Metastatic papillary craniopharyngioma: Case study and study of tumor angiogenesis

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We report a case of suprasellar papillary craniopharyngioma metastatic to the temporoparietal region 2 years after its initial resection. The literature documents examples of craniopharyngioma recurrences along the surgical tract, as well as remote ipsi- and contralateral metastases via cerebrospinal fluid seeding. Ours is the second report of a craniopharyngioma of papillary type to exhibit metastatic behavior. The tumor spread opposite the side of craniotomy. Although a rare occurrence, it confirms the limited capacity of histologically benign craniopharyngiomas to undergo meningeval seeding, likely the result of surgical manipulation. Immunohistochemical demonstration of increased microvascular density and vascular endothelial growth factor expression, as well as a high vascular endothelial growth factor receptor (VEGFR2) signal by in situ hybridization, suggests that tumor vascularity facilitated angiogenesis and may have been involved in the establishment and growth of the metastatic deposit. Neuro-Oncology 4, 123–128, 2002 (Posted to Neuro-Oncology [serial online], Doc. 01-046, February 18, 2002. URL <neuro-oncology.mc.duke.edu>)

Craniopharyngiomas are assumed to arise from epithelial rests of the normally involuted craniopharyngeal duct (Burger and Scheithauer, 1994).

Histologically, they occur in 2 easily recognized forms. Most are adamantinomatous tumors, occurring more often in children than in adults and radiographically characterized by calcification. Histologically, they resemble adamantinoma of the jaw. Occurring less frequently is the papillary variant, which lacks calcification and consists of sheets and crude fronds of simple, nonkeratinizing squamous epithelium. Either tumor may be cystic, solid, or both (Burger et al., 1994). Despite their benign histology, craniopharyngiomas may rarely recur as a result of implantation along the operative tract or as remote deposits or metastases due to cerebrospinal fluid spread (Barlool et al., 1988; Gupta et al., 1999; Israel and Pomerantz, 1995; Ito et al., 2001; Lee et al., 1999; Malik et al., 1992; Raoowanshi and Piepgras, 1991). Our case is an example of the latter—a leptomeningeal metastasis opposite the side of the craniotomy that presented 2 years after removal of the primary tumor. It represents the second papillary craniopharyngioma to behave in this manner. No doubt surgical manipulation may be implicated in its spread. However, the possibility that angiogenesis played a role in facilitating the establishment and growth of the deposit is explored by a study of MVD and of the expression of VEGF and its receptor VEGFR2.

Case Study and Pathology

A 62-year-old woman complained of headaches, dizziness, and visual disturbance. Both the general physical and neurologic examinations were normal. CT and MRI of the sellar region revealed a cystic and noncalcified suprasellar mass (3.8 × 3.5 × 2.5 cm) with rim enhancement (Fig. 1, left). The preoperative diagnosis was craniopharyngioma. The patient underwent a right ptetalional craniotomy. Grossly, the tumor featured both solid and cystic components, and an intrasellar component was identified. A gross total resection was achieved, and,
postoperatively, an MRI scan showed no residual tumor. Both diabetes insipidus and panhypopituitarism ensued, but the patient is well on hormonal replacement therapy at the time of this writing.

Microscopically, the tumor was a typical papillary craniopharyngioma composed of sheets of well-differentiated, nonkeratinizing squamous epithelial cells (Fig. 2A). In some areas, its desiccation resulted in a pseudopapillary pattern around fibrovascular cores. In parts, stromal collagen took the form of distinct hypocellular hyalinized nodules. There was moderate inflammation, particularly in stroma. Palisading of cells, stellate reticulum, wet keratin, calcification, and cholesterol clefts were lacking. A periodic acid-Schiff stain with diastase digestion (PAS-D) showed scattered goblet cells. Various immunostains were performed using the streptavidin-biotin-peroxidase complex method. The MIB-1 labeling index (clone MIB-1, diluted 1/400; Immunotech-Coulter, Hialeah, Fla.) was less than 1% (Fig. 2B). Scattered immunopositivity for ER (clone 6F11, predilute; Ventana Medical Systems, Tucson, Ariz.) was noted in scattered epithelial cells. On the other hand, PR (clone 1A6, predilute; Ventana) immunopositivity was strong.

No postoperative radiation therapy was given. Two years after surgery, the patient developed headaches unresponsive to analgesics. Despite a normal neurologic examination, an MRI scan revealed a heterogeneously enhancing mass measuring 4 × 3 × 2.5 cm in the left temporoparietal region. It featured both solid and cystic components as well as peritumoral edema (Fig. 1, right). A left temporoparietal craniotomy with gross total removal of the mass was performed. The somewhat yellow lesion was leptomeningeal in location, featured a small cyst, and was easily separated from underlying, noninvaded brain. The diagnosis of metastatic papillary craniopharyngioma was confirmed. Its microscopic features were similar to those of the primary tumor. The lesion consisted of papillary, well-differentiated squamous epithelium unassociated with calcification (Fig. 3). Stromal chronic inflammation was more conspicuous than in the primary tumor. Scattered goblet cells were identified on periodic acid-Schiff stain with diastase digestion (Fig. 4A). The MIB-1 labeling index (3%) was a
Fig. 4. Histologic features of the metastatic deposit. A low power view (left) shows the epithelial layer containing scattered mucin production (periodic acid-Schiff stain with diastase digestion). Note the slightly increased proliferative activity (MIB-1 labeling index, 3%) in recurrence tumor (right). Original magnification ×100.

3-fold increase over that of the primary tumor (1%) (Fig. 4B). ER staining showed only a few positive nuclei, but the PR preparation was diffusely positive.

The postoperative period was uneventful. Fourteen months after surgery, the patient is asymptomatic and has no evidence of tumor recurrence.

Angiogenesis Studies

The vascularity of the primary and metastatic tumor was measured in terms of MVD. In addition, expression of VEGF and VEGFR2 mRNA was studied. The MVD of both tumors was determined by computer image analysis (Microimage, Media Cybernetics, Silver Springs, Md.) of microsections immunostained for CD34 (Dako Corp., Glostrup, Denmark; monoclonal; dilution 1:50) using the immunohistochemical methods previously described (Vidal et al., 2001a). Immunoexpression of VEGF (Santa Cruz Biotechnology, Santa Cruz, Calif.; polyclonal; dilution 1:500) was similarly evaluated. Both reactions were quantified in 29 randomly selected fields (6.7 mm²) and expressed as the percentage of tumor area occupied by CD34-positive vessels (Vidal et al., 2001a), and the percentage of tumor tissue occupied by nucleated VEGF-immunoreactive cells. The latter was calculated as previously described (Vidal et al., 2001). In situ hybridization for VEGFR2 mRNA was carried out as previously described (Qian et al., 2001) using an oligonucleotide probe complementary to regions 309-318 of human mVEGFR2. The MVD in CD34-immunostained sections of the primary and metastatic tumors was 5.4% and 5.6%, respectively (Fig. 5A). In the primary tumor, immunoreactivity for VEGF was limited to connective tissue cells surrounding blood vessels. In contrast, in the metastasis, 33% of tumor cells were immunoreactive for VEGF (Fig. 5B). In situ hybridization showed VEGFR2 mRNA expression in a somewhat different pattern. In the primary tumor, it was exclusively expressed in capillary endothelium and pericytes, whereas in the metastasis, the signal was noted in both vessels and tumor cells (Fig. 5C). We have no explanation for the differences in staining and signal pattern observed between the primary and metastatic tumors. The latter exhibited the expected distribution of both VEGF and VEGFR reactivity, whereas the primary lesion did not. The discordance may be attributed to artifacts of tissue preservation or processing of the primary tumor.

Discussion

Craniopharyngiomas arise in the sellar region and represent 2% to 5% of primary intracranial neoplasms (Burger and Scheithauer, 1994). Clinical symptoms result from compression of the optic chiasm, hypothalamic as well as pituitary injury, and extension into the third ventricle with resultant obstruction of cerebrospinal fluid flow (Burger and Scheithauer, 1994; Sorva et al., 1987). Although this benign tumor exhibits slow growth, it typically shows adherence to surrounding structures, including the floor of the third ventricle (Burger and Scheithauer, 1994), adjacent pituitary stalk, and vessels. Recurrences often feature even more extensive adherence to local structures (Demaereel et al., 1993; Petito, 1996). The literature cites only 1 example of histologically malignant transformation of a craniopharyngioma (Nelson et al., 1988), an adamantinomatous tumor. In addition to remote metastases (Gupta et al., 1999; Ito et al., 2001), rare examples of craniopharyngioma arise in ectopic locations, including the pineal gland (Solarski et al., 1978), sphenoid bone (Cooper and Ransohoff, 1972), cerebellopontine angle (Gökalp et al., 1991), optic chiasm (Duff and Levine, 1983), and nasopharynx (Majlessi et al., 1978).
Directly or indirectly, neuroimaging (Crotty et al., 1995; Sorva et al., 1987) and clinicopathologic studies (Crotty et al., 1995; Petito et al., 1976) have documented the occurrence of 2 forms of craniopharyngioma, the adamantinomatous and papillary variants. Adamantinomatous-type tumors predominate, are suprasellar in location, and often show intrasellar extension (Burger and Scheithauer, 1994; Duff et al., 2000; Petito et al., 1976). Most occur in children and young adults. In contrast, papillary craniopharyngiomas present in adulthood and often reside largely within the third ventricle (Crotty et al., 1995). Supra- and intrasellar components may also be seen. Compared with adamantinomatous tumors, papillary craniopharyngiomas are largely solid, composed of anastomosing cords of squamous epithelium, and lack both wet keratin and calcification. Peripheral palisading of tumor cells, a stellate reticulum, and degenerative changes are also absent.

Several authors (Kahn et al., 1973; Petito et al., 1976) have stated that lack of recurrence and a better outcome are associated with tumors of adulthood that lack radiographic evidence of calcification. In addition, Petito et al. (1976) stated that the patients with tumors measuring less than 3.0 cm survive significantly longer than patients with larger lesions. That same study found no correlation between survival and the ratio of adamantinomatous to squamous components (Petito et al., 1976). In our study, the tumor lacked CT evidence of calcification, but exceeded 3 cm in size, at both presentation and recurrence. The significance of distinguishing the 2 histologic variants of craniopharyngioma remains unclear. Whereas both Kahn et al. (1973) and Adamson et al. (1990) found no recurrences in patients with papillary craniopharyngiomas, Weiner et al. (1994), Crotty et al. (1995), and Duff et al. (2000) indicated that the most significant factor associated with recurrence was extent of resection rather than histologic subtype. The clinicopathologic study of Duff et al. (2000) also found lethargy, visual deterioration, papilledema, hydrocephalus, and adhesive tumor growth to be associated with a poorer outcome. Most studies of craniopharyngiomas indicate that radiation treatment is strongly associated with tumor regression or lack of recurrence (Duff et al., 2000; Eldevick et al., 1996; Petito et al., 1976). No radiation therapy was administered in the present case.

Histologically, our tumor showed no evidence of anaplasia (for example, cytologic malignancy, increased mitotic activity, or necrosis). Despite a mild increase in MIB-1 proliferation index in the recurrence, the difference was too minor to be the basis of aggressive behavior. Indeed, studies of MIB-1 proliferation marker labeling in craniopharyngiomas (Nishi et al., 1999; Raghavan et al., 2000) reveal considerably higher mean indices than do our primary and metastatic tumors. The conclusions of these authors differ. One found no relationship between MIB-1 labeling indices and clinical outcome (Raghavan et al., 2000) and the other found an increase in recurrence of tumors with indices greater than 7% (Nishi et al., 1999). The finding of tumoral and stromal chronic inflammation in our 2 specimens is worth noting. The large study of Petito et al. (1976) found that inflammation is a common feature of craniopharyngioma, being present in fully 40% of cases. Reportedly, it is encountered more often in adamantinomatous tumors (Petito, 1996). The suggestion has been made that inflammation promotes tumor adherence to surrounding structures and infiltration of adjacent brain (Petito, 1996).

In a recent in situ hybridization study of craniopharyngiomas, Thapar et al. (1994) demonstrated the presence of ER mRNA in 19 craniopharyngiomas, including 4 papillary tumors. Despite the expression of ER mRNA in all cases studied, the ER protein was demonstrated immunohistochemically in only 2. In our case, immunostains showed only rare, weak positivity for ER in both tumors. In contrast, PR staining was strong in both. PR gene expression has been reported in craniopharyngiomas (Honnegger et al., 1997); the authors suggested it might be biologically active. Whether the expression of ER and PR in craniopharyngiomas will be of therapeutic and prognostic significance remains to be seen.

Tumor growth and spread require an optimal microenvironment, including a well-established blood supply (Folkman 1995; Folkman and Sing, 1992). Angiogenesis depends heavily on the effects of VEGF, the most important factor inducing new vessel formation (Ferrara, 2000). Its presence has been documented in a wide spectrum of human neoplasms, including endocrine tumors (Katoh et al., 1999; Lloyd et al., 1999), and has been implicated in tumor growth and spread. The presence of VEGF has also been documented in craniopharyngioma (Vaquero et al., 1999; Vidal et al., 2002). Thus, we undertook a study of MVD and of the expression of VEGF and its receptor VEGFR2 in this tumor, comparing the results with those of the recent comprehensive study of adult craniopharyngiomas by Vidal et al. (2002). Their MVD values in nonrecurring (3%) and recurring tumors (4.2%) were considerably lower than those in our primary (5.4%) and metastatic tumors (5.6%). Tumoral cells in their study, as well as in our own, exhibited VEGF immunoreactivity and a VEGFR2 (Flk-1) signal. Limiting our consideration to the metastatic tumor in our case, in which VEGF was expressed by 33% of neoplastic cells, the value exceeded the mean values reported in the study by Vidal et al. (2002), which were 12% for adamantinomatous tumors, 25% for papillary tumors, and 17.5% for the overall series. These differences are not dramatic but do support the concept of Vidal et al. (2002) that angiogenesis may play a role in the behavior of craniopharyngioma, facilitating not only recurrence but also, perhaps, the establishment and growth of metastatic deposits. VEGFR activity was not quantified in the study of Vidal et al. (2002), but the distribution of staining in the metastatic growth in our study was the same as in theirs. Thus, our results confirm their demonstration of VEGFR in craniopharyngiomas.

Recurrence in craniopharyngiomas is almost exclusively at the primary site (Demaerel et al., 1993; Duff et al., 2000; Eldevick et al., 1996; Kahn et al., 1973; Weiner et al., 1994; Yasargil et al., 1990). The literature cites only 5 “ectopic” recurrences, all along the tract of the surgical route and presumably the result of operative implantation (Barloon et al., 1988; Israel and Pomeranz, 1993; Lee et al., 1999; Ragoowansi and Piepras, 1991). An epidual craniopharyngioma recurrence, physically separate from the primary site but ipsilateral to the cran-
iom, has also been reported (Malik et al., 1992). The authors rightly suggested that a piece of tumor may have been displaced during surgery and subsequently grew (Malik et al., 1992). However, Gupta et al. (1999) reported a case associated with multiple, contralateral, dural-based metastases of an adamantinomatous craniopharyngioma. A similar case, but of papillary craniopharyngioma, was recently reported by Ito et al. (2001). Both authors considered their tumors to be metastatic, but suggested mechanical, surgically assisted meningeal seeding as the underlying cause (Gupta et al., 1999). Radiologic findings of the remote recurrences of these reported cases and of our own include wide variation in the degree of cystic change and edema (Gupta et al., 1999; Ito et al., 2001).

In summary, this case represents only the second example of a papillary craniopharyngioma to undergo intracranial spread and shares some features with those of Gupta et al. (1999) and Ito et al. (2001). In each instance, metastatic disease was remote from the craniotomy site and was presumably due to meningeal seeding. As in our case, the effects of high-level VEGF and VEGFR2 expression on microvascular density may also have played a role in the successful establishment of the deposits.

References

