Skull Base Neurocytoma: Case Report and Review of the Literature of Extraventricular Neurocytomas

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ABSTRACT

We report a rare skull base neurocytoma. A 44-year-old female with a history of focal seizure and progressive right-sided weakness sought treatment at an outside institution, where she underwent total resection of a "left medial sphenoid wing paraganglioma" in 1984. In 1995 after experiencing intense left-sided headaches for 3 weeks, the patient presented to our institution. Magnetic resonance imaging revealed a large local recurrence. She had deficits dating to her initial surgery, including moderate right-sided hemiparesis, complete left ophthalmoplegia, and left facial numbness.

The patient underwent a craniotomy with extensive removal of the involved sphenoid bone and a subtotal resection of the tumor. Neurocytoma was diagnosed based on strong immunohistochemical staining for synaptophysin and no reactivity for glial fibrillary acidic protein. Postoperatively, her headaches resolved completely and her neurologic status remained at baseline. The residual tumor was treated with radiation therapy. After 5 years, she remains clinically and radiographically stable.

Although typically located adjacent to the foramen of Monro, neurocytomas have now been reported in almost every subcompartment of the craniospinal axis. Finding neurocytomas in extraventricular locations may require revisiting the current theory that subependymal progenitor cells are the cells of origin for these tumors.

KEYWORDS: Brain neoplasm, extraventricular, neurocytoma, skull base

Originally reported in 1982 by Hassoun et al.,¹ central neurocytoma was subsequently recognized as a distinct entity by the World Health Organization (WHO) Working Group on histological typing of tumors of the central nervous system.² These rare tumors account for 0.25 to 0.5% of all brain tumors.^{3,4} Classically, central neurocytomas affect young adults, arise in the lateral ventricles adjacent to the foramen of Monro, and can be cured with gross total resection. The typical clinical manifestation is consistent with the signs and symptoms associated with obstructive hydrocephalus. These tumors also may be associated with epilepsy when they have a large intraparenchymal component.^{5,6} Microscopically, these tumors are composed of neurocytes and small round cells with perinuclear halo formations.³ Immunohistochemically, they stain with markers of neuronal differentiation, such as synaptophysin.⁷ Ultrastructurally, neurites and neurosecretory granules are found in the perinuclear cytoplasm.¹ Treatment typically includes surgical resection of symptomatic tumors. Postoperative radiation is reserved for tumors with malignant characteristics or for cases of subtotal resection.^{8,9}

The growing list of unusual sites in which neurocytomas have been found seems to refute the notion that they originate from subependymal progenitor cells. We describe a skull base neurocytoma, which, to our knowledge, has previously been unreported.

CASE REPORT

In 1983, a 43-year-old female sought treatment for focal seizures at an outside institution. Computer tomography (CT) showed a tumor involving the medial sphenoid wing, which was presumed to be a meningioma. The patient was followed with serial CT. However, in the ensuing 14 months, the size of the mass doubled and started to compress the brain stem, causing progressive right-sided weakness. In 1984, she underwent a left frontotemporal craniotomy for "gross total resection" of the mass. The

original operative report states that the tumor was densely adherent to and deriving its blood supply from the dura along the medial sphenoid wing.

Pathological review revealed a highly cellular neoplasm composed of groups of tightly aggregated, round-to-ovoid cells separated by a small amount of fibrocollagenous tissue. The cells contained small, centrally-located, basophilic nuclei and scant pink-staining cytoplasm. Immunohistochemical studies performed for pituitary hormones were negative. Paraganglioma was diagnosed.

Postoperatively, the patient developed aphasia, right-sided hemiplegia, and multiple neuropathies involving the left cranial nerves (CNs) III, IV, V, VI, and right-sided central VII. The hemiplegia and aphasia improved, but her cranial neuropathies persisted. She remained stable until December 1995, at which time she developed severe left-sided parieto-occipital headaches. A magnetic resonance imaging (MRI) study revealed a large recurrent tumor arising from the floor of the middle fossa with extensive involvement of the sphenoid bone (Fig. 1), and she was referred to the Cleveland Clinic Foundation.

On initial examination, the patient exhibited left-sided ptosis and CN palsies involving III, IV, and VI. Sensation was about 80% normal in the left distributions of V1 and V2. A right central CN VII deficit from her prior treatment was present. Her right upper extremity was densely paretic (2/5), while the strength of her right lower extremity was 4/5. Preoperatively, she underwent cerebral angiography and test balloon occlusion of the left internal carotid artery.

Her previous craniotomy was reopened, and an anterior frontal extension was made to access the orbit. Extensive extradural bone, including the involved orbital roof, posterolateral orbital wall, and middle fossa floor, was removed. Intraoperative frozen section was interpreted as a low-grade neoplasm consistent with an ependymoma or neurocytoma. Macroscopically, the tumor was quite vascular and fairly soft. Intradural resection was limited by severe scarring. After achieving enough decompression to relieve her severe headaches, surgery was stopped.

Figure 1 Gadolinium-enhanced preoperative axial (upper left) and coronal (upper right) T1-weighted MRIs, and axial (lower left) and coronal (lower right) MRIs after subtotal resection.

Final pathological review showed a tumor marked by a proliferation of cells with round nuclei and a moderate amount of eosinophilic cytoplasm (Fig. 2). Mitotic figures, vascular proliferation, and necrosis were not identified. The tumor demonstrated diffuse immunohistochemical staining for synaptophysin (Fig. 3) (1:3 dilution; DAKO Corp, Carpinteria, CA) and no immunoreactivity for glial fibrillary acidic protein (GFAP) (1:600 dilution; DAKO). There were focal areas of infiltration of tumor into the dura. Further immunostaining performed to exclude a pituitary adenoma or paraganglioma was negative: adrenocorticotrophic hormone (1:1,000 dilution; DAKO), growth hormone (1:2,500 dilution; DAKO), prolactin (1:800 dilution; DAKO), follicular stimulating hormone (1:1,500 dilution; DAKO), leutinizing hormone (1:40,000 dilu-

tion; DAKO), thyroid-stimulating hormone (1:8,000 dilution; DAKO), epithelial membrane antigen (1:600 dilution; DAKO), cytokeratin AE1/3 (1:200 dilution; Boehringer Mannheim Corp, Indianapolis, IN), CAM 5.2 (1:10 dilution; Becton Dickson Corp, San Jose, CA), and S-100 protein (1:1,000 dilution; DAKO). A reticulin stain failed to outline the characteristic zellballen or nested architectural pattern associated with paragangliomas. A limited electron microscopy examination (on formalin-fixed tissue extracted from the paraffin block) identified occasional neurosecretory-like granules. These pathological findings were consistent with a neurocytoma. Subsequent re-evaluation of the pathology slides from 1984 confirmed that the tumor was the same and represented a neurocytoma rather than a paraganglioma as previously diagnosed.

Figure 2 Neurocytoma marked by a proliferation of small, round monotonous cells arranged against a fibrillary stroma. (Hematoxylin and eosin, original magnification 200x).

Postoperatively, the patient's intense headaches resolved completely. Her neurologic status remained the same as before surgery. Postoperative MRI revealed subtotal removal of the tumor (Fig. 1). The patient was referred to a radiation oncologist for radiation treatment for local control. She received a total dosage of 5,600 cGy. Five years after her surgery, she remains clinically and radiographically stable.

DISCUSSION

As experience with classical central neurocytomas has increased, so too has the number of case reports of neurocytomas that have fulfilled the same patho-

Figure 3 Diffuse positive immunostaining with synaptophysin antibody is characteristic of neurocytoma. (Synaptophysin, original magnification 200x).

logic criteria but that have been found in unusual extraventricular locations (Table 1). Some reports describe tumors adjacent to but outside the ventricular system. For instance, Sgouros et al.¹⁰ reported a 19-year-old woman with a tumor intrinsic to the right occipital lobe found on imaging. During resection, the tumor was found to arise from the subependymal plate of the occipital horn but did not invade the wall itself. Tumors in the spinal cord that may be recapitulating their cerebral counterparts with their proximity to the central canal also have been described.¹¹⁻¹⁴ A neurocytoma has even been described within a mature cystic teratoma of the ovary. The tumor exhibited "classic" behavior in that it abutted an ependymal-lined cyst within the teratoma.¹⁵

A growing number of neurocytomas far removed from any ventricular or ependymal surface

Table 1 Clinical Features of Published Cases of Pure Extraventricular Neurocytomas in the Literature

Series (Ref. No.)	Age (yr)/ Sex	Location*	Presentation†	Treatment‡	Pathology§	F/U¶
Louis et al., 1990 ¹²	68/M	SC (Cervical)	L UE weakness	Bx + XRT	EM: mt; dcg	?
Miller et al., 1992 ²⁴						
Nishio et al., 1992 ^{6#}	7/F	L Fr	Sz	STR	Im: Syn +; GFAP – EM: mt; dcg; syn	2 yr; NED by CT
Metcalfe et al., 1993 ²⁰	67/M	Retina	Retinal detachment	Vitrectomy	Im: NSE +; GFAP – EM: mt; syn	?
Coca et al., 1994 ¹¹	67/M	SC (T10–T11)	L foot numbness	GTR	Im: Syn +; NSE + EM: mt; dcg	30 mo; NED
Sgouros et al., 1994 ¹⁰	19/F	R Occ	Migraines	GTR	Im: NSE + EM: mt; dcg; syn	15 min; no complaints after resection of nodule at 3 mo
Sgouros et al., 1994 ¹⁸	19/F	Thalamus	Headaches	STR	Im: Syn +; NSE +	?
Tatter et al., 1994 ²⁶	65/M	SC (C3–C4)	L UE parathesias	Bx + 43.2 Gy	EM: mt; dcg	10 yr; sl improved motor and sensory
	49/M	SC (C4)	L hand parathesias	STR + 50.7 Gy	Im: Syn +; NSE +; GFAP –	6 mo; death from recurrence
Sootornniyomkij and Schelper, 1996 ¹⁹	18/M	Pons	Diplopia	GTR	Im: Syn +	14 mo; NED
Hirschowitz et al., 1997 ¹⁵	23/F	Ovary (teratoma)	Abdominal pain	GTR	Im: Syn +; NSE +; GFAP –	1 yr; NED
Enam et al., 1997 ¹⁷	46/F	Cb	Neck pain	GTR	Im: Syn + EM: dcg	?
Giangaspero et al., 1997 ¹⁶	31/F	R Fr	Inc ICP	STR + 54 Gy	Im: Syn +	80 mo; AWD after recurrence at 60 mo
	32/F	L Fr	Inc ICP	GTR	Im: Syn +	24 mo; NED
	61/F	L Par-Occ	Inc ICP	GTR	Im: Syn +	6 mo; NED
	5/F	Hypothalamus	Inc ICP	STR	Im: Syn +	Death postoperatively
	49/M	R Par-Occ	Inc ICP	GTR	Im: Syn +	9 mo; NED
	63/F	L Par	Dizziness	Bx	Im: Syn +	6 mo; AWD
Stapleton et al., 1997 ¹³	12/M	SC (C4–T1)	Interscapular pain	GTR	Im: Syn +; NSE +; GFAP –	24 mo; NED
Stephan et al., 1999 ¹⁴	46/W	Cauda equina	L LE weak	GTR	Im: Syn +; NSE +	1 yr; NED by MRI
<i>Foreign Language Case Reports</i>						
Harada et al., 1991 ²⁷	7/F	L Fr	Sz	STR	EM: "neuritic"	
Liebert et al., 1998 ²⁸	17/F	R Par-Occ				

*SC, spinal cord; Fr, frontal lobe; Occ, occipital lobe; Cb, cerebellum; Par, parietal lobe

†Sz, seizure; UE, upper extremity; LE, lower extremity; Inc ICP, increased intracranial pressure

‡Bx, biopsy; XRT, external beam radiation; STR, subtotal resection; GTR, gross total resection; Gy, Gray

§Im, immunohistochemistry; Syn, synaptophysin; EM, electron microscopy; mt, microtubule; dcg, dense core granule; syn, synapse

¶NED, no evidence of disease; AWD, alive with disease; sl, slight

‡Report appears in abstract form only. Eight cases of tumor in the cortex and superficial white matter and three cases in the spinal cord are mentioned. It is unclear how many were pure neurocytomas and how many were admixtures with astrocytes.

#Report describes three cases, but two contained ganglion cells making it unclear if they represented neurocytomas or ganglioneurocytomas.

have also been reported. These findings have important implications for determining the cell of origin of a neurocytoma. Our patient's tumor in the frontotemporal skull base joins a group of reports that includes all of the lobes of the cerebrum except the temporal lobe,^{6,10,16} cerebellum,¹⁷ thalamus,¹⁸ hypothalamus,¹⁶ and pons.¹⁹ A retinocytoma has also been described.²⁰

When our patient underwent her first surgery in 1984, central neurocytoma had only just been described in 1982. At that time immunohistochemical analysis was limited to pituitary hormones only. We now have the benefit of the experience with central neurocytomas that has accumulated since the patient's first surgery. The strong positivity for synaptophysin and lack of GFAP staining confirmed the diagnosis of neurocytoma. Although this skull base location represents a departure from the typical intraventricular location, the growing body of case reports suggests that extraventricular neurocytomas may be more common than first thought.

Because most neurocytomas tend to be located near the foramen of Monro, usually associated with the septum pellucidum, the nuclei of the septum pellucidum were originally thought to be possible cells of origin. Subsequent studies noted sporadic cells that coexpressed GFAP in addition to the expected synaptophysin and neuron-specific enolase. Therefore, neurocytomas were later concluded to be neuroectodermal tumors originating from bipotential progenitor cells present in the periventricular matrix.²¹ This theory of histogenesis, however, does not adequately explain the possible origin of the numerous cases of neurocytomas now reported throughout the craniospinal axis, far from the ventricular surface.

In the current debate about whether these extraventricular cases represent the same entity as typical central neurocytomas, one of the confounding issues is the discovery of a host of hybrid tumors containing neurocytoma-like components mixed with a variety of other distinct groups of neoplastic cells. Various combinations of two of the three basic cell components—gangliocytes, neurocytes, and astrocytes—have been reported. The resulting tumors

are accordingly named gangliogliomas, ganglioneurocytomas, and glioneurocytomas. The presence of all three neoplastic components, however, is rare. In 1990 Nishio et al.²² described such a tumor, but the term ganglioglioneurocytoma was first coined by Miller et al.²⁴ in 1992. Subsequently, several additional cases have been published.^{6,16,23–25}

Because these extremely rare tumors contain all three cellular components, some have speculated that ganglioglioneurocytomas may represent the differentiation of neurocytoma.²⁵ Ganglioglioneurocytomas are characterized by the presence of large mature binucleated neurons that stain with synaptophysin and chromogranin A, small round cells with perinuclear halos that stain with synaptophysin, and the proliferation of pleomorphic astrocytes.²³ Prognosis seems to follow that of neuronal rather than glial neoplasms, with good outcomes following complete surgical resection. However, others argue that ganglioglioneurocytomas are differentiated from neuroblastomas or medulloblastomas.²³

CONCLUSION

This case adds to the growing list of extremely rare sites in which neurocytomas have been found. Within the current limits of immunohistochemistry and light and electron microscopy, these extraventricular neurocytomas are indistinguishable from typical central neurocytomas. The current theory that subependymal progenitor cells are the cells of origin needs to be revisited. Although the incidence of these findings is relatively low, they warrant inclusion of neurocytomas in the differential diagnosis of intraparenchymal mass lesions.

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Commentary

The authors describe a rare case of a neurocytoma involving the skull base. Through a review of the available literature and based on their patient, they challenge the current theory regarding the origin of this neoplasm. The putative sites of origin and the general clinicopathologic characteristics of this disease are discussed adequately. Such discussion is valuable, not only for those who classify rare neoplasms, but for those involved in the care of patients with such disorders.

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