Management of Metastatic Glomus Jugulare Tumors

Abstract—Metastatic glomus jugulare tumors (jugular paragangliomas) are very uncommon; consequently, no single report has been able to accurately describe their biologic or clinical behavior, and there are no established guidelines on caring for patients with these tumors. Identification of metastatic paraganglioma can be difficult because these tumors are known to occur synchronously, many other tumor types appear histologically similar to paragangliomas, and histologically the metastasis may not resemble the primary tumor. Immunohistochemistry, using neuroendocrine markers, and electron microscopy are the two most useful techniques available to identify definitely paragangliomas. A few studies have shown differences in the immunohistochemical staining patterns between benign and metastatic paragangliomas. We reviewed the literature and include two additional cases of metastatic glomus jugulare tumors in this article. We discuss the clinical management of these patients, the importance and usefulness of immunohistochemistry in characterizing these tumors, and their clinical outcomes. (*Skull Base Surgery*, Volume 2, Number 1, 1992, p. 1)

Glomus jugulare tumors are recognized as the most common tumor of the skull base, the most common benign neoplasm of the middle ear, and the second most common tumor of the temporal bone.¹⁻³ Although considered benign, glomus tumors have been called malignant because of their well-known predilection for local invasion of bone, soft tissue, and neural structures. True malignancy, however, is defined clinically by regional or distant metastasis. Historically, these tumors were thought to be of vascular origin (hence the term “glomus”), but have subsequently been classified as endocrine tumors of neural crest origin. They are histologically similar to tumors of the carotid and vagal bodies. These tumors arise from the extra-adrenal paraganglia of the autonomic nervous system and are more correctly referred to as paragangliomas.³ Because the terms “glomus tumor” or “glomus jugulare” are more widely recognized, we will use these terms in this article to refer to jugulotympanic paragangliomas.

The head and neck area represents the most common site of extra-adrenal paragangliomas, followed by the retroperitoneal region.³ Paragangliomas are most common in the adrenal medulla, and they are referred to as pheochromocytomas in this site. However, unlike adrenal tumors,

head and neck paragangliomas rarely secrete physiologic levels of catecholamines or hormones. Approximately 3% of glomus jugulare tumors have been found to secrete such substances.⁴ Reports of functional carotid body tumors are less common.⁵

Histologically, glomus jugulare tumors classically show an organized pattern and a fibrovascular stroma. The two primary cell types that are identifiable in paragangliomas of the head and neck are the chief cells (type I) and the sustentacular cells (type II). The chief cells are neuroectodermally derived and are the most numerous. They form the characteristic cell nest (Zellballen) pattern in normal paraganglia and in paragangliomas (Fig. 1). The sustentacular cells are derived from Schwann cells. They are situated at the periphery of the cell nests in close apposition to capillaries and collagenous stroma. Sustentacular cells are inapparent with routine staining and are disclosed only with immunohistochemical staining or electron microscopy.

Because of their varying histologic patterns and the frequent misinterpretation of their microscopic features, glomus tumors have been reported under a variety of names.⁵ They can resemble thyroid and parathyroid neoplasms, carcinoid tumors, olfactory neuroblastomas, poorly

Figure 1. Stained preparation of paraganglioma from patient 1 showing classic cell nest (Zellballen) pattern. (H & E.)

differentiated squamous cell or adenocarcinoma, alveolar soft tissue sarcoma, granular cell tumor, melanoma, and metastatic renal cell carcinoma.⁶

Immunohistochemical characterizations of pheochromocytomas have been extensive, but paragangliomas of the head and neck have received less attention. Recent studies using neuroendocrine markers have been used to characterize paragangliomas of the head and neck.⁶⁻⁸ We report the outcome of two patients with malignant glomus jugulare tumors and discuss immunohistochemical evaluation and clinical management of these patients.

MATERIALS AND METHODS

Histologic sections from two malignant (metastasizing) jugulotympanic paragangliomas were obtained. The histologic material was reviewed and representative blocks of tumor were selected for antigen characterization. An avidin-biotin complex (ABC) method was used to stain deparaffinized sections with antibodies to five immunohistochemical markers known to indicate benign para-

gangliomas. Antibodies to S-100 protein (S-100), chromogranin A (CHA), synaptophysin (SYN), neuron-specific enolase (NSE), and cytokeratin (CK) were applied (Table 1). All antibody reactions were controlled by evaluating their staining patterns on multitissue blocks of optimally prepared normal human tissues and multitumor blocks of human neoplasms. Negative controls deleted the incubation step with primary antibody. Immunohistochemical reactivity patterns were evaluated for intensity and distribution. Cellular sites of reactivity (nuclear or cytoplasmic) and the specific cell types (chief cells and sustentacular cells) stained were also noted.

RESULTS

Clinical Reports

Patient 1 presented in March, 1977, as a 25-year-old woman with a 2-year history of right side pulsatile tinnitus and facial weakness. She had an extensive glomus jugulare tumor with facial nerve invasion that was resected via a transmastoid/facial recess approach. The facial nerve was grafted. No metastasis was noted at this time. In March, 1980, recurrent pulsatile tinnitus, fever, and non-productive cough prompted medical investigation. The patient was found to have anemia (hemoglobin of 7.1 gm/dl) and bilateral diffuse, nodular infiltrates on chest radiograph. Lung biopsy revealed metastatic glomus tumor. In October, 1982, a posterior neck mass was excised and also reported to be a glomus tumor. The patient was treated with blood transfusions and intermittent chemotherapy (etoposide). In February of 1984 she had recurrent skull base tumor, ipsilateral neck metastases, and bilateral lung metastases. She was given chemotherapy, but there was no change in the lung lesions. In 1985 she underwent an extensive skull base resection via the infratemporal fossa approach, and a right radical neck dissection for cervical lymph node metastases. The previous facial nerve graft was found to be infiltrated by tumor, and it was resected and grafted again. Cranial nerves XI and XII were sacri-

Table 1. Antibodies*

<i>Antibody</i>	<i>Clone</i>	<i>Specificity</i>	<i>Source</i>	<i>Reference</i>
Anti-cytokeratin cocktail	KA4/UCDPR10.11	CK [†] 14, 15, 16, 19/8, 18	Triton Biosciences	Nagle (1985), Chan (1988)
	CAM 5.2	CK 8, 18, 19	Becton-Dickinson	Leader (1986)
	34 B E 12	CK 1, 5, 10, 14	Enzo Biochemical	Gown (1984)
	AE1	CK 10, 14, 15, 16, 19	ICN Immunobiologicals	Cooper (1985)
anti-S-100	AE 3	CK 1, 2, 3, 4, 5, 6, 7, 8	Boehringer-Mannheim	Cooper (1985)
	Antiserum	Alpha/beta subunits	Dako Corp.	NA
	Antiserum	Neuron-specific enolase	Dako Corp.	NA
anti-CCG	LK2H10	Chromogranin A	Dr. R. Lloyd/University of Michigan	Wilson (1984)
anti-SYN	SY38	Synaptophysin	Boehringer-Mannheim	Gould (1987)

*NSE: neuron-specific enolase; CCG: chromogranin A; SYN: synaptophysin; NA: not applicable.

[†]CK denotes cytokeratin according to the nomenclature of Moll (1982).

ficed in the resection. One high jugulodigastric lymph node and 2 periparotid lymph nodes were involved with metastatic glomus tumor (noncontiguous spread). The patient stayed in the hospital for 3-1/2 months post-operatively but was discharged in good condition. The patient has since had a remarkable improvement in her clinical course. Six years later, the patient is currently alive and well, with no evidence of disease, and her chest radiograph appears clear.

Patient 2 presented in 1963 as a 20-year-old woman with a left side glomus jugulare tumor. At that time the patient had a partial mastoidectomy for removal of tumor. The patient had a family history of multiple endocrine neoplasia type 2 and three of the four siblings were affected with various paragangliomas. In 1964 an ipsilateral carotid body tumor was resected. In 1965 the patient had recurrent glomus jugulare tumor and ipsilateral neck metastases. A left temporal bone resection and neck dissection, and hypoglossal-facial nerve transposition were performed. A brief course of postoperative radiation therapy was given. In 1975 the patient had a neck tumor excised that was reported to be a left carotid body tumor. In October 1983 the patient presented with large retroperitoneal lymph nodes for which she underwent exploratory surgery. The patient also had skeletal pain, and biopsy confirmed metastatic paraganglioma to the skull, scapula, ribs, hip, and vertebral column. The liver, brain, and lung were also found to be involved with metastatic tumor. In November 1983 radiation therapy was given to the bony metastases (40 Gy) and chemotherapy was begun with CYVADIC (cyclophosphamide, vincristine, doxorubicin [Adriamycin], and dacarbazine [DTIC]). For the next 2 years, she seemed to improve clinically and there was definite regression of bony lesions. In 1987 she had recurrent bony disease with marked hypercalcemia, and she was restarted on chemotherapy (cisplatin and etoposide [VP-16]). This time she did not respond well, and in December 1987 she died of massive metastatic paraganglioma.

Immunohistochemistry

Immunohistochemical studies of the metastatic deposits of these two malignant glomus jugulare tumors yielded similar results. As shown in Table 2, there was

Table 2. Metastasis-Malignant Paraganglioma

Antigen	Glomus Jugulare	
	Patient 1	Patient 2
S-100*	Rare +	—
Chromogranin A	+	+
Synaptophysin	+	+
Neuron-specific enolase	+	+
Cytokeratin	—	—

*Denotes sustentacular cell staining

strong, diffuse staining of the chief cells with NSE antibodies in the tumor of both patients. CHA and SYN were also present in the specimens from both patients. CK was not present in either specimen. S-100 weakly stained the periphery of one specimen and was not present in the other.

DISCUSSION

Clinical

Glomus jugulare tumors that have metastasized are rare, about 3% of reported cases. Thirty-one patients with metastatic glomus jugulare tumors have been reported, and we present the 32nd and 33rd cases in this article.^{5,9-13} Several of the previously reported cases do not provide long-term follow-up of patients and some of these reports only noted metastatic disease at autopsy, thus making it difficult to establish the natural course of disease in patients with metastatic glomus jugulare tumor. Virtually all reported patients with metastatic disease had an uncontrolled primary tumor, and many had intracranial extension, making it unclear whether the primary tumor or the metastases led to the patient's death. It is generally believed that patients with metastatic glomus jugulare tumor run a rapidly fatal course, as is evident from the report of McCabe and Fletcher,¹⁴ in which all three patients died within a year. However, exceptions do exist. Winship et al¹⁵ reported on a patient with regional metastasis who had a 20-year history of disease with no progression until the last 5 years. Rosenwasser¹⁶ described a patient with intracranial tumor who developed pulmonary metastasis 11 years later. A more recent report from Japan¹² mentions a patient surviving 5 years with skeletal metastases. Both of our patients survived for long periods after documented metastasis.

We believe that patient 1 is the first to undergo surgical removal of primary glomus jugulare tumor after documented regional and distant metastasis. There has been remission of the pulmonary metastatic disease after local and regional control was obtained. Since our patient has done well clinically, metastases from glomus jugulare tumors may not affect survival (as seen in cases of well-differentiated thyroid cancer). As with carotid body tumors, the eventual outcome of patients with metastatic glomus jugulare tumors is unpredictable. There are reports of patients with metastatic carotid body tumors who have died within a year, but there are also many reports of patients surviving 10 to 25 years with extensive metastases.¹⁷

Glasscock and colleagues¹⁸ have suggested that patients with glomus tumors require follow-up for 10 to 15 years. Patient 2 illustrates why it may be justified to follow patients with head and neck paragangliomas for life, since 20 years elapsed before she manifested systemic metastases of paraganglioma.

The most commonly reported site of metastasis from glomus jugulare tumor is the lung, followed by cervical lymph nodes (see Table 3). Lung metastases usually appear as multiple, nodular densities, as was seen in our patients. However, a diffuse, fine nodular pattern mimicking miliary tuberculosis has been described in a patient with a metastatic carotid body tumor.¹⁹

Bony metastases from glomus tumors usually appear as osteolytic lesions, as seen in our patient 2.^{11,13} External beam irradiation was used with some success in our patient (2) and by other authors.¹¹ Additionally, radioactive functional scintigraphic markers have been used to treat bony metastases of paraganglioma.²⁰

It is now well established that the histologic appearance of glomus tumors does not correlate with the clinical behavior.^{3,5} That is, histologically "benign"-appearing tumors may be locally very aggressive and may metastasize, and tumors with a more "malignant" histology (pyknotic nuclei or bizarre nuclear morphology) may be slow growing and not metastasize. Because of this, malignancy in these tumors must be based on clinically proven metastasis. Additional points of confusion are that glomus tumors are often multicentric (synchronous lesions), they can occur in a variety of sites in the head and neck, and they are histologically mistaken for many types of tumors. For these reasons, a panel of immunohistochemical markers may help to diagnose these tumors accurately.

Immunohistochemistry

CHA, SYN, and NSE are known to stain neuroendocrine cells (chief cells in paragangliomas). The staining pattern observed in our specimens agrees with previous immunohistochemical studies of paragangliomas; chief cells in both tumor specimens were reactive to these markers (Fig. 2). CK reactivity is positive in carcinomas and in only 10% of paragangliomas.⁶ CK staining was, appropriately, negative in our study. This may lead to confusion if interpreted out of context, and therefore we

Figure 2. The dark cells represent staining of chief cells with chromogranin A.

recommend always employing a panel of neuroendocrine markers in cases of uncertain diagnosis. S-100, which is known to react with paraganglioma sustentacular cells, showed focal, rare, or no staining in the specimens from our patients. Interestingly, immunohistochemical studies of paragangliomas that have displayed aggressive and metastatic behavior show marked reduction or absence of S-100 reactivity.^{7,9} "Benign" paragangliomas are more strongly positive for neuroendocrine markers in chief cells, and positive for S-100 in sustentacular cells. Our data verify this, since there was weak or complete lack of staining of S-100 in sustentacular cells in our two specimens of metastatic glomus jugulare tumor (Fig. 3).

SUMMARY

Patients with malignant (metastatic) glomus jugulare tumors have an unpredictable clinical course. Lifelong follow-up of patients with glomus jugulare tumors is warranted, since patients may experience decades free of disease and then recur with primary or metastatic disease.

Table 3. Metastatic Site of Malignant Glomus Jugulare*

<i>Local Metastasis</i>	<i>Distant Metastasis</i>
Lymph nodes, neck, 10	Lung, 16
Skull, 3	Liver, 7
Brain, 2	Lymph nodes, other, 5
Parotid, 1	Vertebra, 5
Dura, 1	Ribs, 4
	Skeleton, multiple, 3
	Spleen, 2
	Chest wall, 1
	Small intestine, 1
	Nasopharynx, 1

*There were 33 patients with metastases.

Figure 3. The dark cell (semilunar) shows staining of sustentacular cells with S-100.

Complete surgical removal of primary tumor with regional control of disease probably represents the most effective modality to achieve a cure. Surgical indications will have to be determined on an individual basis.²¹ Multimodality therapy may be appropriate in the medically infirm, in cases of disseminated disease, or in the case of a locally very aggressive tumor.²¹ In histologically ambiguous cases, a panel of immunohistochemical markers may be important in arriving at the proper diagnosis of head and neck paraganglioma. Further characterization of head and neck paragangliomas with immunohistochemical markers will probably allow a more accurate prediction of malignant tendency.

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