Malignant peripheral nerve sheath tumors of the head and neck: Two cases and a review of the literature

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Abstract
Malignant peripheral nerve sheath tumors are uncommon lesions that occasionally affect the head and neck. We describe 2 new cases of head and neck pathology. One tumor involved the parotid gland and resulted in erosion of the temporal bone, and the other affected the lower lip. A rapid diagnosis has significant implications for management because of the tumor’s potential for aggressive behavior and its high rate of recurrence. To the best of our knowledge, lip involvement is rare and temporal bone involvement has not been previously described.

Introduction
Malignant peripheral nerve sheath tumors derive from the mesenchymal cells of the neural crest. They account for approximately 5% of all malignant soft-tissue tumors; of these, only 15% occur in the head and neck. When head and neck tumors do occur, most are located in the parotid gland or in the infratemporal fossa; they have also been reported in the mandible and, very rarely, on the lips. Invasion of the temporal bone, resulting in otorrhea and conductive hearing loss, has not been heretofore described. Surgical resection with adjuvant radiotherapy (even with clear resection margins) is the recommended treatment modality. Radiotherapy is desirable even when resection margins are clear because of the tumor’s high rate of recurrence. Regional lymph node metastases are rare.

In this article, we describe 2 new cases of malignant peripheral nerve sheath tumor of the head and neck. One case featured temporal bone involvement, and the other was characterized by the location of the tumor on the lip.

Case reports
Patient 1. A 32-year-old man had been referred to his local hospital for evaluation of a 4-year history of right-sided hearing loss and recent otorrhea. Examination of the right ear at that time revealed an attic polyp. No external swelling, parotid enlargement, or cervical lymphadenopathy had been noted. A pure-tone audiogram revealed a 65-dB conductive hearing loss in the right ear. Computed tomography (CT) of the temporal bones detected a soft-tissue mass that involved the temporal bone and tegmen tympani.

A mastoid exploration was performed, and biopsy specimens obtained from the middle ear and mastoid were subjected to histologic examination, which identified only a nonspecific inflammatory reaction. Because the histology was not consistent with the clinical findings, the patient was referred to the Department of Otolaryngology and Skull Base Surgery at our hospital for further evaluation.

We obtained magnetic resonance imaging (MRI), which showed that a well-defined, lobulated, enhancing mass had arisen from the deep lobe of the right parotid gland (figure 1, C). The mass involved the external auditory meatus laterally (figure 1, D), and it extended inferiorly posterior to the temporomandibular joint and ramus of the mandible. It also extended medially into the parapharyngeal space anterior to the carotid sheath (figure 1, C). The brain appeared to be normal, as there was no evidence of intracranial extension. No cervical lymphadenopathy was detected.

Angiography of the right internal and external carotid arteries excluded aneurysmal dilatation and a vascular tumor. A chest radiograph was normal, as were the complete blood count, erythrocyte sedimentation rate, autoantibody screen, and levels of angiotensin-converting enzyme, antineutrophil cytoplasm antibody (ANCA), and the immunoglobulins. The C-reactive protein level was elevated at 45 mg/L (range of normal: 0 to 6).
The histology of a second biopsy identified fragments of chronically inflamed connective tissue that were covered by hyperplastic and hyperkeratotic squamous epithelium. No evidence of dysplasia was seen, and malignancy was not suspected. In order to obtain tissue for definitive histology, we performed a right temporal bone exploration. The previous mastoid cavity was enlarged, and the incus, lateral semicircular canal, and facial nerve (which was exposed in its descending portion) were identified. The posterior wall of the ear canal was removed to allow for visualization of the erosion of the anterior wall of the canal.

The myxomatous mass was noted to involve the middle ear cavity, and it extended anterosuperiorly to the middle fossa dura. The mastoid cavity and eustachian tube were obliterated with fat and fascia and secured with Tisseel, and a blind sac closure of the ear canal was performed.

Histologic examination revealed that the tumor was largely made up of spindle cells that had a myxomatous appearance secondary to the presence of abundant intercellular connective tissue mucin. The spindle cells contained small hyperchromatic nuclei and long, wavy cytoplasmic processes. This cell morphology blended into a more
epithelioid appearance with clumps and cords of nuclei. Focally, there was a cribriform pattern created by cells and cell processes that encompassed pools of connective tissue mucin.

Immunohistochemistry showed strong staining of tumor cells for neuron-specific enolase (NSE), patchy staining for S-100 protein, and weak but definite diffuse positivity for protein gene product (PGP) 9.5. The reactions to epitheal membrane antigen (EMA) and cytokeratin were negative. Mild-to-moderate nuclear pleomorphism was noted, but mitoses were not apparent. The proliferation marker MIB-1 showed only a low proportion of cells in cycle.

The combined morphologic and immunohistochemical features were consistent with the epithelioid variant of malignant peripheral nerve sheath tumor. The infiltrative behavior of this tumor clearly confirmed its malignant nature.

The patient underwent complete excision of the tumor by means of an extended total conservative parotidectomy. This was performed through a postauricular incision extended into the neck, reflecting the pinna forward with the skin flaps elevated over the parotid gland. The main trunk of the facial nerve was identified, which allowed us to preserve its branches while removing the superficial and deep lobes of the parotid gland. The fat obliterating the temporal bone was removed, which resulted in complete exposure of the tumor in the parapharyngeal space and in the anterior part of the temporal bone. A complete macroscopic excision of the tumor was achieved with the assistance of intraoperative frozen sections. The deep lobe of the parotid gland was completely excised medial to the facial nerve. Despite wide surgical clearance, the pinna, the meniscus of the temporomandibular joint, and the head of the mandible were preserved. The temporal bone was obliterated with fat and fascia in the same fashion as the mastoid cavity and eustachian tube were obliterated in the previous surgical procedure.

The final histology report confirmed that the tumor arose from a large myelinated nerve and was made up of interlacing spindle cells set in a mucinous matrix. Focally, these cells coalesced to form acinar and cribriform patterns. Immunohistochemistry yielded strong cytoplasmic staining for S-100 protein and moderate staining for PGP 9.5 and NSE. The reactions to EMA and desmin were negative. No evidence of lymph node involvement was noted. As was the case with the previously analyzed specimen, mitoses were scant and proliferation marker MIB-1 showed only a low proportion of cells in cycle.

The patient subsequently received postoperative radiotherapy. Follow-up was carried out regularly for 3 years at our center with serial MRIs. Subsequent follow-up was conducted at the referring hospital, and there has been no sign of recurrence.

Patient 2. A 64-year-old man was referred to us by his general practitioner for evaluation of a progressive bilateral sensorineural hearing loss, primarily in the high frequencies (4 to 8 kHz).

During clinical examination, we made an incidental finding of a firm, nonulcerated, 3-mm nodule on the lower lip just to the left of the midline. Findings on the remainder of the examination were completely normal. The patient reported that the lip lesion had been present for at least 3 months, and it had become more sensitive to touch over the previous 3 weeks. Our clinical impression was that this lesion represented a fibroma, and a wedge excision was performed.

On macroscopic examination, we noted that the gray-tan soft-tissue mass was covered by surface epithelium. The mass contained a 0.4-cm nodule, which was identified on histologic examination as a cellular infiltrative lesion made up of pleomorphic spindle cells and cuboidal cells with indistinct eosinophilic cytoplasm (figure 2, A and B). The nuclei were enlarged and hyperchromatic, and a few mitotic figures were seen. No evidence of necrosis was noted. Cells were arranged in fascicles in some places and in loose cords of less dense cells in other areas. There was a prominent myxoid change of the intervening stroma. Nerve twigs within the biopsy specimen (figure 2, B) indicated perineural infiltration by the tumor.

On immunocytochemistry, the tumor cells expressed S-100 protein, confirming the tumor’s neural origin (figure 2, C). The cells also expressed glial fibrillary acidic protein (GFAP); although GFAP is often positive in low-grade lesions, it is usually lost in high-grade neoplasms. The tumor did not express smooth-muscle actin or pancytokeratin markers. The tumor’s morphologic appearance and immunocytochemical phenotype were consistent with a low-grade epithelioid-type malignant peripheral nerve sheath tumor.

Despite the clear resection margins, the patient underwent postoperative radiotherapy because of the perineural invasion. No recurrence was observed during follow-up.

Discussion

The estimated yearly incidence of malignant peripheral nerve sheath tumors is 1 per 100,000 population. These tumors usually occur between the third and fifth decades of life, and their distribution between the sexes is equal. They have been associated with neurofibromatosis in as many as 38% of cases. Malignant peripheral nerve sheath tumors usually arise in major nerve trunks, such as the sciatic nerve, brachial plexus, and sacral plexus. Therefore, they typically occur in the extremities and the trunk. These tumors can arise de novo as a solitary mass or multiply, as is seen in cases of neurofibromatosis type 1.

Roughly 15% of all malignant peripheral nerve sheath tumors occur in the head and neck. Approximately 100 cases of malignant peripheral nerve sheath tumors...
of the head and neck have been reported, some of which involved the parotid and infratemporal fossa (table).\(^2\)

The overall prognosis is poor, and reported 5-year survival rates range from 23 to 67%\(^3\).\(^6\).\(^1\).\(^1\).\(^1\)\(^5\)

Survival is worse in patients with centrally located or large tumors and in patients with neurofibromatosis type 1.

Malignant peripheral nerve sheath tumor, which is a sarcoma that arises from a nerve or displays features of neural differentiation, must not be confused with its benign counterpart, neurilemoma.\(^2\)

Malignant peripheral nerve sheath tumor can originate in any cell of the nerve sheath, including Schwann’s cells and fibroblasts that surround motor and sensory nerve axons.\(^2\)

These tumors grow longitudinally along the length of a nerve. They assume a fusiform appearance without compromising the morphologic or functional integrity of the nerve. As a result, they can be surgically separated from their nerve of origin.

In our patient 1, no neurologic deficit was elicited pre- or postoperatively as a consequence of the tumor or its excision (with the exception of some weakness of the mandibular branch of the facial nerve after surgical exposure). That tumor might have arisen from any of the lower four cranial nerves where they pass through the skull base, from the auriculotemporal nerve, or from the otic ganglion (which acts as a relay station for parasympathetic secretomotor fibers to the parotid gland).

The histologic appearance of these tumors can vary considerably,\(^1\)\(^6\) but most masses are made up primarily of a monomorphous population of small spindle cells that are usually arranged in fascicles in a herringbone pattern. These more solid areas normally alternate with areas that have a loose or myxoid appearance. Microvascular proliferation and perineural spread are common findings, and in approximately 20% of cases there is focal divergent differentiation toward mesenchymal elements (e.g., rhabdomyosarcoma, chondrosarcoma, osteosarcoma, angiomyxoma, and liposarcoma) or toward glandular and squamous-type epithelial tumors.\(^6\)

The explanation for this wide range of neoplastic phenotypes is that cells of the neural crest also contribute to the formation of leptomeninges, bone, cartilage, and muscle in the head, neck, and face.\(^7\)

Secondary features of malignant peripheral nerve sheath tumors include myxoid change, hyalinization, and geographic necrosis. Approximately two-thirds of cases feature a benign neurofibromatous component, supporting the view that malignant peripheral nerve sheath tumors arise as a result of malignant transformation in a preexisting benign lesion.\(^3\)

Imaging with CT, MRI, and angiography can differentiate this tumor from other possible pathologies, such as an aneurysmal formation, vascular tumor, lipoma, or an aneurysm in the temporal bone or infratemporal fossa, such as a cholesteatoma, meningocele, metastasis, ossifying fibroma, osteosarcoma, or fibrous dysplasia. In this regard, CT and MRI are superior to other imaging techniques and to physical examination.\(^1\)\(^8\)

Although CT and MRI do not provide information regarding a specific histologic diagnosis, they may yield useful information that may differentiate benign from malignant tumors.\(^1\)\(^0\).\(^1\)\(^9\)

Bony destruction of the mandible or skull base is best visualized on CT (figure 1, A and B), whereas bone marrow involvement is best demonstrated on MRI.\(^2\)\(^0\)

MRI is superior to CT in demonstrating the internal architecture of salivary gland tumors in a multiplanar fashion and in delineating the interface between the tumor and the normal parotid gland.\(^2\)\(^0\)

Neurogenic tumors usually enhance intensely with gadolinium diethylenetriamine penta-acetic acid (DTPA), whereas glomus tumors have the characteristic serpiginous areas of flow void (salt-and-pepper pattern) on MRI.\(^2\)\(^5\)

On MRI, most malignant peripheral nerve sheath tumors demonstrate moderate enhancement on T1-weighted imaging and marked enhancement on T2-weighted imaging, especially with gadolinium contrast (figure 1, C and D).\(^1\)\(^9\)

The diagnosis is based on histology and confirmed by a positive reaction to immunohistochemical markers.
Malignant peripheral nerve sheath tumors usually demonstrate focal S-100 protein positivity, although as many as one-third of tumors may be S-100-negative. They may show reactivity for Leu-7 or myelin basic protein, but they are negative for cytokeratins. Tumors are occasionally positive for the melanocytic marker HMB-45. NSE has been widely used to demonstrate neural or neuroendocrine differentiation in tumors, and it may also be found in many gliomas and carcinomas of nonendocrine origin. NSE is positive for the melanocytic marker HMB-45. NSE has been widely used to demonstrate neural or neuroendocrine differentiation in tumors, and it may also be found in many gliomas and carcinomas of nonendocrine origin. NSE is best used only in conjunction with other markers to provide supportive evidence of neural differentiation.

The optimum treatment is combined surgical excision with radiotherapy. Radiotherapy is indicated because of the technical difficulties posed by anatomic constraints to achieving complete clearance.

Table. Summary of reported cases of malignant peripheral nerve sheath tumors of the head and neck (excluding triton tumor)

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>Treatment</th>
<th>5-year survival* (%)</th>
<th>Recurrence* (%)</th>
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<td>18</td>
<td>Sx + RT</td>
<td>49</td>
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<td>Sx</td>
<td>66</td>
<td>18</td>
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<tr>
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<td>Sx + RT</td>
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<td>Sx + RT</td>
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* Reported rates include patients without head and neck cancers.
† Present report.

References