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Neurofibromatosis type 2: growth stimulation of mixed acoustic schwannoma by concurrent adjacent meningioma: possible role of growth factors

Case report

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The authors report the case of a young man suffering from neurofibromatosis type 2 (NF2) who harbored bilateral acoustic schwannomas and a parasellar meningioma. Neuroimaging studies performed during a 4-year follow-up period showed that the bilateral schwannomas had grown very little and at similar rates. However, after the meningioma had infiltrated the tentorium and approached the ipsilateral schwannoma at the incisura, both Schwann cell tumors started to grow rapidly, particularly the one adjacent to the meningioma, of which the percentage of annual growth rate increased by approximately a factor of 10^2 . At the same time, magnetic resonance imaging showed that this tumor also changed its features. During surgery, the acoustic schwannoma was firmly adherent to both meningioma and tentorium. Histological examination revealed meningotheiomatous cells in the schwannoma adjacent to the meningioma. Antiphosphotyrosine immunoblotting of PC12 cells was compatible with the presence of an epidermal growth factor (EGF)-like molecule in the cerebrospinal fluid (CSF) of the patient. This factor was not detected in the CSF of five other NF2 patients, two of whom bore associated bilateral acoustic schwannomas and meningioma in remote locations. It is hypothesized that the meningotheiomatous cells infiltrating the schwannoma triggered an autocrine/paracrine growth-stimulatory mechanism that involved an EGF-like factor.

Key Words * meningotheiomatous cells * mixed tumor * neurofibromatosis * acoustic schwannoma * epidermal growth factor * cerebrospinal fluid

Multiple, contemporarily slow-growing, and mixed central tumors are typical features of neurofibromatosis type 2 (NF2).[8,12,13,17,30,32,44,47,50,51,57] The genesis of such tumors is still a subject of speculation. Total or partial loss of chromosome 22, which would contain a suppressor gene that inhibits the genesis of several neoplasms (meningiomas, schwannomas, neurofibromas),[6,21,43,46,49,55] as well as the action of growth factors (GFs) derived from sources

within or outside the developing tumor,[2,4,7,15,22,27,29,31,33,34,45,52,58,59] have been hypothesized. We report the case of a young man suffering from NF2, who harbored bilateral acoustic schwannomas and a skull base meningioma that had grown adjacent to one of the schwannomas. This case suggests that a GF, which belongs to the epidermal growth factor (EGF) family, may be implicated in the autocrine/paracrine growth stimulation of acoustic schwannomas.

CASE REPORT

This 17-year-old right-handed boy experienced onset of symptoms in May 1988 with partial motor seizures. Computerized tomography showed a 6 X 6.5 X 6.2-cm homogeneously enhancing mass lesion in the left parasellar area and small bilateral cerebellopontine angle (CPA) tumors. He had undergone surgery twice (August 1988 and March 1989) at another institution for partial resection of the parasellar tumor with a diagnosis of syncytial meningioma. In the following 4 years, magnetic resonance (MR) imaging studies documented regrowth of the meningioma that extended to the cavernous sinus area, sella turcica, and tentorium (Fig. 1 left and center). At the same time, the CPA tumors had grown very little (Fig. 1 center and right; Table 1).

Fig. 1. Enhanced T₁-weighted coronal MR images (March 1992) showing the left parasellar meningioma with cavernous sinus involvement (left) and the bilateral symmetrically growing acoustic schwannomas (center and right). Note that the meningioma has extended over the tentorium approaching the ipsilateral schwannoma (center).

Neuroimaging Date	Follow-up Interval (mos)	Volume of Acoustic Schwannoma (cm ³)		Annual Growth Rate (%)	
		Left	Right	Left	Right
July 1988	none	1.08	1.04	none	none
May 1989	10	1.12	1.13	4.4	10.3
March 1992	44	1.73	1.61	14.8	11.6
September 1993	18	43.42	8.93	1673.2	369.7

* Tumor volume was calculated by measuring the enhancing tumor area with planimetry. After the tumor areas was calculated on each image in square millimeters, volumes were determined in cubic centimeters by multiplication with the distance between adjacent images (2–5 mm). The initial volume was estimated from computerized tomography scans; follow-up volumes were obtained from MR images.

Suffering from intracranial hypertension, right-sided weakness, speech disturbances, and dysphagia, the patient was admitted to our institution in September 1993. Physical examination revealed stigmata of NF2 (subcutaneous nodules, "café-au-lait" spots), right-sided hemiparesis, motor aphasia, left-sided cerebellar syndrome and deafness, right hypoacusis, and palsy of the ninth, 10th, and 11th cranial nerves on the left. Magnetic resonance imaging showed that the meningioma had grown adjacent to the ipsilateral CPA tumor at the tentorial incisura (Fig. 2 left and center); moreover, the CPA tumors of both sides had increased considerably in size, particularly the one on the left side (Fig. 2 center and right; Table 1). This schwannoma had also changed its features on MR imaging, enhancing less homogeneously after gadolinium administration and appearing less hyperintense on T₂-weighted sequences as compared with both previous MR studies and the contralateral schwannoma.

Fig. 2. Enhanced T₁-weighted axial MR images (September 1993) showing the meningioma in the frontobasal area (left) and medial temporal fossa (center), and the bilateral acoustic schwannomas (center and right). Note the close relationship between the meningioma and the ipsilateral schwannoma at the tentorial incisura (center). The left schwannoma has infiltrated the temporal bone (right) (arrow).

Staged surgical treatment was planned. At the first operation (March 1994), a partial resection of the meningioma was performed and a ventriculoperitoneal shunt was placed. Histological examination

confirmed the previous diagnosis. In the second (October 1994) and third stages (June 1995), the left and right CPA tumors were partly removed via retrosigmoid craniectomies. During surgery, the cranial portion of the left CPA tumor was firmly attached both to the capsule of the meningioma at the tentorial hiatus and to the tentorium.

Pathological Examination. Approximately 85% of the left CPA tumor specimen corresponded to a typical schwannoma, with areas of compact fascicular tissue that alternated with areas of loose-textured spongy tissue. In the remaining areas, lobules of cells with round to oval nuclei and indistinct cell borders resembling islands of meningotheliomatous cells were found (Fig. 3 left). At the periphery of the lobules, meningotheliomatous cells were grouped in strings clearly separated from schwannomatous tissue by a thin fibrous wall. When sections were analyzed after S-100 protein immunolabeling, Schwann cells appeared strongly and uniformly stained, whereas lobules and strings of meningotheliomatous cells were unstained (Fig. 3 right). The latter showed a weak membranous pattern of immunoreaction for epithelial membrane antigen that was absent in Schwann cells. These histological and immunohistochemical findings allowed for a diagnosis of schwannoma with meningotheliomatous foci. Proliferative activity, as evidenced by mitotic figure counts and proliferating cellular nuclear antigen, ranged from zero to three mitoses or proliferating cellular nuclear antigen-positive cells per 10 hpf. The right CPA tumor surgical specimens corresponded to a typical schwannoma.

Fig. 3. Photomicrographs showing lobules of meningotheliomatous cells with syncytial appearance growing inside the schwannoma. A thin capsule (arrows) is present between meningothelial lobules and Schwann cells (left) (H & E). When sections of schwannoma tissue are treated with anti-S-100 protein antiserum, immunostaining is restricted to Schwann cells that surround islands of unstained meningothelial cells (right). Original magnification X 400.

Cultured rat pheochromocytoma-derived cell line PC12 was used as a model to investigate for the presence of GFs in the cerebrospinal fluid (CSF). Whereas nerve GF (NGF) induces a dramatic differentiation of PC12 cells to neuronal phenotype, EGF promotes a mitogenic nondifferentiative response that results in an immediate tyrosine phosphorylation of its receptors.[3,39,42]

Bioassay of CSF. Ventricular CSF was obtained from our patient (Case 1) at the time of shunt placement and then, for retesting the results, 1 month later through the reservoir of the ventriculoperitoneal shunt device. For comparison, samples of CSF were also obtained from five other patients (Cases 2-6) suffering from NF2 (Table 2). The patients in Cases 2 and 3 had bilateral acoustic schwannomas with associated meningioma of the parietal convexity and cervical spine, respectively. The patients in Cases 4,

5, and 6 had bilateral eighth nerve tumors. The patients and/or their parents gave informed consent for CSF withdrawal and analysis. The CSF samples were immediately frozen at -70°C for storage until use. For analysis, the CSF was concentrated fivefold by ultrafiltration with Centricon 3 devices (Amicon, Beverly, MA) and sterile filtered. The PC12 cells were plated on collagenated plastic petri dishes and allowed to grow to confluence in RPMI 1640 supplemented with 10% heat-inactivated horse serum and 5% newborn calf serum at 37°C in a 5% CO₂ atmosphere in a humidified incubator. The NGF (50 ng/ml) or volumes of 10, 40, and 50 µl of concentrated CSF was added directly to the incubation media. The cultures were observed with the aid of an inverted microscope at specific time intervals. The NGF treatment induced typical morphological cell changes, consisting of the production of short spikes (within 3 hours) and axons (after 8 hours) that were detectable for up to 5 days. Conversely, the addition of CSF from the patients did not induce any persistent phenotypic changes in PC12 cells. These results indicate that the CSF samples did not contain NGF or NGF-like activities.

TABLE 2 SUMMARY OF DATA FROM PATIENTS WITH NF2 INCLUDED FOR CSF ANALYSIS OF NEUROTROPHIC ACTIVITY				
Case No.	Age (yrs), Sex	Central Tumors Associated with the Bilat Acoustic Schwannoma		CSF Sample
		Type	Location	
1	17, M	syncytial meningioma	parasellar, tentorial hiatus	lat ventricle
2	16, F	syncytial meningioma	parietal parasagittal	lat ventricle
3	23, F	fibroblastic meningioma	cervical spine	lumbar spine
4	31, F	Grade II astrocytoma	cerebellar hemisphere	lat ventricle
5	19, M	none		lumbar spine
6	20, M	none		lumbar spine

Antiphosphotyrosine Immunoblotting. The PC12 cells were prepared and cultured as above. The growth medium was then replaced with fresh medium without serum and incubated for an additional 12 hours. The cells were then treated with NGF (100 ng/ml), EGF (50 ng/ml), or with the same aliquots of CSF as stated in the bioassay for 5 minutes and lysed in sodium dodecylsulfate (SDS) sample buffer containing 1 mM Na₃VO₄. Immunoblotting was performed as described by Towbin, et al.[54] The lysates were separated by 7.5% SDS polyacrylamide gel electrophoresis and subsequently electrotransferred to a polyvinylidene difluoride membrane (Immobilon P; Millipore Corporation, Bedford, MA). After incubation with 5% bovine serum albumin in tris-buffered saline to block nonspecific binding sites, the filters were incubated overnight at 4°C with antiphosphotyrosine antibodies (PY 20; Transduction Laboratories, Lexington, KY). After washing in tris-buffered saline, the secondary antibody (peroxidase-conjugated anti-mouse immunoglobulin G) was added for 30 minutes at room temperature. The membranes were washed, soaked in emission chemiluminescence reagent (Amersham, Arlington Heights, IL), and visualized using Hyperfilm ECL. Figure 4 shows the pattern of tyrosine-phosphorylated proteins observed in PC12 cells after stimulation with NGF (lane 2), EGF (lane 3), and the CSF from the patient in Case 1 (lanes 4, 5, and 6). The phosphorylated proteins observed at approximately 170-kD in EGF- and CSF-treated cells are thought to be EGF receptors.[42] Analysis of these findings indicates that the CSF in Case 1 contained either EGF or EGF-like molecules. However, the stimulation of PC12 cells with the CSF obtained from the other patients produced no increase in tyrosine phosphorylation of proteins migrating at molecular weights of approximately 170 kD. Experiments with the CSF of all the patients, including the two samples from Case 1, were completely repeated, and similar profiles were obtained.

Fig. 4. Tyrosine phosphorylation in PC12 cells treated with NGF (100 ng/ml) (lane 2), EGF (50 ng/ml) (lane 3), and CSF of the patient in Case 1 (10, 40, and 50 μ l) (lanes 4, 5, and 6) for 5' at 37°C. The cells were lysed and cell lysates were fractionated by SDS-polyacrylamide gel electrophoresis, transferred to nitrocellulose, and probed with anti-Ptyr antibody. The band of immunoreactivity observed at approximately 170-kD (arrow) in EGF- (lane 3) and CSF-treated (lanes 4, 5, and 6) cells corresponds to EGF receptors. Lane 1 represents the culture media.

DISCUSSION

Mixed Acoustic Schwannoma and Meningioma

The association of meningioma tissue with and within acoustic schwannomas has been known since the writings of Harvey Cushing.[10] Cushing first drew attention to the fact that, in some instances, the microscopic structure of an acoustic schwannoma displays a conspicuously whorled pattern strongly resembling that of certain meningiomas. On the other hand, a meningioma may, in some areas, exhibit certain features that bear such a close resemblance to a schwannoma that the two tumors become almost indistinguishable. Furthermore, in NF2 there is an obvious similarity between the nerve sheath tumor tissue and the fibroblastic variant of meningioma.[14] In spite of the overlapping morphological features, cases have been reported, such as the present one, in which the two components of the mixed acoustic tumor show different antigenic profiles, with S-100 protein immunoreactivity being positive in schwannomatous areas and negative in meningotheomatous foci.[16]

Linthicum and Brackmann[30] have noted that those acoustic tumors composed of intermixed schwannoma and meningioma can infiltrate the temporal bone. Other authors, however, have not confirmed the aggressive nature of these tumors.[14] The consociation of schwannoma and meningioma has also been described in the neural compartment of the jugular foramen,[35-37] frontal and temporal lobes,[50,51] cerebellar convexity,[50] and spinal cord.[14] There are several possible mechanisms by which to explain the presence of meningioma tissue in a Schwann cell tumor, including divergent differentiation from a common cell line,[20] metaplasia in a typical schwannoma,[5,56] entrapment of hyperplastic arachnoidal cells,[16], and collision of separate tumors in which two contiguous neoplasms merge into one.[48]

Possible Role of EGF-Like Molecules in Modulating the Growth Rate of Schwannomas

In NF2, bilateral eighth nerve tumors are known for their potential to reach a remarkable size as well as their propensity for asymmetrical growth.[23,28,32,40] The temporal growth profile of these tumors is unpredictable, with periods of relative stability and phases of growth stimulation during which growth rates ranging from 1.5 to 30 mm per year have been reported.[9,28,38,41] In our case, however, there is a close temporal relationship between the contact established by the schwannoma and meningioma at the tentorial incisura, increased growth rate of both schwannomas, and MR imaging changes of the schwannoma adjacent to the meningioma. One may speculate that these phenomena may not be coincidental occurrences and that a local factor may be involved. The possibility that the meningioma infiltrated the ipsilateral schwannoma, although not directly demonstrated on serial histological sections, is supported by the surgical findings. It remains difficult, however, to explain the impressive growth of the schwannoma simply by considering the infiltration of meningioma cells, which represented only approximately 15% of the tumor mass. A feasible explanation may be that the meningioma cells infiltrating the schwannoma triggered an autocrine/paracrine mechanism and that totipotent cells inside the schwannoma responded to the stimulation of tumor-derived GFs. These factors may diffuse into the CSF, thus modulating the growth rate of the contralateral schwannoma.

One major result from this study is that the CSF of our patient contained a GF that induced the molecular differentiation of rat PC12 cells in a manner similar to EGF. This EGF-like factor seems to be related to the mixed tumor itself, not to the NF2 condition per se or to the mere consociation of schwannoma and meningioma, because it was not detected in the CSF of the other NF2 patients, two of whom had associated schwannoma and meningioma. It is known that 85 to 95% of intracranial meningioma express high levels of the EGF receptor[11,18] and that the growth of meningioma cell cultures is stimulated by EGF.[1] However, an actual secretion of EGF by meningioma cells themselves in an autocrine manner, although demonstrated for several GFs like fibroblast GF, platelet-derived growth factor (PDGF), and insulin-like GF,[29,53] has not been proven. Recently, a schwannoma-derived growth factor (SDGF) has been isolated from a schwannoma cell line as a mitogen and neurotrophic protein that belongs to the EGF family.[25,26] This factor reproduces some of the responses shown in our patient to be elicited by the CSF from PC12 cells, like phosphorylation of cellular proteins. However, SDGF differs from the GF of our patient in that the former, like NGF, induces morphological responses of PC12, whereas the latter, like EGF, does not. It is interesting to note that SDGF activates the EGF receptor and induces receptor kinase activity that is required for SDGF to stimulate DNA synthesis.[24] Thus, it seems reasonable to postulate a condition in which meningioma cells, putatively expressing EGF receptors, infiltrated the Schwann cell tumor and triggered an autocrine mechanism to produce an EGF-like factor.

A similar mechanism has been proposed to have a role in the development and progression of malignant glioma, in which an autocrine and paracrine growth stimulation loop is established between glioblastoma cells that express high levels of PDGF and the PDGF receptors that are present in the hyperplastic capillarities of the tumor.[19]

CONCLUSIONS

Although the hypothesis noted in this paper is admittedly highly speculative and additional data on patients of this type are needed, the case being described in this report is of particular interest because it provides evidence that an EGF-like activity was associated with the CSF. It will be important in future research to investigate the appearance of specific GFs in the CSF of NF2 patients harboring mixed

schwannoma and meningioma. This report may also stimulate researchers to study GF expression in cocultures of schwannoma and meningioma cells.

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