Meningothelioma as the predominant histological subtype of midline skull base and spinal meningioma

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Object. This study was undertaken to test a hypothesis that meningiomas of the midline skull base and spine are predominantly of the meningothelial histological subtype.

Methods. The cases of 794 consecutive patients who underwent resection for meningioma at the Cleveland Clinic between January 1991 and March 2004 were reviewed retrospectively. The authors analyzed the relationship between the tumors' histological subtypes and sites of origin in the 731 patients from this group who harbored tumors that were determined to be benign histologically (World Health Organization Grade I).

Meningothelial meningiomas (MMs) accounted for 63.5% (464/731) of the Grade I tumors. The incidence of MM according to the site of origin was as follows: 84.9% (186/219) in the midline skull base, 58.3% (35/60) in the lateral skull base, 48.5% (183/377) in a non–skull base location, and 80% (60/75) in spinal locations. The incidence of MM in the midline skull base and spinal locations were significantly higher than in non–skull base or lateral skull base locations.

Conclusions. Meningiomas of the midline neuraxis are predominantly meningotheliomas. Analysis of the increasingly available data on genetic and topographic characteristics of MMs suggests that they may represent a unique entity, contrary to the prevailing belief that all benign meningiomas are identical tumors.

KEY WORDS • meningioma • meningothelial • skull base • location

MENINGIOMAS are a histologically heterogeneous group of tumors that have been classified into three grades on the basis of behavior. Grade I tumors, according to the 2000 WHO classification for meningiomas, are considered benign. Nine histological subtypes are included in Grade I: meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic. Grade II tumors, which are more aggressive than the Grade I meningiomas in their behavior, include the clear cell, chordoid, and atypical subtypes; papillary, rhabdoid, and anaplastic meningiomas are considered Grade III tumors.[9,15]

The prevailing attitude among most neurosurgeons and pathologists is that all benign meningiomas are identical tumors, and that their wide variation in histological appearance has no bearing on the tumor location or on their overall biological behavior.[24] Recently, however, results of our studies and those of other investigators have indicated that the MM is a unique tumor. Shortly after the identification and cloning of the *NF2* gene,[23,27] we investigated the expression level of NF2 protein, the schwannomin/merlin, in human sporadic meningiomas. Because the incidence of meningioma in patients who have the *NF2* gene is known to be high, the authors of one study[13] tested the hypothesis that the NF2 protein level would be reduced in sporadic meningiomas. In that analysis, 57% of meningiomas studied (8/14) showed a significant reduction in NF2 protein levels. The remaining 43% of the meningiomas tested, which showed the normal NF2 protein level, were uniformly of the meningothelial subtype. Subsequently, a larger study of *NF2* mutational analysis involving 20 MMs and seven non-MMs was done, revealing that the *NF2* gene mutation was present in only 5% (1/20) of MMs.[4] Similar findings of relatively rare *NF2* gene mutations in MMs have been reported by other investigators.[14,18,28,29] The results of these studies suggest that *NF2* may be a critical tumor suppressor gene in the pathogenesis of non-MM tumors such as fibrous, transitional, and other subtypes of meningiomas, whereas one or more as yet unidentified genes are involved in the tumorigenesis of MMs.

Meningothelial meningiomas

In 2001, we encountered an interesting finding while conducting a clinical study of clinoidal meningiomas. After analyzing the pathology reports relating to 14 benign meningiomas, we were surprised to find that all 14 tumors were of the meningothelial subtype.[12] Around the same time, Kros, et al.,[10] showed an association between meningiomas of anterior skull base locations (olfactory groove and clinoid process) and an intact chromosome 22 in a series of 42 tumors, and found that anterior skull base tumors were often MMs. Given these interesting observations and other reports[6,7] indicating that MMs may be unique tumors having a predilection for certain locations of origin, we sought to test the hypothesis that meningiomas of the midline neuraxis—namely the midline skull base (Fig. 1) and spine—are predominantly meningothelial.

Clinical Material and Methods

We retrospectively reviewed 794 consecutive surgical cases of cranial and spinal meningiomas, among which were 731 cases of benign meningioma (WHO Grade I). Our primary goal was to examine the relationship between the site of tumor origin and its histological subtype. All patients had undergone surgery at the Cleveland Clinic Foundation between January 1991 and March 2004, and all specimens were reviewed by a neuropathologist. The site of origin was determined from operative reports and from magnetic resonance images obtained preoperatively. Non–skull base locations included the convexity, falx, tentorium, ventricle, parasagittal and pineal regions, and the cerebellar convexity and scalp. The skull base locations were subdivided into the medial and lateral skull base. Medial skull base locations were the olfactory groove, planum sphenoidale, tuberculum sella, anterior clinoid process, optic sheath/canal, cavernous sinus, cerebellopontine angle, ventral petrous pyramid, middle fossa (midline temporal bone), petroclival region, clivus, neural foramina (jugular foramen and hypoglossal canal), and foramen magnum. Lateral skull base locations included the middle and lateral sphenoid wing, orbitosphenoid region, posterior petrous region, orbital roof, and temporal fossa floor/temporal bone. Spinal meningiomas were defined as those arising from the meninges caudal to the foramen magnum.

Comparisons of the number of MMs in the following locations were performed using the chi-square test: skull base and non–skull base, midline skull base and lateral skull base, non–skull base and spinal, and lateral skull base and spinal locations. A probability value less than or equal to 0.05 was considered statistically significant.

Results

Of the 794 patients with meningiomas initially reviewed, 92.1% (731/794) had WHO Grade I, 5.9% (47/794) had Grade II, and 2% (16/794) had Grade III meningiomas.

Among the 731 Grade I meningiomas, 63.5% (464/731) were MMs, 19% (139/731) were transitional, 13.5% (99/731) were fibrous, 1.8% (13/731) were psammomatous, and 2.2% (16/731) were of the other histological subtypes (Table 1). The tumor origins were as follows: 377 (51.5%) were from non–skull base locations, 219 (30%) were from the midline
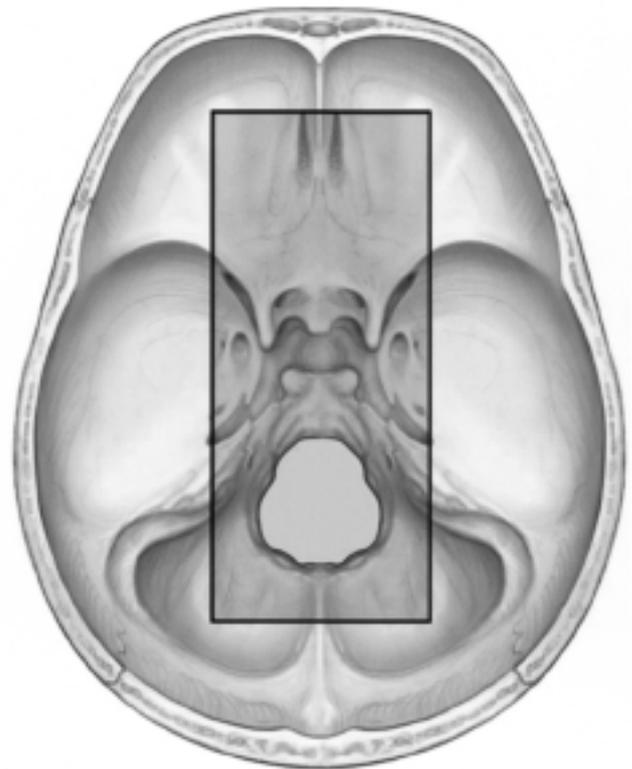

FIG. 1. Drawing depicting the median/paramedian skull base region (*shaded area* inside the *square*). Included are the olfactory groove, planum sphenoidale, tuberculum sella, anterior clinoid process, optic sheath/canal, cavernous sinus, ventral petrous pyramid, middle fossa (midline temporal bone), cerebellopontine angle, petroclival region, clivus, neural foramina (jugular foramen and hypoglossal canal), and foramen magnum.

skull base, 60 (8.2%) were from the lateral skull base, and 75 (10.3%) were from the spinal regions.

The meningothelial subtype was observed in 221 (79.2%) of 279 skull base meningiomas as compared with 183 (48.5%) of 377 at non–skull base locations (p < 0.001). Of the 219 tumors located in the midline skull base, 186 (84.9%) were MMs, compared with 35 (58.3%) of 60 located in the lateral skull base (Table 2; p < 0.001); MMs accounted for 60 (80%) of 75 spinal meningiomas.

Discussion

In this study, a significant association between the meningothelial subtype and site of tumor origin was found. The majority of tumors arising from the midline neuraxis (that is, the midline skull base and the spine) were meningotheliomas, in contrast to the meningiomas arising from the non–skull base or the lateral skull base sites. This relative overrepresentation of MM at the midline skull base and spine suggests that its tumorigenesis and/or leptomeningeal embryogenesis at the midline neuraxis may be unique.

Meningioma Cells of Origin

The outer layer of the arachnoid membrane is formed by the arachnoid cap cells, whereas the trabecular cells form the inner layers, which are separated by the basal lamina.[20]

TABLE 1
*Incidence of histological subtypes in 731 WHO
Grade I meningiomas*

Subtype	Incidence (%)
meningothelial	464 (63.5)
transitional	139 (19)
fibrous	99 (13.5)
psammomatous	13 (1.8)
other	16 (2.2)

TABLE 2
*Incidence of MM according to origin in 731 WHO
Grade I meningiomas*

Origin	No. of Tumors	Incidence of MM (%)
skull base	279	221 (79.2)*
midline skull base	219	186 (84.9)*
cavernous sinus	38	37 (97.3)
cerebellopontine angle	30	23 (76.7)
clinoid process	30	25 (83.3)
olfactory groove	25	23 (92)
petroclival region	25	21 (84)
tuberculum sellae	17	13 (76.5)
foramen magnum	12	7 (58.3)
temporal bone	12	11 (91.6)
optic sheath	12	11 (91.6)
planum sphenoidale	10	8 (80)
other	8†	7 (87.5)
lat skull base	60	35 (58.3)*‡
lat/middle sphenoid wing	32	24 (75)
orbitosphenoid region	12	7 (58.3)
posterior petrous region	10	1 (10)
orbital roof	6	3 (50)
non–skull base	377	183 (48.5)*
spine	75	60 (80)*‡
overall	731	464 (63.5)

* p < 0.001.
† Five clivus and two osseous foramina meningiomas.
‡ p < 0.01; lateral skull base compared with spine.

Histologically, fibrous and transitional meningioma subtypes have features similar to the fibroblasts found in the deeper layers of the arachnoid close to the subarachnoid space (which resemble the cells of the arachnoid trabeculae), whereas MM cells resemble the arachnoid cap cells of the outer layers.[5,8,10]

Leptomeningeal Embryogenesis

In the early stages of embryogenesis, the primitive mesenchyme around the neural tube condenses to form the primary meninx.[17,24] The unsegmented mesoderm rostral to the somites contributes to the primary cranial meninx, and its somatic counterpart is involved in the formation of the spinal meninges. The neural crest cells combine with the mesenchyme to participate in the development of the hindbrain and spinal pia, whereas the prechordal plate has been offered as having a role in the formation of the tentorium cerebelli. The frontal bone periosteum and the nasal septum cells, both of which are derived from the neural crest cells, contribute to the development of the falx cerebri and adjacent dura mater.[17,24]

Other authors have stated that the meninges around the brainstem arise from the cephalic mesoderm, whereas the telencephalic meninges likely arise from the neural crest cells.[2,3,10,20] Given the available information, it is not possible to infer the exact embryogenic sources of the leptomeninges of the midline skull base. These findings suggest, however, that the meninges covering the brainstem and spinal cord arise from a clearly different embryological lineage than the meninges of the cerebral convexity, which may form the basis of the observed predominance of the MM subtype in the central neuraxis. One possibility is that differential leptomeningeal embryogenesis may result in a predominance of one cell type (cap cells as opposed to trabecular fibroblasts) in certain locations. The second possibility is that the differential leptomeningeal embryogenesis creates a unique host environment that selectively favors activation of the tumorigenesis of MMs from activation of the cap cells in the central neuraxis.

Tumorigenesis of Meningiomas

The development of meningiomas likely results from interactions of genes and environmental factors, such as the *NF2* tumor suppressor gene, growth factors, the Ras signal transduction pathway, telomerase activity, sex hormone receptors, and radiation.[4,20,25] The role of *NF2* tumor suppressor gene mutation or protein inactivation has been well demonstrated in all meningiomas, except for the meningothelial subtype.[4,5,14,18,20,28,29]

In various other studies, MMs have been shown to possess different characteristics at the molecular level. For instance, compared with transitional or fibroblastic types, they have significantly higher PR expression.[30] This distinct feature led Perry, et al.,[19] to suggest that PR immunohistochemistry may have a diagnostic utility in regard to meningothelial neoplasms. The fact that PR expression is associated with benignity and is inversely proportional to tumor proliferation as well as histological grade[5,19,20] may imply a more benign course for the meningothelial subtype than for the other Grade I subtypes. In their recent analysis of data obtained in 588 patients suffering from WHO Grade I meningiomas, Roser and colleagues[22] also found a higher PR positivity for MM as compared with fibrous or transitional subtypes. They demonstrated that higher PR positivity was related to increased time to recurrence and suggested the combined use of it and the proliferation index as a prognostic tool for benign meningiomas. Sanson, et al.,[26] have suggested that the loss of some chromosome 22 alleles may be a potent genetic marker of the aggressiveness of meningiomas, and because MMs show this genetic abnormality rarely, they may exhibit a more benign phenotype.

In other studies, the expression of the matrix metalloproteinases MMP-2 and MMP-9, which are important mediators of angiogenesis and tumor invasion, has been found to be the weakest in MM compared with the other most common meningioma subtypes.[21] P-glycoprotein, a major factor in multidrug resistance, is also less expressed in MM.[1] Interestingly, the expression level of VEGF has been shown to be higher in MM, although no correlation with tumor vascularity or invasiveness was found.[11] Results of xenon-enhanced computed tomography studies have documented an increased blood flow in MM compared with other histological subtypes, such as fibrous meningioma,[16] which may

be relevant to the increased expression of VEGF in MM. The amplification of the *INS* gene located on the short arm of chromosome 11 and the *TCL1A* gene located on the long arm of chromosome 14 occur more frequently in MMs;[21] however, the clinical significance of these changes is unknown.

Implications for Research and Treatment

Treatment strategies precisely targeting the molecular abnormalities underlying tumorigenesis are promising. In this context, an awareness of the possible different genetic background in MM compared with other Grade I meningioma subtypes becomes important. Previous trial results have shown no benefit from antiprogesterone drugs in the management of meningiomas. Because PR is significantly more expressed in MM,[19,22,30] it would be interesting to see the results of new anti–PR trials focusing on MMs only. Similarly, anti–VEGF agents, which appear to be a promising treatment for other types of tumors, may be a potential venue for exploration in the treatment of MM as well. A significantly lower expression of drug-resistance factors in MM1 may also imply a more encouraging outcome when trials of antineoplastic agents are used in the treatment of meningiomas in more specifically defined patient populations.

Finally, meningiomas located in the central skull base, which are predominantly of the meningothelial subtype, are difficult tumors to remove completely and safely. In the future, once the exact mechanism of MM tumorigenesis is fully elucidated and molecular treatment specifically targeting MM is made available, risky surgery can perhaps be avoided and the appropriate molecular therapy administered with a confidence level approaching 85% on average, and even 97% for tumors of certain locations, such as the cavernous sinus (Table 2). Surgical indications, especially for high-risk central skull base meningiomas, may therefore be reevaluated and revised in the future.

Conclusions

The results of the current study support our initial hypotheses that meningiomas of the midline/paramedian skull base are predominantly of the meningothelial histological subtype. The increasing data on genetic and topographical characteristics of MMs suggest that they are indeed a unique subgroup of meningiomas. We believe that future studies focusing on the genetic characteristics and treatment of meningiomas should be designed with this new information in mind instead of accepting all histological subtypes of WHO Grade I meningiomas as a homogeneous group.

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