Salivary gland hyalinizing clear cell carcinoma with cutaneous metastasis: a rare and deceptive tumor

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Abstract

Clear cell carcinoma (CCC) is an uncommon malignant tumor of minor salivary glands. It characteristically has a low-grade morphology and a favorable outcome by most reports. An EWSR1-ATF1 fusion can be detected in the majority of cases. We present a rare case of CCC which had an aggressive course with the development of cutaneous metastases. Practicing dermatopathologists should be aware of this tumor given its low-grade appearance and histologic resemblance to other primary cutaneous adnexal and metastatic neoplasms.

Introduction

Salivary gland clear cell carcinoma (CCC), also known as hyalinizing clear cell carcinoma is a rare malignant tumor of salivary gland origin. It has a reported incidence of 0.011 per 100,000 and accounts for approximately <5% of all salivary gland cancers. Most CCCs harbor an EWSR1-ATF1 fusion, which is helpful diagnostically. Typically, CCC demonstrates a low-grade morphology and a favorable course based on a few small case series. However, it has become increasingly recognized that aggressive cases do occur, with one larger study finding lymph node positivity and distant metastasis rates of up to 14% and 3.3% of cases, respectively. Herein, we report a CCC with an aggressive clinical course and ensuing cutaneous metastasis. To our knowledge, this represents the first cutaneous metastasis of CCC. We emphasize the immunomorphologic resemblance of this metastasis to primary cutaneous adnexal neoplasms and other metastases, which can potentially lead to diagnostic confusion.

Case Report
In 2015, a 44-year-old pregnant woman presented with a large exophytic tongue base mass. A biopsy demonstrated a nodular proliferation of monomorphic, glycogen-rich clear cells in cords and nests separated by hyalinized stroma (Figure 1). An EWSR1-ATF1 fusion was identified via a RNA-based next generation sequencing panel, which supported the diagnosis of CCC of salivary gland origin. The patient underwent transoral robotic partial glossectomy and modified radical neck dissection. Five of 56 examined lymph nodes were positive for metastasis. Despite receiving postoperative adjuvant radiation therapy, she developed local recurrence along with cervical and lung metastases in 2018. Following 2 cycles of cisplatin, adriamycin, and cyclophosphamide, she was switched to lenvatinib along with 6 cycles of pembrolizumab, due to disease progression. In late 2019, she presented with two scalp lesions and was referred to dermatology for evaluation. Skin examination revealed a 1.8-cm dome shaped nodule on the medial frontal scalp and a 0.6-cm erythematous papule on the right parietal scalp (Figure 2). Saucerization biopsies of both lesions revealed a trabeculated cords of monotonous cuboidal cells filling the dermis and abutting and focally extending into the epidermis (Figure 3). The intervening stroma was fibromyxoid and the overlying epidermis demonstrated thin cord like extensions that interdigitated between the superficial tumor aggregates Many of the cells had pale-staining cytoplasm and there were occasional mitotic figures (Figures 4, 5). The tumor cells stained for p63, CK5/6 and CD99 and were negative for D2-40, Ber-EP4, Androgen Receptor and Calretin. Fluorescent in-situ hybridization (FISH) with an EWSR1 break-apart probe set revealed separation of the probe set in the tumor cells confirming cutaneous metastasis from the patient's known CCC (Figure 6).

Subsequently, the patient developed proptosis with increased intraocular pressure. Imaging revealed tumor extension into the lacrimal glands, cavernous sinus, suprasellar region and cerebral hemispheres.
with encasement of the internal carotid artery. She received palliative radiation therapy to her brain and was referred for palliative/hospice care.

**Discussion**

Most CCCs present as palate or tongue base masses and are thought to arise from minor salivary glands. While a broad age range has been described, most CCCs are reported in patients >60 years with a relatively equal sex distribution. Histologically, clear cells rarely predominate and most neoplasms are composed of cells with pale-eosinophilic cytoplasm or a mixture of both. The neoplastic cells are generally configured as small nests, cords, interconnecting thin trabecula and occasionally individual units. A desmoplastic or fibrocellular stroma is typically present, with occasional juxtaposition of myxoid areas. The individual cells are characteristically small and monomorphic with minimal atypia. The presence of an EWSR1-ATF1 translocation can be detected in most cases, though there are a few reports of similar lesions containing an EWSR1-CREM fusion product.

There are various benign and malignant pale (‘clear’) cell neoplasms that can arise in the skin. Albeit rare, metastatic CCC is an entity that dermatopathologists should be aware of given its morphologic similarity to other more commonly observed entities. Moreover, its relatively low-grade and monotonous appearance can lead to a misdiagnosis of a benign neoplasm. The vast majority of primary cutaneous adnexal tumors express p63, which can usually be used to distinguish such lesions from metastatic adenocarcinoma that are most often p63 negative. Since p63 and high molecular weight keratins (e.g. CK5/6) are often expressed in CCC these stains can represent an additional pitfall when attempting to discriminate from a primary cutaneous adnexal tumor.
Primary cutaneous adnexal neoplasms such as clear-cell (‘nodular’) hidradenoma (and the less common malignant form hidradenocarcinoma) are encountered more routinely in daily practice and share many overlapping features with CCC. Both hidradenoma and CCC demonstrate similar monomorphic, pale and cuboidal-to-polygonal cells in nests and cords within a hyalinized stroma. Moreover, the presence of cystic degeneration, ductal differentiation and squamous metaplasia, which are common in hidradenoma have also been reported in CCC. Focal epidermal involvement was seen in our case of metastatic CCC, as can be seen in some hidradenomas, further contributing to the potential for diagnostic difficulty.

Clear cell sarcoma, which more typically presents in the deep soft tissues, can occasionally be dermal-based and therefore mimic CCC. These neoplasms have a similar architecture and growth pattern, with both harboring EWSR1-ATF1 fusions. Unlike clear cell sarcoma, CCC is consistently positive for cytokeratins and p63, while being negative for S100 and HMB45. Moreover, there are subtle cytologic differences that can help discriminate the two neoplasms. The tumor cells of clear cell sarcoma have vesicular nuclei with a single enlarged nucleolus, while those of CCC have nuclei with condensed chromatin and inconspicuous nucleoli.

Conventional renal cell carcinoma is one of the more commonly reported visceral malignancies with clear cell morphology to metastasize to the skin. The degree of cytologic atypia can be variable (from the authors experience). It can be distinguished from CCC by the presence of a highly vascularized and ‘bloody’-appearing stroma along with the expression of Pax8.

Finally, primary cutaneous perivascular epithelioid tumor (PEComa) is another uncommon mesenchymal tumor to consider in the setting of a dermal based tumor with pale-staining tumor cells. However, in contrast to the hyalinized and fibromyxoid stroma seen in CCC, the stroma in PEComa consists of
vasculature with delicate thin-walled capillaries. PEComa also has a unique immunophenotype with expression of both myogenic and melanocytic markers.

In summary, we present the first case description of CCC with the development of cutaneous metastasis. The histologic features of the metastatic foci largely resembled those of the primary site, though with fewer pure clear cells. Dermatopathologists should be aware of this rare salivary gland tumor, as it can mimic other more commonly encountered cutaneous pale-clear cell neoplasms.

Acknowledgments
None

Figure Legends

Figure 1. Tumor cells are arranged in nests, trabeculae and solid sheets and are embedded in dense hyalinized stoma (Base of tongue: H&E, 100x original magnification). INSERT: Monomorphic cells with clear to eosinophilic cytoplasm, distinct borders, and round nuclei (Base of tongue: H&E, 200x original magnification).

Figure 2. Erythematous papulonodule on the right parietal scalp.

Figure 3. Diffuse dermal infiltrate consisting of pale-staining cells within a fibromyxoid stroma (Parietal scalp: H&E, 20x original magnification).

Figure 4. Monotonous appearing small-to-medium sized tumor cells with round nuclei and clear and eosinophilic cytoplasm resembling the primary tumor from the tongue. Note the presence of occasional mitotic figures (Parietal scalp: H&E, 200x original magnification).

Figure 5. Nests of tumor cells are seen extending into the epidermis (Parietal scalp: H&E, 100x original magnification).

Figure 6. Fluorescent in-situ hybridization (FISH) with EWSR1 break-apart probe set. Separation of the probe set is seen in most interphase nuclei, as is one preserved allele (fused probes with yellow signal). Insert: Representative nucleus with one abnormal (separated probe set) and one preserved signal (yellow).

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