Primary carcinoid tumor of the parotid gland: A case report and review of the literature

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Abstract
Salivary gland tumors account for 3 to 6% of all head and neck neoplasms in adults. Some 70 to 85% of these lesions are found in the parotid. Carcinoid tumors, which represent a distinct and relatively uncommon subset of neuroendocrine tumors, are most commonly found in the gastrointestinal tract, although in rare cases they are known to occur in extragastrointestinal locations, including the larynx, middle ear, and pancreas. Malignancies of the parotid gland are uncommon (approximately 25% of parotid neoplasms), and to the best of our knowledge, a primary carcinoid tumor of the parotid has not been previously described in the literature. Reports of parotid carcinoid tumors during the past 30 years have described the presence of nonparotid primary carcinoid tumors (usually gastrointestinal) that had been diagnosed and treated several years prior to the presentation of the parotid lesion. Under such circumstances, the parotid lesion may be assumed to have been a metastatic rather than a primary carcinoid. This report documents what we believe is the first case of a primary carcinoid tumor of the parotid gland. We detail the clinical, surgical, radiologic, immunologic, and histochemical findings associated with its diagnosis, and we describe our management of this case. Although a primary carcinoid in this location is exquisitely rare, knowledge of such lesions is important because their management is substantially different from that of other parotid tumors. In particular, it is important to differentiate them from metastatic tumors from other sites.

Introduction
Tumors of the salivary glands account for 3 to 6% of all head and neck neoplasms in adults.1 Their clinical and histologic appearance varies markedly. Most of these tumors (70 to 85%) are found within the parotid gland. Among the parotid tumors, 25% are malignant at diagnosis.1 Carcinoid tumors are characterized by distinct biologic, histologic, and functional properties, and they represent a unique, relatively uncommon subset of neuroendocrine neoplasms. Although approximately two-thirds of carcinoid tumors are identified within the gastrointestinal tract, it is well known that carcinoid tumors may arise within any anatomic location that is populated with endocrine or endocrine-like cells.2

Carcinoid tumors are known to arise in extragastrointestinal locations in exquisitely rare cases, and such a finding in the parotid gland is among the very rarest. Scattered reports have documented the presence of parotid carcinoid tumors, but all such cases have been associated with a primary carcinoid tumor elsewhere in the body.3-6 After conducting an extensive search of the world literature, we report what to the best of our knowledge is the first case of a primary carcinoid tumor of the parotid gland. We detail the clinical, surgical, radiologic, immunologic, and histochemical findings associated with its diagnosis, and we describe our management of this case.

Case report
In November 1992, a 40-year-old man presented with a painless enlargement of his left face. He reported no other symptoms or complaints. Incisional biopsy initially revealed the presence of a parotid tumor, and it was excised by superficial parotidectomy. On gross examination, the specimen was made up of two portions of firm, tan-to-pink tissue that measured 0.3 and 0.5 cm in their greatest dimension. The tissue had a firm, yellow-to-pink cut surface. The tumor was initially characterized as a ductal salivary gland carcinoma with solid and basaloid patterns. Light microscopy revealed nesting of the tumor cells into cohesive groups of various sizes, with large, pleomorphic nuclei and granular cytoplasm (figure 1, A). Further immunohistochemical analysis with neuroendocrine markers stained strongly positive for chromogranin A and neuron-specific enolase, and the lesion was designated...
as an atypical carcinoid tumor (figure 1, B). Electron microscopy further confirmed the diagnosis, demonstrating the presence of numerous neuroendocrine-type, dense-core, secretory granules that ranged in size from 350 to 400 nm and were mostly round in shape (figure 2).

When the patient initially presented in 1992, he had no other significant medical history, and he was not taking any medication. His family history was notable for thyroid cancer in his mother that was treated successfully with surgery and radioactive iodine therapy. The patient denied any history of smoking or of radiation exposure during childhood. He did not have any symptoms suggestive of carcinoid syndrome, such as diarrhea, flushing, bronchospasm, or right-sided heart failure. Furthermore, he displayed no signs or symptoms of liver disease, such as pruritus, edema, or jaundice.

Two months postoperatively, in January 1993, abdominal computed tomography (CT) detected two contrast-enhancing hypodense lesions in the liver. Nuclear single-photon emission CT (using tagged red blood cells) and percutaneous liver biopsy of the lesions revealed no evidence of malignancy. As a result, both lesions were diagnosed as hepatic hemangiomas. At that time, a 24-hour level of urinary 5-hydroxyindole acetic acid (5-HIAA), an excreted by-product of serotonin degradation and a clinical marker of carcinoid disease, was within the range of normal (2.0 to 8.0 mg/24 hr). Normal levels were subsequently documented in March, June, and July 1994 (figure 3). Findings on chest x-ray, bone scan, small bowel x-rays, and upper and lower gastrointestinal series were normal, and no lesions suggestive of primary or metastatic disease were evident elsewhere. Serial CTs over the next few years revealed no change in the two liver masses, and annual urinary 5-HIAA levels remained within the normal range.

By July 1998, however, the patient’s urinary 5-HIAA level had become elevated (10.3 mg/24 hr) (figure 3), and he was referred to our clinic. We obtained an octreotide scan, which revealed multiple focal areas of isotope uptake in both the right and left lobes of the liver; this finding is consistent with somatostatin subtype-2–expressing hepatic metastatic disease. No evidence of abnormal uptake was observed in the region of the parotid gland on the left or right side or anywhere else in the body.

In September 2000, baseline measurements revealed that the patient had elevated serum levels of serotonin (1,120 ng/ml; normal: 55 to 260), chromogranin A (300 ng/ml; normal: 2.3 to 14.3), and pancreatic polypeptide (307 pg/ml; normal: 64 to 243); the substance P level
was normal (figure 4). Yet despite clear biochemical and radiographic evidence of diffuse metastatic disease, the patient was clinically stable, in excellent condition, and without overt evidence of any disease. He declined therapeutic intervention, opting instead to be monitored regularly in the clinic.

In September 2001, the patient’s serum serotonin and pancreatic polypeptide levels had risen even higher (1,386 ng/ml and 471 pg/ml, respectively), and his serum chromogranin A had more than tripled to 970 ng/ml (figure 4). Abdominal ultrasound confirmed evidence of hepatic metastatic disease within the liver; the kidneys were normal.

One year later, a repeat octreotide scan demonstrated widespread metastatic foci in the liver with intense uptake; these findings were not appreciably different from the first scan. Again, the patient exhibited no evidence of any disease elsewhere, including the left parotid region. Repeat biochemistry revealed consistently elevated serum serotonin and chromogranin A levels (1,446 ng/ml and 1,050 ng/ml, respectively) (figure 4).

Despite evidence of disseminated disease, the patient nevertheless remained asymptomatic and in excellent condition, and he reported no diminution of performance status or quality of life. He again declined any interventional therapy, including radiofrequency ablation, receptor-mediated isotope therapy, or liver resection.

Discussion

The reported annual incidence of salivary gland tumors is 1 to 3 per 100,000 population. Pleomorphic adenoma, which represents approximately 60% of all parotid gland neoplasms, is the most common benign neoplasm, while mucoepidermoid carcinoma accounts for most malignant lesions of the salivary glands. In fact, mucoepidermoid carcinoma is the most common salivary gland malignancy in children. Metastatic tumors of the salivary glands are typically melanomas (46%) or squamous cell carcinomas (37%), and a small percentage (<1%) of metastatic lesions are carcinoid tumors arising mostly from a gastrointestinal primary.

Patients with malignant salivary gland neoplasms are usually older (55 to 65 yr), while those with benign neoplasms are usually somewhat younger (mean age: 45 yr). Most patients who present with carcinoid tumors are aged 60 to 65 years.

The annual incidence of carcinoid tumors is similar to that of salivary gland tumors (2 to 3 per 100,000 population). Two-thirds of these lesions occur in the gastrointestinal tract, while approximately 25% occur in the tracheobronchopulmonary complex.

Although the risk factors associated with salivary gland neoplasia or carcinoid tumors are not well known, there is clearly an established relationship between radiation exposure and the development of salivary gland tumors; Schneider et al reported that 3% of patients who had been
irradiated during childhood (for tonsillitis, acne, or chronic ear disease) developed salivary gland tumors, 90% of which were found in the parotid gland. Unlike other head and neck neoplasms, malignant salivary gland tumors have not been found to have an established relationship with tobacco exposure. It is interesting, though, that an association between salivary gland tumors and breast cancer has been suggested. In fact, one study demonstrated that women who developed a salivary gland tumor before the age of 35 years had a higher risk of breast cancer than did women with no history of salivary gland tumor, although this relationship was not statistically significant.

Malignancies within the parotid gland, particularly those of a neuroendocrine origin, are extremely rare. Nicod first described the presence of a carcinoid tumor associated with the parotid in 1958. However, the technology at that time was not sophisticated enough to identify the presence of a primary tumor elsewhere.

In the few other cases reported during the late 20th century, all described the presence of a carcinoid tumor in the context of a preexisting primary tumor that was diagnosed and subsequently treated years before the patient presented with a parotid lesion, suggesting that the parotid lesion represented a manifestation of metastatic carcinoid disease arising from a primary tumor elsewhere. Chan and Sizeland described a case of a parotid carcinoid tumor in a patient who had been diagnosed with metastatic carcinoid disease 5 years previously (primary site unknown). While Dilkies and Birchall reported bilateral metastatic parotid carcinoid tumors that presented 3 years after resection of a primary carcinoid tumor of the bronchus. Similarly, Eusebi et al described a case of a parotid endocrine carcinoma in a patient who had had a bronchial carcinoid removed 7 years earlier.

As a consequence of its intrinsic slowly growing nature and the nonspecific presenting symptomatology, the diagnosis of carcinoid tumors has often been made only as an incidental finding at surgery or autopsy. Fewer than 10% of patients with carcinoid tumors actually present with the classic “carcinoid syndrome,” characterized clinically by the presence of flushing, diarrhea, edema, bronchospasm, and right-sided heart failure; these findings are usually indicative of hepatic metastatic carcinoid disease.

Increases in our understanding of carcinoid tumors have led to significant advances in diagnostic modalities. As a result, investigation and management have been considerably facilitated. In particular, octreotide scanning and analysis of distinctive serum markers—such as serotonin, chromogranin A, pancreatic polypeptide, and substance P—have enabled clinicians to better assess and monitor patients with carcinoid tumors. Furthermore, the widespread use of somatostatin analogues has augmented the therapeutic options for carcinoid syndrome and provided symptomatic relief to these patients.

Unlike the protean manifestations of carcinoid disease, the presenting manifestation of patients with parotid tumors is usually a discrete, asymptomatic, solitary lump. In some circumstances, pain may be a feature and reflect involvement (usually malignant) of the facial nerve, whose lower branches course through the gland itself. Asymptomatic masses of the parotid gland may also represent manifestations of various inflammatory and infiltrative diseases, including sarcoidosis and Sjögren’s syndrome, as well as salivary and branchial cleft cysts. Benign epithelial proliferation, most notably in the parotid gland, occurs in 30 to 50% of patients with Sjögren’s syndrome, who commonly present with firm, nontender glands. However, the parotid enlargement in such patients may be episodic or diffuse, which would suggest an inflammatory etiology.

Facial nerve palsy in a patient with a parotid mass is almost uniformly associated with malignancy, although sarcoid infiltration of the parotid gland is a well-known
exception to this rule. Diagnostic investigation includes physical examination, CT,18,19 and fine-needle aspiration biopsy.20,21 Cytologic evaluation by means of electron microscopy can reliably confirm the diagnosis of a parotid malignancy, and immunohistochemical analysis (using chromogranin A antibodies) may be particularly useful in establishing the neuroendocrine basis of the disease process.4 The overall sensitivity of fine-needle aspiration biopsy for the detection of malignant cells in salivary gland tumors is variously reported as 87 to 94%, with a specificity of 75 to 100%.22-25 Magnetic resonance imaging has been proposed as useful in assessing the degree of soft-tissue involvement and perineural invasion.18,19

Microscopically, the structure of the salivary glands is similar to that of the pancreas, with a duct system made up of acinar and duct cells ensconced in a sheet of myoepithelial cells. The acinar cells line the intercalated and striated ducts through which the saliva travels before it is expelled into the mouth. While the salivary glands themselves are mesodermal in origin, endocrine cells may be found within these glands, most likely derived from embryonic neural crest cells of the diffuse neuroendocrine system. It is likely that such cells give rise to neuroendocrine tumors in this location, although it has been proposed that pluripotential stem cells capable of dual epithelial and endocrine differentiation may be the source of the tumor.26

Unlike secretions from other digestive organs populated with neuroendocrine cells (particularly the stomach, pancreas, and liver), where evidence exists for the paracrine regulation of secretion, salivary gland secretions are considered to be predominantly regulated by the autonomic nervous system. Current views maintain that the role of hormones in the salivary glands—particularly aldosterone and antidiuretic hormone—is solely to modify the ionic content of the saliva. Salivary secretion is regulated by either sympathetic or parasympathetic stimulation, with the latter exhibiting a more dominant influence. While the most common mediators of salivary gland secretion are autonomic, neuropeptides are involved, with substance P, thereby stimulating acinar cells to release calcium and secrete saliva.27

One should be aware of the distinct anatomic and physiologic relationship of the salivary glands and pancreas when considering the genisnses and behaviorofcarcinoid tumors in these locations. As early as 1798, Sömmering recognized this unique relationship when he referred to the pancreas as the “abdominal salivary gland.”28 Carcinoid tumors are known to derive from the neural crest or neuroendocrine (APUD) tissues, although we are not certain whether APUD cells are present in normal salivary glands.29 Authors of reports of other neuroendocrine tumors in the parotid gland have proposed that such tumors arise from neuroendocrine stem cells that have migrated to the salivary gland from the neural crest30 or possibly from cells of the salivary duct system that have differentiated into cells with either neuroendocrine or epithelial features.31 While our understanding and characterization of the neuroendocrine function of the pancreas have evolved, the presence and role of neuroendocrine cells in the salivary glands have yet to be established or reported in the literature. The analogous structural and functional properties of the two organs might suggest similar neuroendocrine composition and regulation, although the significance and extent of their similarities remain unknown.

Carcinoids are often classified as typical (well-differentiated) and atypical (moderately differentiated). The designation reflects the tumor’s clinical features.32 For example, atypical carcinoids are overtly malignant tumors that behave more aggressively than typical carcinoid tumors (which are often indolent, benign neoplasms) and must therefore be managed accordingly.33

Treatment of any parotid malignancy is mainly surgical. The most successful intervention is extirpation or debulking of the tumor by means of a superficial or total parotidectomy. Preservation of the facial nerve is indicated if a plane between the tumor and the nerve can be identified and if the nerve was functionally intact before surgery.17 For benign parotid neoplasms, simple enucleation of the tumor is discouraged because the incidence of local recurrence is high.34 Adjunctive radiation or chemotherapy may be useful,35,36 particularly in patients in whom surgical intervention is either contraindicated or of limited utility—for example, patients with metastatic disease, patients of advanced age, and patients who are unable to tolerate surgery.4 Advanced salivary gland tumors respond most favorably to postoperative fast neutron-beam radiation therapy, which may be used as the sole therapeutic intervention for unresectable tumors.37 Furthermore, Armstrong et al reported that patients with a stage III or IV salivary gland neoplasm who had undergone combined surgery and radiotherapy had a higher rate of local control (51 vs. 17%) and a better prognosis (5-year survival: 51 vs. 10%) than did patients treated with surgery alone.38 However, it is interesting that combined therapy has demonstrated no benefit in patients with a stage I or II lesion. Systemic chemotherapy—most commonly with cyclophosphamide, doxorubicin, and cisplatin—is typically reserved for metastatic or unresectable salivary gland cancers. Although these tumors are chemotherapy-sensitive, chemotherapeutic regimens are effective yet ephemeral, with response rates averaging 40 to 50% and the average duration of responses ranging from 3 to 7 months.39-43

Often highly aggressive, malignant tumors of the parotid gland are associated with a poor prognosis. Malata et al44 reported 5- and 10-year survival rates of 68 and 49%, respectively, and Vander Poorten et al45 reported a 5-year survival rate of 62%. Factors that have the most
Influence on prognosis included the tumor's histopathologic type and stage, local tumor extension, and the presence or absence of facial nerve palsy. In particular, 10-year survival decreases with increasing stage, with rates of 85, 69, 43, and 14% corresponding with stage I through IV lesions, respectively. Furthermore, patients without local tumor extension have a more favorable 10-year survival (79 vs. 34%). Finally, one series demonstrated no 8-year survival for patients with primary facial nerve palsy; the 8-year survival rate observed in patients whose facial nerve was intact was 57%. In general, patients with tumors in the major salivary glands have a better prognosis than those with minor salivary gland lesions. After treatment, patients must be followed for several years because as many as 20% of tumor recurrences occur after 5 years.

In patients with hepatic metastases, local resection, hepatic artery embolization, or chemoembolization may be useful for control of liver disease. Given the novelty of a carcinoid tumor in this region, the utility of radioactive-labeled somatostatin analogues is not known; in fact, it has yet to be explored. In general, surgical resection of carcinoid tumors, particularly among those that are localized, is associated with relatively favorable 5-year survival rates.

In conclusion, our case represents what to the best of our knowledge is the first reported instance of a primary atypical carcinoid tumor of the parotid gland. Despite its exquisite rarity, this newly characterized disease entity is of considerable interest to clinicians who evaluate any masses in the parotid region. Likewise, the possibility of a primary carcinoid tumor of the parotid gland ought to be considered by any surgeon who encounters an anaplasia of the parotid gland. Indeed, the management of any carcinoid disease must include recognition of the possibility of metastatic spread to uncommon anatomic locations, as secondary carcinoid tumors in the parotid gland have been described multiple times in the literature. Although a primary carcinoid tumor of the parotid gland is extremely rare, the differential diagnosis of any parotid swelling or mass ought to include the possibility of carcinoid tumor because timely recognition and intervention are critical for successful treatment of this enigmatic disease.

References
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