the surrounding dermis was noted. No epidermal connection was noted. Immunohistochemical staining for p63 was focal and of weak to moderate intensity (see Figure 2e).

Figure 2. Histological slides of the second patient. (2a, H&E 20×) Non-encapsulated dermal nodule surrounded by a brisk lymphoplasmacytic infiltrate. (2b, 2c, H&E 200×) Mixture of squamoid, intermediate and mucin-filled goblet cells. (2d) The admixed mucous cells are readily highlighted by dPASstaining. (2e) Immunohistochemical staining for p63 is focal and of weak to moderate intensity.

3 Discussion
MEC is a distinct type of tumour, comprising epidermoid cells, mucus-secreting, and intermediate cells in various proportion [1, 4, 10, 11]. It is most commonly found in the salivary glands, but has also been reported in the oral cavity, bronchi, oesophagus, thyroid or breasts [1-3, 5, 10]. Primary cutaneous MEC is uncommon, and the clinical behaviour is different from cutaneous metastasis of salivary gland MEC. Since its first description by Gallager in 1954, only about 20 cases were identified (see the table) [6]. The aim of our study is to report our experience and summarise current understanding of this disease from the literature to shed light on this poorly understood disease.

The etiopathogenesis of primary cutaneous MEC is unclear. Salivary glands have been suggested to derive from sweat glands due to their similarities in embryonic germ layer origin, histological structures, and functions [6]. It has also been supported by several authors that the embryonic precursor of both salivary glands and sweat glands are analogous to the
cutaneous mucin-secreting glands of amphibians \cite{6,12-14}. It is thus postulated that the primary cutaneous MEC may have
developed from an ectopic salivary gland derived from a sweat gland.

Table. Demographics, clinical patterns, and treatment outcomes of primary cutaneous mucoepidermoid carcinoma

<table>
<thead>
<tr>
<th>Age</th>
<th>Race</th>
<th>Sex</th>
<th>Site</th>
<th>Size (mm)</th>
<th>Grade</th>
<th>Treatment</th>
<th>Follow up (months)</th>
<th>Survival outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>Caucasian</td>
<td>M</td>
<td>External ear</td>
<td>6</td>
<td>Low</td>
<td>Mohs</td>
<td>8</td>
<td>AND</td>
</tr>
<tr>
<td>54</td>
<td>Black</td>
<td>M</td>
<td>Dorsal foot</td>
<td>25</td>
<td>UNK</td>
<td>WLE + ND + Adj RT</td>
<td>72</td>
<td>DWD</td>
</tr>
<tr>
<td>35</td>
<td>UNK</td>
<td>M</td>
<td>Lower eyelids</td>
<td>UNK</td>
<td>UNK</td>
<td>WLE + ND + Adj RT</td>
<td>30</td>
<td>AND</td>
</tr>
<tr>
<td>74</td>
<td>UNK</td>
<td>M</td>
<td>Lower eyelids</td>
<td>UNK</td>
<td>UNK</td>
<td>RT</td>
<td>24</td>
<td>AWD</td>
</tr>
<tr>
<td>52</td>
<td>UNK</td>
<td>F</td>
<td>Neck base</td>
<td>22 × 13</td>
<td>UNK</td>
<td>WLE</td>
<td>UNK UNK</td>
<td>UNK UNK</td>
</tr>
<tr>
<td>51</td>
<td>UNK</td>
<td>F</td>
<td>Cheek</td>
<td>5</td>
<td>Low</td>
<td>WLE</td>
<td>168</td>
<td>AND</td>
</tr>
<tr>
<td>49</td>
<td>UNK</td>
<td>F</td>
<td>Adnexa, eyelid</td>
<td>4</td>
<td>Low</td>
<td>WLE</td>
<td>50</td>
<td>AND</td>
</tr>
<tr>
<td>71</td>
<td>UNK</td>
<td>M</td>
<td>Vulva</td>
<td>4</td>
<td>Low</td>
<td>WLE</td>
<td>79</td>
<td>DND</td>
</tr>
<tr>
<td>56</td>
<td>UNK</td>
<td>M</td>
<td>Adnexa</td>
<td>9</td>
<td>Low</td>
<td>Mohs</td>
<td>228</td>
<td>AND</td>
</tr>
<tr>
<td>77</td>
<td>UNK</td>
<td>F</td>
<td>Vulva</td>
<td>22</td>
<td>High</td>
<td>UNK</td>
<td>2</td>
<td>DWD</td>
</tr>
<tr>
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<td>UNK</td>
<td>M</td>
<td>Postauricular</td>
<td>7</td>
<td>Low</td>
<td>WLE</td>
<td>31</td>
<td>AND</td>
</tr>
<tr>
<td>9</td>
<td>Black</td>
<td>M</td>
<td>Scalp</td>
<td>50</td>
<td>Low</td>
<td>WLE</td>
<td>34</td>
<td>AND</td>
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<tr>
<td>79</td>
<td>Caucasian</td>
<td>F</td>
<td>Axilla</td>
<td>37</td>
<td>Low</td>
<td>WLE</td>
<td>69</td>
<td>AND</td>
</tr>
<tr>
<td>81</td>
<td>UNK</td>
<td>M</td>
<td>Cheek</td>
<td>12 × 5</td>
<td>Intermed</td>
<td>WLE + ND + Adj RT</td>
<td>24</td>
<td>AND</td>
</tr>
<tr>
<td>83</td>
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<td>M</td>
<td>Cheek</td>
<td>35 × 33</td>
<td>Low</td>
<td>WLE</td>
<td>UNK UNK</td>
<td>UNK UNK</td>
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<td>Forehead</td>
<td>7</td>
<td>Low</td>
<td>WLE</td>
<td>UNK UNK</td>
<td>UNK UNK</td>
</tr>
<tr>
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<td>UNK</td>
<td>M</td>
<td>Finger</td>
<td>18</td>
<td>High</td>
<td>WLE</td>
<td>12</td>
<td>DWD</td>
</tr>
<tr>
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<td>UNK</td>
<td>M</td>
<td>Lower lip</td>
<td>18</td>
<td>Low</td>
<td>WLE</td>
<td>30</td>
<td>AND</td>
</tr>
<tr>
<td>31</td>
<td>UNK</td>
<td>F</td>
<td>Finger</td>
<td>2</td>
<td>Low</td>
<td>WLE</td>
<td>6</td>
<td>AND</td>
</tr>
<tr>
<td>74</td>
<td>Chinese</td>
<td>F</td>
<td>External auditory canal</td>
<td>45 × 45</td>
<td>Low</td>
<td>WLE + Adj RT</td>
<td>12</td>
<td>DWD</td>
</tr>
<tr>
<td>81</td>
<td>Chinese</td>
<td>F</td>
<td>Scalp</td>
<td>13 × 8</td>
<td>High</td>
<td>EB</td>
<td>120</td>
<td>AND</td>
</tr>
</tbody>
</table>

Note. UNK: Unknown; NS: Nevus sebaceus; Mohs: Mohs surgery; WLE: Wide local excision; ND: nodal dissection; RT: radiotherapy; Adj RT: adjuvant radiotherapy; EB: excisional biopsy; AND: Alive no disease; AWD: Alive with disease; DND: Dead no disease; DWD: Dead with disease

Primary cutaneous MEC has a peak incidence in the 50-70 year age group but can occur as early as nine years of age. There appeared to be a slight male predominance. The head and neck regions are the most commonly affected sites, accounting for two thirds of the cases, followed by axillae and vulvae. Cases involving finger, dorsal foot and thigh have also been reported. Most patients presented as nodular lesions sizing around 10 mm to 30 mm. Majority of patients had low grade lesions. Surgery has been the mainstay of treatment for most cases, occasionally with nodal dissection and adjuvant treatment. While the paucity and heterogeneity of studies render a meaningful survival analysis impossible, a significant proportion of patients do appear to remain disease-free for years after surgery.

It is of utmost importance to distinguish primary cutaneous MEC from cutaneous metastasis of salivary MEC as they carry different implications on treatment and prognosis. Histology alone is often inadequate as both are dermal lesions with variable proportions of epidermoid, intermediate and mucus-secreting cells. The presence of an epidermal connection appeared to favour a primary cutaneous neoplasm, although metastatic cutaneous MEC originating in the bronchus has been reported \cite{15,16}. On the other hand, metastatic lesions seemed more likely to be high-grade tumours, perhaps due to its intrinsically more aggressive behavior \cite{4}. Two cases of immunohistochemical profile of cutaneous MEC have been
documented\textsuperscript{[2, 9]}, showing positive results for CK7, PanCK, EMA, and carcinoembryonic antigen, and negative results for CK20 and anti-human gross cystic disease fluid protein. These markers, however, are non-specific and of little use clinically. Perhaps a more reliable way to distinguish primary cutaneous MEC from metastatic MEC to skin is by staining p63 gene, which is a member of p53 family. Primary cutaneous MEC was reported to be diffusely and strongly stained by p63 gene, although metastatic MEC to skin may also be focally positive\textsuperscript{[2, 3]}. Immunohistochemical staining for p63 was diffuse and strong for our first patient but rather focal and weak for our second patient. Larger series of primary cutaneous MEC are needed to evaluate the role of immunohistochemical staining in the diagnosis.

In salivary MEC, a classic genetic alteration, t(11;19)(q21;p13), has been described\textsuperscript{[17]}. It creates a fusion gene between exon 1 of CRTC1/MECT1/TORC1 at 19p13 and exons 2-5 of MAML2 at 11q21 \textsuperscript{[17]}. This alteration is complemented by a related CRTC3-MAML2 fusion as well as rearrangements in other chromosomal regions \textsuperscript{[18]}. A different pattern seems to be present in cutaneous MEC. Lennerz \textit{et al.} have shown that while primary cutaneous MEC harbours CRTC1 rearrangements like its salivary counterparts, MAML2 rearrangements were absent in all of their studied cases \textsuperscript{[19]}. As MAML2 mutations were associated with greater metastatic potential, higher recurrence rate, and worse prognosis \textsuperscript{[17, 20, 21]}, Lennerz \textit{et al.} suggested that their absence in cutaneous MEC may suggest a less aggressive clinical course compared to salivary MEC \textsuperscript{[19]}.

Systemic workup should always be performed to rule out a primary MEC site elsewhere in the evaluation and diagnosis of lung cancer bronchoscopic biopsy is the gold standard. Positron Emission Tomography (PET) scan may reveal an occult primary although it has been reported to show low uptake on PET occasionally. The combined use of 18F-FDG PET-CT scan and 68Ga DOTA-TOC PET-CT scan was shown to reveal different uptake patterns in various bronchial tumours but merits further evaluation of their role in larger studies \textsuperscript{[22]}.

While there is currently limited evidence on treatment efficacy for primary cutaneous MEC, surgical removal is generally preferred in most centres \textsuperscript{[2, 3]}. Radiotherapy can also be considered in local extensive relapses. Roles of both primary and adjuvant radiotherapy with or without chemotherapy are uncertain. From the limited cases, survivals from two months to two years have been reported in cases treated with adjuvant radiotherapy.

In salivary gland MEC, the histological grading is an important survival prognosticator. Whether or not this observation can be extrapolated to cutaneous MEC is currently unknown. From limited data available in the literatures, low grade cutaneous MEC does appear to have a survival advantage when compared to their high grade counterparts. While no definitive conclusion could be drawn from such heterogeneous data, it does warrant further investigation into its prognosticating role. Most patients treated with surgery appear to remain disease-free beyond three years both in our series and in the literature, with the longest survival of 19 years, and in one of our cases, 10 years.

\textbf{4 Conclusion}

Primary cutaneous mucoepidermoid carcinoma is a rare tumour that tends to present as asymptomatic nodules in the head and neck region. Current mainstay of treatment is surgical removal. Role of radiotherapy and chemotherapy is poorly understood.

\textbf{Reference}

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