Metastatic Neuroendocrine Tumors of the Parotid Gland

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Objectives: To present 2 cases of neuroendocrine tumors of the parotid gland and to review the clinical presentation, histopathologic, and immunohistochemical findings and treatment of these rare tumors.

Study Design: Case series.

Methods: This study reviews 2 patients who both presented with firm masses in the parotid gland diagnosed as neuroendocrine carcinoma by histopathologic and immunohistochemical examination. The evaluation, diagnosis, and treatment are discussed.

Results: Both patients underwent complete tumor extirpation via a total or subtotal parotidectomy. Both patients received postoperative radiation therapy and chemotherapy.

Conclusions: Neuroendocrine tumors of the parotid gland are uncommon lesions; however, they have a favorable prognosis as compared to their pulmonary counterparts with early diagnosis and aggressive treatment. Diagnosis is based on the immunohistochemical characteristics of the tumor. Appropriate treatment includes complete surgical excision with postoperative radiation therapy to the parotid bed with the addition of postoperative chemotherapy in patients suspected to have metastatic disease.

Primary salivary gland carcinomas with neuroendocrine differentiation are quite rare, accounting for 3.5% of all malignant minor salivary gland tumors and less than 1% of all parotid gland carcinomas. The majority of these tumors are small cell carcinomas. Although rare in the salivary glands, small-cell carcinoma is a common lung neoplasm accounting for 25% to 35% of all primary lung tumors. Four percent of all small-cell carcinomas arise in extrapulmonary sites, including the esophagus, skin, gastrointestinal tract, pancreas, uterus, prostate, and kidney. In the head and neck, small-cell carcinomas have been reported in the larynx, pharynx, paranasal sinuses, trachea, and oral cavity. To date, there are approximately 38 cases of small-cell carcinomas arising in the parotid gland reported in the English literature.

We would like to present 2 additional cases of small-cell neuroendocrine tumors of the parotid gland with a review of the appropriate diagnostic evaluation, histopathological, and immunohistochemical characteristics and treatment strategies.

CASE 1

An 84-year-old white man initially presented with complaints of left-sided otalgia. A complete head and neck examination was performed including otoscopy and flexible fiberscopic laryngoscopy and found to be normal. He had no evidence of a parotid mass at this time. Over the course of the next 2 months, the patient developed a firm, 2-cm lesion in the superficial lobe of the left parotid. He denied odynophagia, dysphagia, dysphonia, and weight loss. His review of systems was negative, and he was otherwise in his usual state of health. He had no significant past medical history and did not smoke or drink alcohol. Computed tomography (CT) scan of the neck showed no evidence of adenopathy. Fine-needle aspiration of the parotid mass revealed a population of entirely malignant "small blue cells." Immunohistochemical studies showed strong cytoplasmic staining for epithelial membrane antigen and neuron-specific enolase. The tumor cells showed a
very strong localized perinuclear dot positivity to cytokeratin 20 and were negative to cytokeratin 7 and vimentin.

A full metastatic workup was pursued including a full-body CT scan and positron-emission tomography (PET) scan, as well as a bone scan. There was no evidence of a distant primary. The patient was scheduled for a surveillance panendoscopy and a left parotidectomy. The panendoscopy, including flexible bronchoscopy was normal. The tumor was located in the superior most portion of the parotid gland so the superior two thirds of the parotid was removed, which provided a generous cuff of normal tissue. Microscopic examination of the specimen showed an intraparotid lymph node largely replaced by metastatic carcinoma surrounded by essentially normal-appearing parotid salivary gland tissue. The tumor showed irregular nests of cells with large ovoid nuclei with distinct red nucleoli and fine chromatin. There was prominent nuclear molding and high mitotic activity. Further immunohistochemical staining revealed positive staining for chromogranin and synaptophysin (Fig 1). The final pathological diagnosis was a high-grade neuroendocrine carcinoma metastatic to an intraparenchymal lymph node.

Despite our previous negative metastatic evaluation, the patient was referred to a dermatologist to evaluate the possibility of a primary cutaneous neuroendocrine (Merkel cell) carcinoma, to a urologist to evaluate for a urinary tract primary, and to a gastroenterologist to perform colonoscopy and a thorough gastrointestinal evaluation. All evaluations failed to find a primary site. The patient received a full-course of postoperative concurrent chemotherapy and radiation therapy. At his 2-year follow-up he has no evidence of recurrent disease.
CASE 2

An 83-year-old woman presented with a 6-month history of a progressively enlarging left parotid mass that had recently begun draining through the overlying skin. The review of systems was negative, and she was neither a smoker nor a drinker. Her past medical history was significant for hypertension and hyperlipidemia. Physical examination revealed an unremarkable nasal, oral cavity, and oropharyngeal examination. Flexible fiberoptic laryngoscopy was additionally normal. She did not have palpable cervical adenopathy. Examination of the left parotid revealed a 6 × 7 cm firm mass fixed to the overlying skin with drainage through a central opening. The facial nerve was intact except for weakness of the buccal branch on the left side. Initial CT scanning showed a large parotid mass abutting or possibly involving the left masseter muscle. Fine-needle aspiration was performed and was consistent with small cell undifferentiated carcinoma of the parotid gland. Full body CT and PET scans were ordered to determine if the parotid mass was a metastasis from another site. These scans revealed intense activity in the left parotid. There were no additional foci of activity in the neck to suggest adenopathy; however, a 1.5-cm focus of activity was found in the left breast. The remainder of the scan was negative. Evaluation of the breast was conducted via mammography and biopsy and found to be an invasive ductal carcinoma with neuroendocrine features. The breast tumor expressed synaptophysin and chromogranin and was negative for TTF-1. Estrogen and progesterone receptors were positive in a "patchy" fashion.

The patient was initially taken to the operating room and underwent left total parotidectomy in continuity with wide local excision of the overlying skin with 1-cm margins. Cutaneous margins were sent for frozen section analysis and were found to be free of tumor involvement. The facial nerve was identified with preservation of the upper branches; however the buccal and marginal mandibular branches were sacrificed because they were intimately involved with the tumor. The tumor was dissected off the deep tissues, and a cuff of sternocleidomastoid and masseter muscles were included with the specimen. The mandible was uninvolved. After complete tumor extirpation and copious irrigation, the proximal marginal mandibular nerve and the buccal branch of the facial nerve were dissected free up to the takeoff from the main trunk. The distal branch of the buccal nerve was dissected in the area of Stenson's duct, and the distal branch of the marginal mandibular nerve was located in the region of the oral commissure. The operating microscope was used to perform epineural reanastomoses of the nerve branches. A pedicled cervical rotation flap was used to close the defect.

Pathological evaluation of the left parotid specimen confirmed the frozen section findings of a small-cell neuroendocrine carcinoma. Immunohistochemical analysis was chromogranin positive. Additionally, it was strongly positive for CK 8, 18, and CK 903. It stained negatively for CK 5, 6, and synaptophysin. After the parotidectomy, the patient then underwent resection of the left breast mass. Final pathology of the breast tissue revealed invasive ductal carcinoma with neuroendocrine features. Again, the breast tissue showed positivity to synaptophysin and chromogranin. Although the parotid and breast tumors were not histologically identical, the parotid mass was favored to be metastatic from the breast and the patient underwent postoperative concurrent chemotherapy and radiation. She remains disease free at 12-month follow-up.

DISCUSSION

Extrapulmonary neuroendocrine tumors are uncommon tumors and represent less than 1% of all malignant neoplasms of the major salivary glands. The parotid gland is the most common location among the major salivary glands, representing 83% of all neuroendocrine carcinomas in these locations. Undifferentiated neuroendocrine carcinomas can be composed of either small cells with scant cytoplasm and uniform nuclei or more pleomorphic, large cells. The majority of these tumors are small cell carcinomas; however, 4 cases of neuroendocrine differentiation in large cell carcinoma of the major salivary glands have recently been reported. The small-cell variety has been historically classified into 2 groups based on the ultrastructural...
presence or absence of intracytoplasmic neuroendocrine granules: small-cell neuroendocrine carcinomas and small-cell ductal carcinomas. However, in an immunohistochemical study by Gnepp and Wick, they showed the presence of at least 1 neuroendocrine marker in 11 primary small-cell carcinomas of the major salivary glands that had been originally classified as small-cell ductal carcinomas based on their ultrastructural appearance. They determined that virtually all small-cell carcinomas had neuroendocrine characteristics by immunohistochemical examination even if dense core granules could not be shown ultrastructurally. Therefore, they concluded that all small-cell carcinomas can be considered to be of a neuroendocrine lineage.

The use of a battery of immunohistochemical stains is typically used to determine if a tumor possesses a neuroendocrine phenotype. Common immunohistochemical stains used include antibodies to epithelial membrane antigen, cytokeratin, Leu 7, vimentin, synaptophysin, chromogranin, and neuron-specific enolase. In our first patient, the tumor was positive for synaptophysin, chromogranin, neuron-specific enolase, epithelial membrane antigen and cytokeratin 20 but negative for cytokeratin 7 and vimentin. Our second patient showed positive staining for chromogranin and cytokeratins 8, 18, and cytokeratin 903. In a recent study by Chan et al., they found that cytokeratin 20 immunoreactivity distinguished Merkel cell (primary cutaneous neuroendocrine) carcinomas and salivary gland small-cell carcinomas from small-cell carcinomas of other sites. Our first patient had small-cell carcinoma only within an intraparenchymal parotid lymph node, and his tumor was positive for cytokeratin 20; therefore, we promptly sent him to a dermatologist for further evaluation of several small lesions that had developed on his forearms. Multiple biopsies of these sites showed only granulation tissue with no evidence of malignancy or atypia. Additionally, he had no evidence of suspicious skin lesions on a complete cutaneous examination. Because it remained highly likely his tumor was of metastatic origin, we opted to perform postoperative chemotherapy in addition to a full course of radiation therapy to the parotid bed and left neck.

The presentation of a patient with a parotid neuroendocrine tumor is typically a painless mass that has been growing slowly over several months. It is usually seen in older patients (50-70 years old) and is more commonly seen in men (61.7%). After the diagnosis is established with fine-needle aspiration, the patient should undergo a full metastatic evaluation because these lesions may be both metastatic to the parotid gland, as seen in our 2 cases, or have distant metastatic disease associated with a primary parotid malignancy. Evaluation should include CT scanning of the head, neck, chest, abdomen, and pelvis, in addition to a full-body PET scan. If the metastatic evaluation is negative, treatment should proceed to surgery with complete tumor extirpation with planned postoperative radiation therapy. Chemotherapy may be included in the treatment regimen especially if there is a high likelihood that the tumor is of metastatic origin.

The prognosis for a neuroendocrine tumor of the parotid is favorable as compared with its pulmonary counterpart. Small-cell carcinoma of the lung has a 5-year survival rate with chemotherapy of only 2 to 8% and an increased survival of 6% to 12% with the addition of radiation therapy. Patients who receive supportive therapy alone have a mean survival of 2 to 4 months. In contrast, the overall 2- and 5-year survival for small-cell carcinoma of the major salivary glands is reported as 70% and 46%, respectively. Various modalities of treatment have been described in the literature, however, primary surgical therapy seems to ensure the best long term survival.

CONCLUSION

Neuroendocrine tumors of the parotid are rare entities; however, with appropriate diagnosis and aggressive treatment, these tumors are potentially curable. Appropriate evaluation includes the use of fine-needle aspiration for diagnosis followed by a thorough metastatic evaluation. Immunohistochemical stains are used for diagnosis and characterization of the tumor. Treatment should include complete surgical removal followed by postoperative radiation therapy with the addition of concurrent chemotherapy in select patients.
especially if the tumor is suspected to be of metastatic origin. Although uncommon, neuroendocrine tumors should be included in the differential diagnosis for all parotid masses.

REFERENCES