Small Cell Carcinoma ex-Pleomorphic Adenoma of the Parotid Gland

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Abstract Small cell carcinoma (SCC) is a high-grade malignancy usually encountered in the lungs but also seen in almost any site including the salivary glands. SCC is important to recognize because it often metastasizes widely and is treated with systemic chemotherapy. Carcinoma ex pleomorphic adenoma is a malignant epithelial neoplasm arising in a pre-existing benign mixed tumor (i.e., pleomorphic adenoma, PA). While virtually any salivary carcinoma can arise from a PA, to our knowledge SCC ex-PA has not been described. We report a case of a woman presenting with fullness of the right neck and a parotid gland mass. The tumor was resected and evaluated grossly, by light microscopy, and by immunohistochemistry. Grossly, a 1.6 cm well-circumscribed nodule was identified within the parotid. Microscopic examination revealed foci of SCC associated with high-grade adenocarcinoma, in the background of a PA. The SCC was immunoreactive for cytokeratin in a dot-like pattern and neuroendocrine markers synaptophysin and CD56. Despite the focal nature

of the SCC in the parotid, a pure SCC metastasis was present in one neck level II lymph node. The patient was free of disease with 8 months of follow-up. Our case illustrates that: (1) although rare, in the salivary glands SCC may arise from lower grade neoplasms including PAs; (2) SCC ex PA may metastasize as pure SCC even if the primary SCC component was focal; (3) adequate sampling of PAs is crucial to prevent missing a rare SCC that must be treated with chemotherapy.

Keywords Carcinoma ex pleomorphic adenoma · Carcinoma ex mixed tumor · Malignant mixed tumor · Small cell carcinoma · Parotid gland · Salivary glands

Introduction

Carcinoma ex pleomorphic adenoma (CXPA) is a malignant epithelial neoplasm arising from a pleomorphic adenoma (i.e., benign mixed tumor or PA). CXPAs most commonly occur in the parotid gland [1]. CXPA is uncommon, accounting for only approximately 3.6 % of salivary gland neoplasms and 12 % of salivary gland malignancies [1]. A variety of carcinoma types can arise in a PA, with high grade adenocarcinoma, not otherwise specified (N.O.S.), and salivary duct carcinomas being the most common [1–3].

Small cell carcinoma (SCC) is a form of high grade neuroendocrine carcinoma. Although classically a lung neoplasm, approximately 2.5–5 % of SCCs are extrapulmonary [4, 5]. SCC of the head and neck is rare. Among head and neck sites, it is most commonly encountered in the larynx but has also been reported in the sinonasal tract, trachea, oral cavity, oropharynx, and salivary glands [6–8]. SCC accounts for approximately 2 % of all salivary gland

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malignancies [9]; however, to our knowledge SCC arising as a CXPA has not been previously reported.

Case Report

A 48-year-old Caucasian female presented with a three-year history of right cheek mass. The mass had been growing gradually over the last 3 years, with recent development of right neck swelling and tenderness. Physical exam revealed an enlarged and mobile right level II

lymph node. Subsequent computed tomography (CT) and positron emission tomography (PET) scans revealed a heterogeneous partially calcified mass measuring 2.1 cm in the right parotid gland and an adjacent necrotic appearing lymph node measuring up to 2.3 cm. Fine needle aspiration and core biopsies were diagnosed as “poorly differentiated carcinoma.” The patient underwent a right superficial parotidectomy with facial nerve preservation and a right modified neck dissection in levels I–IV.

On gross examination, the parotid was dissected to reveal a single, firm, well-circumscribed nodule measuring

Fig. 1 Small cell carcinoma ex-pleomorphic adenoma of the parotid gland. **a** The parotid tumor contained a large zone of central hyalinizing fibrosis (hematoxylin and eosin, $\times 40$). **b** Part of the epithelial component consisted of benign, bland tubules embedded in the fibrotic stroma (hematoxylin and eosin, $\times 400$). **c** In areas, the glandular component was overtly malignant, with striking nuclear atypia and an elevated mitotic rate (hematoxylin and eosin, $\times 400$). **d** These malignant glands (*left*) transitioned to nests and sheets of

cells with minimal cytoplasm and hyperchromatic nuclei (*right*), suggestive of dedifferentiation to small cell carcinoma (hematoxylin and eosin, $\times 400$). **e** The small cell component exhibits single cell necrosis and angulated nuclei with molding (hematoxylin and eosin, $\times 400$). **f** The small cell component expressed synaptophysin, indicating neuroendocrine differentiation (synaptophysin immunohistochemistry, $\times 400$)

Fig. 2 Metastatic small cell carcinoma to a neck lymph node. **a** The carcinoma grew as sheets of cells, punctuated by areas of geographic necrosis (hematoxylin and eosin, $\times 100$). **b** Unlike the tumor in the parotid, the lymph node metastasis consisted purely of small cell

carcinoma (hematoxylin and eosin, $\times 400$). **c** The carcinoma was positive for synaptophysin (synaptophysin immunohistochemistry, $\times 400$), and **d** had a very high Ki67 index of approximately 80 % (Ki67 immunohistochemistry, $\times 400$)

1.6 cm. An accompanying right neck level 2 lymph node dissection was notable for a dominant, necrotic lymph node measuring 2 cm. Microscopic examination of the parotid gland revealed a fibrotic, hyalinized nodule with epithelial nests scattered throughout (Fig. 1a). Some of the epithelium consisted of bland tubules (Fig. 1b). These nests transitioned to glands that had marked cytologic atypia in the form of nuclear enlargement and hyperchromasia, prominent nucleoli, and an elevated mitotic rate (Fig. 1c, d). This appearance is typical of a high grade adenocarcinoma not otherwise specified (N.O.S.) arising in a pleomorphic adenoma (i.e., carcinoma ex-PA). These areas focally transitioned to zones comprised of small angulated cells with little or no cytoplasm. The nuclei displayed molding, inconspicuous nucleoli, and granular, “neuroendocrine-type” chromatin (Fig. 1d, e). The malignant components of the tumor were extensively infiltrative beyond the capsule of the pleomorphic adenoma. Examination of the lymph node showed that it was involved only by the population of small round blue cells, with zones of geographic necrosis (Fig. 2a). The margins of resection were negative for tumor. The immunophenotype for the small cell component in the lymph node and parotid was identical: cytokeratin positive in a dot-like pattern, synaptophysin positive (Figs. 1f, 2c), CD56 positive, neurofilament positive in a dot-like pattern,

Ki67 very high at approximately 80 % (Fig. 2D), but TTF-1 and CK20 negative. These findings were diagnostic for small cell carcinoma arising in association with a high grade adenocarcinoma N.O.S. ex-PA, and metastatic SCC to the lymph node.

The patient underwent postoperative chemotherapy and radiation therapy. Radiation therapy was performed at 6 MV of energy, with a total dose of 6,660 cGy over 7 weeks. At 8 months post-surgery, the patient has had no evidence of disease recurrence.

Discussion

Small cell carcinoma (SCC) is a highly aggressive malignancy that typically occurs in the lung [10], but up to 5 % of primary SCCs are extrapulmonary [8]. Although primary SCC of the head and neck most commonly involves the larynx [8], SCC can also rarely arise in the salivary glands, and it accounts for approximately 2 % of salivary gland malignancies [9]. In addition, metastatic disease must always be considered if SCC is encountered in an extrapulmonary site [10]. Metastatic SCC to the parotid gland has been described at the initial presentation of primary lung SCC [11, 12].

It is important to recognize SCC in the salivary gland because, unlike other primary salivary gland neoplasms, SCC often metastasizes widely and is treated with systemic chemotherapy. As in the lung, extrapulmonary SCC is characterized by small round cells with hyperchromatic nuclei, granular chromatin, inconspicuous nucleoli, nuclear molding, high nuclear-to-cytoplasmic ratios, frequent mitoses and varying degrees of neuroendocrine differentiation [13, 14]. Small cell carcinoma of the salivary glands is somewhat peculiar because it often expresses CK20, similar to Merkel cell carcinoma of the skin [13]. Various theories exist as to the cell of origin of salivary gland SCC. Possibilities include divergent differentiation of myoepithelial or epithelial carcinoma cells, as well as a multipotent stem cell with the capacity to differentiate into a variety of cell types [8]. Various reports of SCC of the head and neck have demonstrated admixed areas of SCC with conventional adenocarcinoma or squamous cell carcinoma [8]. The differential diagnosis for primary SCC of the salivary gland includes other high-grade neoplasms such as poorly differentiated adenocarcinoma, adenoid cystic carcinoma, lymphoma, and metastatic SCC.

As is seen in the larynx, SCCs of the major salivary glands most commonly occur in male patients [7, 13, 15–17]. The overall prognosis for SCCs of the major salivary glands is poor but notably better than in the larynx or lung, with a reported 5-year survival of 46 % [9]. In the largest reported series of SCCs of the major salivary glands (n = 15) [13], 73 % of patients were male and 67 % of patients died of disease at an average of 16 months after diagnosis. One patient developed local recurrence and 9 developed distant metastases accounting for the cause of death due to disease.

Carcinoma ex pleomorphic adenoma (CXPA) is a malignant epithelial neoplasm that arises in a preexisting benign mixed tumor (pleomorphic adenoma, PA) [1]. Invasive CXPA (i.e., invasion >1.5 mm beyond capsule) has an overall 5-year survival of just 30 % [18]. Adenocarcinoma, NOS, and salivary duct carcinomas are the most common type of carcinoma arising in a CXPA [2], however virtually any type of salivary carcinoma can be seen. However, to our knowledge, SCC ex-PA has never been previously described.

This case sheds some light on the biology of the rare SCC of the salivary glands by illustrating that some cases may arise from lower grade lesions including even benign neoplasms. Indeed, although SCC ex-PA has not been previously reported, it is possible that cases of parotid SCC described as having areas of dense fibrosis [19] may represent cases of SCC ex-PA with no residual or unsampled viable mixed tumor. Moreover, while in most cases of salivary gland SCC a metastasis from another organ (especially lung) cannot be excluded, documenting the

evolution from a lower grade neoplasm made searching for other possible sites of origin unnecessary in this case. This case also emphasizes that even when a SCC component of a salivary gland tumor is focal, it may metastasize as pure SCC. In the case presented, had the SCC ex-PA not been sampled, finding SCC in the patient's neck lymph node would have caused considerable diagnostic confusion. Indeed, adequate sampling of PAs is crucial to avoid missing a rare SCC that, even if focal, has significant prognostic and treatment implications.

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