Leiomyosarcoma of the Skull Base—A Diagnostic Challenge

Abstract—Soft tissue sarcomas often present a frustrating diagnostic challenge for the pathologist as well as the surgeon. Despite the development of better defined criteria for histopathologic and immunohistochemical evaluation, definitive diagnosis may not be immediately apparent. We report two cases of leiomyosarcoma of the skull base that presented with the clinical diagnosis of schwannoma, a diagnosis confirmed on initial histopathologic examination. It was only after closer review and special immunohistochemical studies that the diagnosis of leiomyosarcoma was made. The methods for diagnosing such tumors using both standard histopathologic criteria and immunohistochemical methods are reviewed. We suggest that all extracranial soft tissue tumors of the skull base be examined by both techniques to avoid delayed or missed diagnosis. (*Skull Base Surgery, Volume 2, Number 2, 1992, p. 103*)

Soft tissue sarcomas are rare tumors that arise primarily from poorly differentiated connective tissue, fat, muscle, synovium, vascular endothelium, or the supporting tissue of peripheral nerves.¹ Criteria for the diagnosis of particular subtypes of soft tissue sarcomas are not universally employed, making it difficult to know the true incidence of these subtypes.² These tumors have a bimodal distribution with peak incidences in the second and the fifth to sixth decades of life. They are more common in children than in adults, accounting for 6.5% of all pediatric tumors, and are the fifth leading cause of malignancy in ages below 15 years.³ No definite locations for occurrence of sarcomas in general can be found; however, certain groups of sarcomas may have sites of notable predilection.⁴

In the head and neck, the most common sarcomas are rhabdomyosarcomas and malignant schwannomas. Leiomyosarcomas account for about 1% of head and neck sarcomas; they are most often found in the retroperitoneum.⁴

These sarcomas often present a frustrating diagnostic challenge for the pathologist as well as the surgeon. Despite the development of better defined criteria for histopathologic and immunohistochemical evaluations, a definitive diagnosis may not be apparent immediately. There remain confusion and disagreement on the diag-

nosis of these tumors as is evident from retrospective peer reviews of soft tissue sarcoma specimens.^{2,5}

In this article we present two cases, which initially were confused as schwannomas of the skull base by standard histopathologic examination. It was only after further review of the specimen with immunohistochemical techniques that the diagnosis was made.

CASE REPORTS

Case 1

A 12-year-old girl presented to her local physician in December 1987 with a left laterocervical mass that caused bulging of the sternocleidomastoid muscle. Magnetic resonance imaging (MRI) suggested a tumor arising from the parotid gland. Arteriography had demonstrated a fistula between the vertebral and the carotid arteries passing through the tumor. Surgery performed elsewhere in March 1988 showed a tumor in the subcutaneous tissue between the sternocleidomastoid and the digastric muscles, with firm attachment to the deep structures of the neck. It appeared to involve the carotid artery, the jugular vein, and the lateral process of C2. It was described as "tenacious and hard," making removal impossible. Immediate

histopathologic report showed the tumor to be consistent with neurofibroma. It was believed that the tumor was arising from the skull base in the region of the foramen jugulare. Further histopathologic examination seemed to confirm the diagnosis of neurofibroma with some chronic nonspecific reaction in the lymph nodes. The patient was then referred to the University Hospital in Zurich for further evaluation. She was admitted for diagnostic imaging, arteriography, and embolization of the tumor in June 1988 (Fig. 1). She was readmitted in September 1988 and underwent surgical extirpation using an infratemporal fossa type A approach.

The operation was quite difficult secondary to extensive scarring, which made the carotid artery and structures of the jugular foramen difficult to identify. The trunk of the facial nerve was identified, dissected free from the tumor, and rerouted anteriorly. The tumor was more densely attached to the vagus and glossopharyngeal nerves. Some vagal fibers entering the tumor were divided, leaving the bulk of the vagus nerve intact. The glossopharyngeal nerve was grossly involved and was removed with the specimen. The accessory nerve was preserved. The operative cavity was obliterated with abdominal fat. The postoperative course was uneventful and the facial function remained intact.

The initial histopathologic report was of a tumor consistent with schwannoma with infiltration of the glossopharyngeal nerve. However, when special immunohistochemical stains were used, the tumor was found to be negative for S-100 protein and positive for desmin and

smooth muscle α -actin. After thorough review of the tissue, it was believed that most likely the tumor was a leiomyosarcoma grade I–II (Figs. 2, 3).

In December 1989 MRI showed recurrent tumor apparently attached to the carotid artery (Fig. 4). The patient underwent preoperative balloon occlusion of the internal carotid artery followed by extirpation of the recurrent tumor. At surgery, the facial nerve was left intact in its anterior position. The recurrent tumor involved the vertical segment of the internal carotid artery and had infiltrated cranial nerves X, XI, and XII. A postoperative MRI scan confirmed that the entire tumor was removed. The patient had an uneventful postoperative course.

Five months later, she developed swelling and tenderness behind the left ear. A new MRI scan showed recurrence of tumor at the jugular foramen and a separate infra-auricular nodule (Fig. 5). She underwent revision surgery in August 1990. The facial nerve appeared infiltrated by the tumor and was removed distal to the geniculate ganglion. The defect was reconstructed with an anterior temporoparotid sural nerve graft.

Analysis of the specimen was negative for the S-100 protein; the tumor exhibited immunoreactivity for desmin and α -actin. The mitotic activity was more pronounced than in the previous specimens, leading to the diagnosis of a leiomyosarcoma grade II–III.

Two months later, a chest x-ray film revealed pulmonary lesions consistent with metastasis. She underwent radiation therapy to the operative site and systemic chemotherapy.

Figure 1. Preoperative magnetic resonance imaging scan of the patient in case 1. Tumor involves the skull base in the region of the jugular foramen, extending inferiorly and adjacent to the parotid gland.

Figure 2. Histopathologic appearance of the tumor in case 1. Spindle cell tumor with pseudo-palisading (A, H & E). Immunocytochemical reactions demonstrate expression of the muscle antigens desmin (B) and α -actin (C) and of the mesenchymal intermediate filament protein vimentin (D). S-100 protein is not detectable (E). The recurrent tumor (F, H & E) shows an increase in mitotic activity and cellular pleomorphism.

Case 2

A 49-year-old man presented in February 1988 with a 1-year history of paresthesia and progressive pain in the distribution of his right mandibular nerve as well as numbness in the right oral mucosa and tongue. He had been treated for trigeminal neuralgia with aspirin and carbamazepine with no significant improvement. His medical history was significant for migraine headaches. He had congenital retinopathy in his left eye and had had episodes of amaurosis since a cataract operation several years earlier in that eye.

The oral cavity, nasopharynx, and tympanic membranes were normal. He had decreased sensation of the right oral mucosa and tongue, and his uvula deviated to the left. Atrophy of the right masseter was noted. Sensation was partially decreased in the distribution of V-2 and absent in V-3. Facial nerve function was symmetrical. There was no light perception and there was a mild ptosis secondary to his previous surgery in the left eye.

Computerized tomography (CT) showed a clearly defined mass in the right infratemporal fossa just below an enlarged foramen ovale. There was deformation and destruction of bone in the pterygomaxillary fossa. It was

Figure 3. Postoperative computed tomography scan after initial resection of tumor in case 1 showing complete removal of the tumor.

Figure 4. Magnetic resonance imaging scan of patient in case 1 after initial recurrence showing tumor adjacent to the carotid artery.

believed that this most likely represented a neuroma of the trigeminal nerve (Fig. 6).

The patient underwent resection of this tumor in April 1988 with an infratemporal fossa type D approach. This is a modification of the type C approach, which consists of temporary resection of the zygomatic arch and body while leaving the temporal bone and eustachian tube intact.⁶ The tumor was tightly adherent to the mandibular division of the trigeminal nerve. The preliminary histo-

pathologic report described a pattern consistent with a schwannoma (WHO grade I). After completion of the special stains and immunohistochemical analysis, the tumor was found to be without reaction to the S-100 protein marker and positive for desmin, vimentin, and α -actin. In addition, many cells contained periodic acid-Schiff positive glycogen granules. The final histopathologic diagnosis was that of a malignant leiomyosarcoma grade I (Fig. 7). Postoperatively, the patient healed un-

Figure 5. Magnetic resonance imaging scan showing second recurrence of tumor that had invaded the facial nerve.

eventfully with complete resolution of his pain. A post-operative CT scan showed no complications and confirmed the complete removal of tumor (Fig. 8).

In April 1990, the patient complained of a low-grade fever with chest pain. A chest x-ray film demonstrated densities in both lower lung fields consistent with metastatic disease. An attempt was made to obtain a CT-guided

needle biopsy without success. A subsequent open lung biopsy confirmed the diagnosis of metastatic leiomyosarcoma. Morphologically, the metastatic tumor was indistinguishable from the original tumor, including its immunohistochemical expression of desmin and α -actin. No S-100 expression was found. Chemotherapy and radiation treatments were begun.

Figure 6. Preoperative scans of patient in case 2 showing a tumor of the right infratemporal fossa with bony destruction of the skull base and pterygomaxillary fossa. A: axial; B: coronal.

Figure 6, cont.

Figure 7. Histopathologic appearance of the tumor in case 2. Spindle cell tumor with fascicular architecture (A, H & E) and immunoreactivity for α -actin (B). Lung metastasis (C) with increased cellularity and immunocytochemical expression of desmin (D).

Figure 8. Coronal computed tomography scan of patient 2 after complete removal of the tumor.

DISCUSSION

Soft tissue sarcomas are rare tumors that can be confused with other spindle cell neoplasms if not carefully examined by both routine histopathologic and immunohistochemical methods. In the head and neck, the most common sarcomas are embryonal rhabdomyosarcomas, neurofibrosarcomas, and malignant schwannomas.^{1,4} Sarcomas in general cause a great deal of confusion and disagreement in both diagnosis and staging. In a retrospective peer review of 216 consecutive patients with soft tissue sarcomas by Presant et al,² there was total agreement by the original pathologist and the reviewer in only 66% of cases. The majority of disagreements in 27% of cases were concerned with the subtype of the sarcoma or its grade; in 6% of cases, the tumors were not thought to be sarcomas. Alvegård and Berg reviewed 240 cases retrospectively and found a similar margin of error. They concluded that histopathologic peer review was important in the study of soft tissue sarcomas.⁵ These studies not only point out the problems associated with making the correct diagnosis, but also point out that one must be cautious in accepting reports at face value when determining both prognosis and therapy. The biologic characteristics of different types of tumors can drastically affect these determinations. The propensity for local recurrence and for regional or distant metastasis and the sensitivity to modes of therapy other than surgery make the correct diagnosis of paramount importance. The prognosis and treatment for a benign schwannoma versus those for a

leiomyosarcoma are very different indeed. Torosian et al,⁷ in their review of soft tissue sarcomas, found patients with leiomyosarcoma more likely to develop metastasis than those with other histologic types.

Little has been reported about soft tissue sarcomas of the skull base. Most such reports are of malignant schwannomas. Hoffmann et al⁸ reported their experience with what they referred to as "malignant nerve sheath tumors." These occurred in nine patients treated over a 12-year period. Most of the tumors presented in the region of the trigeminal nerve but did not necessarily arise from the main nerve trunk. Five of the patients had undergone one or more local resections of what were initially diagnosed as benign lesions.

The histologic criteria suggested for diagnosing nerve sheath tumors have been discussed elsewhere.^{7,9} Electron microscopy also has been used to help characterize peripheral nerve sheath tumors.¹⁰ Because morphologic criteria remain confusing, immunohistochemical studies can prove invaluable when used in conjunction with traditional studies.¹¹

Immunohistochemical techniques have proved useful for identifying subtypes of spindle cell tumors. The various immunohistochemical techniques available for identifying nerve sheath tumors have been compared. None has been shown to be more sensitive in the identification of tumors than S-100 protein immunoreactivity.¹² The S-100 protein is found primarily in supporting cells of both the central and the peripheral nervous tissue but is not restricted to the nervous system.¹³ In well-differentiated tumors of Schwann cell origin, the test will be positive in

all cases. In highly undifferentiated malignant Schwann cell tumors, expression of S-100 protein may be significantly reduced.¹³ From this, one might be able to suggest that the expression of the S-100 protein may correlate with the degree of differentiation in Schwann cell tumors. In the tumors reported herein, the complete absence of S-100 immunoreactivity is a strong argument against Schwann cell origin.

Leiomyosarcoma is a spindle cell tumor of smooth muscle origin, which can be identified by immunohistochemical detection of smooth muscle antigens. The principal examples are the intermediate filament protein desmin and the smooth muscle α -isoform of actin. The identification of these proteins in a spindle cell tumor strongly points to an origin from smooth muscle cells. S-100 will not be expressed in smooth muscle or smooth muscle tumors, nor will α -actin and desmin be found in Schwann cells or schwannomas.^{14,15}

We noticed in case 1 that the expression of α -actin and desmin was almost completely lost in the recurrent tumor. This tumor also showed an increased degree of anaplasia and dedifferentiation. These findings suggest that the identification of these proteins may become increasingly difficult in highly malignant forms of leiomyosarcomatous neoplasms.

Rhabdomyosarcomas exhibit a distinct morphology compared with that of spindle cell tumors. Cross-striated muscle fibers may be seen. Immunocytochemistry is positive for α -actin and desmin, and also for myoglobin. It is important to distinguish rhabdomyosarcomas from other sarcomas because of the therapeutic approaches used.¹⁵

Malignant fibrous histiocytomas demonstrate a storiform growth pattern and express histiocyte markers, including α_1 -antitrypsin, α_1 -antichymotrypsin, and lysozyme.¹⁵ Fibrosarcomas are spindle cell tumors that are negative for S-100 protein and positive for vimentin, but have no specific immunohistochemical marker.¹⁵

CONCLUSIONS

In the cases presented here, the importance of using both traditional histopathologic and immunohistochemical analysis in the diagnosis of soft tissue tumors is apparent. These cases demonstrate that without the information gained by such immunologic staining, the diagnosis may be delayed or possibly missed completely.

The histologic grading of these tumors not only is confusing to pathologists,^{2,5} but also may be very misleading to the surgeon. Despite the fact that our patients demonstrated only low-grade malignancy histologically, they both developed distant metastases. The tumor in case 1 appeared to have become increasingly malignant with the passage of time. In both cases, it was believed that, in view of the low histologic grade, "radical" surgical removal would be curative. The question arises, then, of

whether such patients should be treated with postoperative radiation therapy regardless of the histologic grade. From the report of Goepfert et al¹ concerning other subtypes of sarcomas and considering the behavior of the tumors presented here, this may be a valid conclusion.

From our experience with these cases, we would suggest that the routine screening of all extracranial soft tissue tumors of the skull base should include immunohistochemical analysis for S-100 protein, desmin, α -actin, and myoglobin in addition to the traditional histopathologic examinations to avoid confusing spindle cell tumors of neural origin with soft tissue sarcomas. The need for review by an experienced pathologist or neuropathologist familiar with the subtle differences in these tumors should also be considered.

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REVIEWER'S COMMENTS

In this era of expanding frontiers in cranial base surgery, Dr. May and his colleagues appropriately caution us regarding the high propensity for error in diagnosing many soft tissue tumors. Misdiagnosis is especially prevalent in sarcomatous lesions because of the confusion regarding nomenclature and histologic grading and subtyping, as well as the lack of uniformly applicable criteria. This confusion has fueled disagreements among pathologists as frequently as 30% of the time. The diagnostic dilemma is especially accentuated in dedifferentiated tumors. Not surprisingly, therefore, determining optimal treatment, surgical or otherwise, can be particularly treacherous. Although immunohistochemical methods clearly establish the diagnosis in the authors' two reported cases, accurate diagnosis requires collective interpretation of histologic techniques, electron microscopy, and immunohistochemical methods. Certainly, second pathology opinion should be sought when any doubt remains concerning diagnosis of sarcomas or other soft tissue tumors.

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