Malignant progression in meningioma: documentation of a series and analysis of cytogenetic findings

OSSAMA AL-MEFTY, M.D., PAULO A. S. KADRI, M.D., SVETLANA PRAVDENKOVA, M.D., PH.D., JEFFREY R. SAWYER, PH.D., COLIN STANGEBY, B.S., AND MUHAMMAD HUSAIN, M.D.

Department of Neurosurgery, University of Arkansas for Medical Sciences, Little Rock, Arkansas

Object. The malignant progression of benign tumors is well documented in gliomas and other systemic lesions. It is also well known that some meningiomas become progressively aggressive despite their original benign status. The theory of clonal evolution is widely believed to explain malignant progression in meningioma; however, the data used to explain stepwise progression have typically been derived from the cytogenetic analysis of different types of tumors of different grades and in different patients. In this study, the authors examined the data obtained in a group of patients with meningiomas that showed clear histopathological progression toward a higher grade of malignancy and then analyzed the underlying cytogenetic findings.

Methods. Among 175 patients with recurrent meningiomas, 11 tumors showed a histopathological progression toward a higher grade that was associated with an aggressive clinical course. Six tumors progressed to malignancy and five to the atypical category over a period averaging 112 months. Tests for MIB-1 and p53 and cytogenetic studies with the fluorescence in situ hybridization (FISH) method were performed in successive specimens obtained in four patients.

The MIB-1 value increased in subsequent samples of tumors. Cytogenetic analysis with FISH showed deletions of 22, 1p, and 14q. In all but one case, these aberrations were also present in the previous specimen despite its lower histopathological grade.

Conclusions. The authors documented the progression of meningiomas from one to a more histologically aggressive grade. These tumors were associated with a complex karyotype that was present ab initio in a histologically lower-grade tumor, contradicting the stepwise clonal evolution model. Although it was limited to the tested probes, the FISH method appears to be more accurate than the standard cytogenetic one in detecting these alterations. Tumors that present with complex genetic alterations, even those with a benign histological grade, are potentially aggressive and require closer follow up.

KEY WORDS • brain tumor • malignant meningioma • progressive disease • cytogenetics

SOME tumors become more aggressive clinically and histologically during their development, although the time course can vary drastically.\(^1,10,50\) This phenomenon in which a neoplasm changes irreversibly in one or more of its characteristics has been termed tumor progression.\(^1\) This biological and clinical progression might reflect the sequential appearance of a genetically altered subpopulation of cells with the new characteristics.\(^18,59,60\) In some instances the properties of advanced malignancy may be established before the neoplasm reaches macroscopic size; in other cases, well-differentiated and slow-growing tumors may persist for years before shifting to more aggressive behavior.\(^7,9,30\) Among the brain tumors, gliomas are the best example of this transformation. A significant number of recurrent, low-grade gliomas dedifferentiate to a more malignant form.\(^13,20,22,24,49,59\) This continuum of dedifferentiation is in clear relation to genetic alterations, with high-grade gliomas showing a larger number of genetic changes that are absent in low-grade tumors.

Meningiomas are the most common primary intracranial lesion and the second most common primary symptomatic intracranial lesion.\(^13,37,67,73\) They are generally slow-growing, benign tumors, most of which are classified as WHO Grade I.\(^9\) Nonetheless, certain histological subtypes are associated with a less favorable outcome and correspond to WHO Grade II or III. Studies applying the model of clonal evolution to meningiomas have shown that a loss of material from chromosome 22 is the primary and fundamental event in the oncogenesis of these tumors.\(^8–10,14,15,22,26,29,32,35,48,50,57,67,74,87,90\) More aggressive meningiomas also have a tendency to appear with more complex genetic alterations, corroborating the hypothesis that the formation of aggressive tumors follows a multistep progression model.\(^5–10,22,29,34,51,60,99\) The stepwise progression of genetic abnormalities toward a higher-grade tumor is postulated based on cytogenetic findings in large groups of patients with different grades of tumor, and these findings are applied to define the rule of progression in meningiomas. In this study, we focused on the clinical course of 11 patients in whom the tumor showed histopathologically confirmed malignant progression. In four cases, we analyzed the biological and genetic findings in successive specimens to identify the cytogenetic alteration responsible for this malignant progression.

Clinical Material and Methods

We reviewed the findings in 175 patients with recurrent meningioma treated by the senior author (O.A.). The first patient underwent radiosurgery for a lesion of the orbit and sent a protocol explaining the subject of and plan for the study. We collected data about the patients (hospital, clinic, department, and follow-up notes) and reviewed the clinical and pathological samples. A search for the results of previous standard genetic studies.

Fluorescence In Situ Hybridization

The methods used were the same as those of Paternoster, et al.\(^55,56\) Tissue blocks were examined and corresponding areas were collected from the resection specimen. The tissue was manually disaggregated with a pipette tip and was dissolved at room temperature with three 10-minute treatments and then subjected to microwaves for 5 minutes. The tissue was rehydrated with 100% ethanol and then subjected to a 30-minute X-ray and sent to another institution, we requested the second try of the MIB-1 value. The tissue was manually disaggregated with a pipette tip. Enzymatic digestion was done by adding 100% proteinase K for 30 minutes; nuclei were then pelleted and the proteinase K was removed. Each pellet was washed twice with phosphate-buffered saline and then resuspended in 100% ethanol. The tissue was rehybridized with 100% probes. The tissue was rehybridized with 100% probes. Multiple tissue cores were responding areas were marked. The tissue was rehybridized with 100% probes. The tissue was rehybridized with 100% probes. Multiple tissue cores were responding areas were marked.

Abbreviations used in this paper: FISH = fluorescence in situ hybridization; MR = magnetic resonance; WHO = World Health Organization.
Malignant progression in meningioma: cytogenetic findings

**TABLE 1**

<table>
<thead>
<tr>
<th>Age (yrs), Sex</th>
<th>1st Diagnosis</th>
<th>Interval (mos)</th>
<th>2nd Diagnosis</th>
<th>Interval (mos)</th>
<th>3rd Diagnosis</th>
<th>Interval (mos)</th>
<th>4th Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>67, F</td>
<td>benign</td>
<td>24</td>
<td>benign</td>
<td>36*</td>
<td>malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27, F</td>
<td>benign</td>
<td>188</td>
<td>atypical</td>
<td>74</td>
<td>atypical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42, F</td>
<td>benign</td>
<td>72</td>
<td>atypical</td>
<td>3</td>
<td>malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47, F</td>
<td>benign</td>
<td>25*</td>
<td>benign</td>
<td>51</td>
<td>malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50, M</td>
<td>benign</td>
<td>89</td>
<td>benign</td>
<td>156</td>
<td>atypical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54, M</td>
<td>benign</td>
<td>108</td>
<td>benign</td>
<td>38</td>
<td>benign</td>
<td>113*</td>
<td>atypical</td>
</tr>
<tr>
<td>53, M</td>
<td>atypical</td>
<td>12</td>
<td>malignant</td>
<td>9*</td>
<td>malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54, M</td>
<td>atypical</td>
<td>73</td>
<td>atypical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53, M</td>
<td>atypical</td>
<td>37*</td>
<td>malignant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patient underwent radiosurgery before diagnosis of higher-grade tumor.
† Patient underwent radiation therapy before diagnosis of higher-grade tumor.

Clinical Data

The clinical data for each patient are listed in Table 1. Of the 11 patients selected, four were women and seven were men. Eight patients had a first pathological report of a benign tumor, whereas three (all men) had atypical tumors. Four tumors occurred at the base of the skull, four at the cranial vault, and three (all atypical) at the falx. The mean age of the patients at diagnosis was 48.65 years (range 27–72 years) for the group who first had benign tumors and 53.3 years (range 53–54 years) for the group with atypical tumors.

The mean period between the first surgery and the histopathologically confirmed diagnosis of progression was 138.7 months (range 24–188 months) for the group with initially benign tumors and 40.6 months (range 12–73 months) for the group with atypical tumors.

Five patients, three with benign and two with atypical tumors, underwent radiation therapy or radiosurgery before the histopathologically confirmed diagnosis of progression was made.

Presence of MIB-1 and p53

We were able to perform tests for MIB-1 and p53 in nine samples obtained in four patients (Table 2). In one, however, the result could not be interpreted because of a large amount of necrosis. The first surgical samples were available in three cases.
The value for MIB-1 ranged from 0 to 1.7 (mean 0.72) in the first available samples. The MIB-1 value in the last surgical samples, which were obtained in the most aggressive tumors, ranged from 2.6 to 34.2 (mean 10.25). A consistent increase in the MIB-1 value was seen in all subsequent samples. The p53 value increased only in the sample in which it was originally positive (0.1–2).

**Fluorescence In Situ Hybridization**

The results obtained using the probes for /H11002, /H11002, and /H11002 are listed in Table 3. A deletion of chromosome 22 was found in all samples; however, in one of the samples of a lower pathological grade its deletion was the only alteration detected. A complex karyotype with the deletion of 1p and 14q was found in three of the lower-grade samples before progression. In one case cytogenetic progression accompanied the progression to a higher histopathological grade, adding deletions of 1p and 14q to the previously deleted 22 in the initial sample. In one case a better karyotype was found in the recurrence, a finding appropriate for tumor heterogeneity.

The results of standard cytogenetic analysis were available for three of these cases. In all of the studies compared, the results of FISH analysis showed more sensitivity to the detected alterations in the same sample.

**Illustrative Case**

This 72-year-old man presented with a history of headaches and a "bump" in his skull. He exhibited no neurological or systemic alterations on physical examination. Admission MR images revealed a 2.5 × 5.5 × 4-cm frontal supraorbital mass crossing the midline (Fig. 1A). The patient underwent a right frontal craniotomy with total resection of the mass. The resection was classified as Simpson Grade 0, which was confirmed on the postoperative MR images. The original pathological report disclosed a benign fibroblastic meningioma, and analysis of the paraffin block showed an MIB-1 of 1.7% (Fig. 1B). The p53 value was positive at 0.1, and FISH analysis revealed deletions of 22, 1p, and 14q (Fig. 1C).

Two years later, the patient suffered worsening headaches and MR images revealed a 2-cm recurrence with prominent edema (Fig. 2A). The patient underwent gross-total resection of the mass. The pathological report showed an atypical meningioma. Analysis of the paraffin block showed an MIB-1 of 19.7, and the FISH results showed a deletion of 22 and 1p (Fig. 2B). Three months later, another recurrence with bifrontal spread was detected (Fig. 3A). A bifrontal craniotomy was performed and the tumor was found infiltrating the brain tissue and skin. The lesion was extensively resected and the surgical site was reconstructed with a free skin and vascularized muscle flap. The results of histopathological analysis were consistent with a malignant meningioma. The MIB-1 analysis of this sample showed a higher index (34.2) and the p53 value was also elevated.2

Fluorescence in situ hybridization analysis of the surgical sample showed the same alteration as that detected in the original sample, with deletions of 22, 1p, and 14q. The patient underwent radiation therapy and extensive consultation for chemotherapy (which the patient’s family declined), and his neurological condition progressed. Yet another recurrence was seen on postoperative MR images, and pulmonary nodules that were believed to be consistent with metastatic lesions were seen on the chest x-ray films. The patient died 6 months later, but no postmortem studies were performed.

**DISCUSSION**

Meningiomas are the most common intracranial neoplasms.79,86,78 Even though most of them are asymptomatic and are discovered incidentally,77,64,74,75 they occupy the

**TABLE 2**

<table>
<thead>
<tr>
<th>Presence of MIB-1 and p53 in subsequent samples of recurrent tumor*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Case No.</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

*— = not tested: no sample available.

**TABLE 3**

<table>
<thead>
<tr>
<th>Findings of FISH and G-Band analysis in subsequent specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case No.</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>11</td>
</tr>
</tbody>
</table>
Malignant progression in meningioma: cytogenetic findings

Fig. 1. Illustrative case. A: Original presentation: Gd-enhanced MR images in axial (upper) and sagittal (lower) cuts. B: Photomicrograph showing a section of meningioma, with spindle-shaped cells and occasional whorls. H & E, original magnification × 100. C: Photomicrograph with MIB-1 staining of the first biopsy sample, showing a low proliferation index (1.7) Original magnification × 100. D: Fluorescence in situ hybridization analysis showing deletion of 1p, 14q, and 22.

Fig. 2. Illustrative case. A: First recurrence: Gd-enhanced MR images in axial (upper) and sagittal (lower) cuts. B: Photomicrograph of atypical meningioma obtained in the second surgery showing pleomorphic hyperchromatic nuclei of spindle-shaped tumor cells. H & E, original magnification × 100. C: Photomicrograph with MIB-1 staining of the second biopsy sample, showing a higher proliferation index (19.7). D: Fluorescence in situ hybridization analysis showing deletion of 1p and 22.
second place in the pantheon of symptomatic primary brain tumors.12,37,67,73–75 A major concern is the discrepancy that arises between the histological appearance of the tumor and its clinical behavior.2,5,11,23,25,33,40,42,47,65,69,72,101 When malignant histological variants of meningiomas are diagnosed, however, we face a different and difficult disease with a median survival duration of only 1.5 years and a fatal outcome in most cases.69

The question of malignant transformation compared with de novo malignant tumors has been well studied with regard to gliomas.14,16,20,21,31,45,49,70,82,91–97 Extending this question to aggressive meningiomas, it is not clear whether these lesions originate from a precursor benign tumor or if they originate as aggressive tumors that do not completely express their malignancy histopathologically but that carry the genetic potential to do so. Some series have shown that 0.16 to 2% of all meningiomas transform into malignant variants27,29,78 and that 14 to 28.5% of recurrent benign meningiomas transform into atypical or malignant lesions.24,25 This rate of progression is even higher in atypical lesions, with approximately 26 to 33% showing malignant features in the recurrent tumor.24,25,65 The reported history of malignant meningiomas shows that 14 to 29% were first diagnosed at a lower grade of malignancy.71,78 In the literature, the period of time that elapsed to the malignant transformation ranged from 8 months to 26 years.28,46,55,99,100 In our series, this period ranged from 99.7 months (in women) to 177.75 months (in men) for tumors first diagnosed as benign, and was considerably shorter (40.8 months) for tumors first diagnosed as atypical.

In the series of reports that describe this rate of transformation2,23–25,29,65,69,78 there is no discussion of or details about the multiple, relevant facts that could be involved and no attention is paid to this potential. Furthermore, there is no discussion of the stepwise evolution because the subject is restricted to isolated case reports in which the progression is mapped based on one parameter.6,9,10,15,23,25,29,33,46,53–55,63,77,86,88,99 Studies of genetic evolutionary pathways and biological behavior markers are performed in large groups of patients, and the results from different tumors in different individuals are used to postulate the rule of the progression. The uniqueness of our study is in the analysis of the clinical course of 11 cases, in four of which we could conduct biological and genetic studies in samples of recurrent tumor.

**Genetic Basis of Tumor Progression**

The model of clonal evolution, which can be applied to most neoplasms,17,59,60,79–81 states that the development of a tumor is initiated by a single cell carrying a mutation (the mutation model),17,59,60,79–81 which gives it a select growth advantage. As the tumor progresses to a more malignant stage, it accumulates mutations.59,60,79,89 There is also a tendency over time for tumor cells to speed up their growth rate, escaping from local growth control mechanisms.60 This issue has been well studied in gliomas, in part because 49 to 86% of recurrent low-grade gliomas dedifferentiated to a more malignant form,31,49,93 allowing mapping of the genetic progression in successive specimens.14,16,20,21,45,82,92,94–97

Meningiomas have been intensively studied with cytogenetics in recent years.4,6,7–10,14,15,22,26,29,32,34–36,38,43,45,51,68,77,86,87,90,92,101,102 Approximately 20 to 57% of meningiomas show no
cytogenetic abnormalities, an initial diploid stage that is associated with more benign behavior. Following this diploid stage comes the so-called primordial chromosome event, which is the alteration in chromosome 22, the event most implicated in the oncogenesis of meningiomas.\(^{4,6,7-10,15,22,26,29,32,34,36,45,68,86,87,90,92,101,102}\) The alteration is present in 33 to 46% of benign,\(^{6,8,88}\) 68 to 100% of atypical,\(^{34,77}\) and 73 to 100% of malignant tumors.\(^{6,8,89}\) The rate of other chromosomal alterations also increases according to the histopathological grade. The deletion of chromosome 1p is present in 8 to 15%\(^{8,88,90}\) of benign, 29 to 76%\(^{14,51,90}\) of atypical, and 58 to 100%\(^{29,34,35}\) of malignant tumors. The deletion of 14q occurs in 4 to 20% of benign, 40 to 47% of atypical, and 55 to 100% of malignant tumors.\(^{34,51,90}\) The occurrence of abnormalities in chromosomes 3, 6, 9, 10, and 17 also increases with the histopathological grade.\(^{6,8,9,29,34,35,51,68,77,90,101}\) Such observations show that more malignant tumors present a more complex karyotype. Nonetheless, a complex karyotype can be observed even in benign tumors,\(^{6,8}\) and the cytogenetic results in a series of patients with benign, atypical, and malignant meningiomas can be extrapolated for the construction of a stepwise progression. Few studies have included successive, recurrent specimens obtained in an individual patient whose tumors began benign but become malignant.\(^{8,29,90,100}\) Unfortunately, we could not obtain all the paraffin blocks of the tumors resected in each of our patients, but our results nonetheless contradict the proposed stepwise progression found in the literature. Our specimens showed the same complex genetic alterations that we see in malignant tumors already apparent in the early, benign stages of those tumors. Of course, because we were limited to the probes that we tested with the FISH method, we could not determine whether there was an unknown key genetic alteration guiding the histopathological progression.

**Predicting Clinical Behavior**

The main problem, regardless of the treatment used for a meningioma, is how to predict recurrence rates. Recurrence not only complicates control of the neoplasm but also drastically increases the morbidity rate.\(^{2,5,13,21,22,31,41,44,48,55,58,81,111}\) Well-established factors influencing the recurrence rate include the histopathological grade,\(^{5,13,19,22,23,25,40,41,48,55,57,58}\) the extent of resection,\(^{2,3,11,14,19,23,28,30,39,43,52,54,56,61,62,71,72,81,85}\) and the presence of biological markers.\(^{1,5,13,14,19,23,28,30,39,43,52,54,56,61,62,71,72,81,85}\)

**Histological Classification**

The incidence of benign tumors varies from 73 to 94.3%, that of atypical lesions from 4.7 to 19.8%, and of malignant tumors from 1 to 7.2%.\(^{2,5,21,71}\) The descriptive histopathological criteria for diagnosing meningiomas vary considerably, however, making it difficult to apply them in a reliable and reproducible fashion. The different criteria used to define the benign, atypical, and malignant histological types make it troublesome to compare the data from different studies.\(^{1-3,5,6,9,11,15,19,24-26,32,39,40,42,48,50,52,54,56,60,69,70,77}\) The proposed classifications are based on published series of qualitative and quantitative parameters.\(^{2,5,13,25,48,50,53,64,70,79,92}\) The qualitative criteria are difficult to correlate among the different seres. In an attempt to solve the problems of the grading system, quantitative criteria have been studied. In fact, the criteria currently used by the WHO\(^{98}\) to define benign, atypical, and malignant meningiomas include the number of mitotic figures as a key parameter. A finding of more than four mitoses per 10 hpf is considered atypical, and the presence of more than 20 mitoses per 10 hpf categorizes the tumor as malignant, independent of the presence or absence of any other qualitative criteria. Counting mitotic figures is a simple, low-cost procedure that requires no additional preparation. Nevertheless, measurement can be extremely difficult depending on the quality of the tissue sample, and predicting tumor behavior according to the histopathological features alone seems to be problematic.\(^{1}\)

**Biological Markers**

To solve the problems of the grading system, quantitative criteria have been studied. Because there is a tendency toward an increased growth rate in more aggressive specimens, proliferation indices have been created to try to predict the behavior of a tumor. This cell proliferation index usually correlates with the aggressiveness of the meningioma,\(^{1,3,5,19,22,23,25,33,54,56,61,70,71,76,83,85}\) High mitotic rates are usually associated with malignancy\(^{9}\) and can be measured by determining the mitotic activity,\(^{28}\) the percentage of the S phase,\(^{28,47,72}\) bromodeoxyuridine,\(^{30,77}\) argyrophil organizer region protein,\(^{43}\) Ki-67, or MIB-1,\(^{1,6,9,30,31,32,22,23,29,30,39,43,47,54,56,62,71,72,83-86}\) and proliferating cell nuclear antigen.\(^{11,54}\)

The MIB-1 antibody detects the same or a similar epitope as the original Ki-67 and has the advantage over Ki-67 that it can be used in frozen, paraffin-embedded, or decalcified tissue, and it is easier to interpret.\(^{9,10,72}\) The value of MIB-1 corresponds to the histological findings in the tumor, increasing with the grade of malignancy,\(^{30,31,72}\) and it also corresponds to the risk of recurrence.\(^{4,5,29,46,71,84,86}\) In our series, the value of MIB-1 was increased in all of the recurrent tumors, accompanying the pathological transformation.

**Fluorescence In Situ Hybridization**

Proliferation indices supplement the morphological findings in predicting tumor recurrence.\(^{1,3,5,19,23,25,29,30,44,47,63,72,76,83,86}\) Like the histopathological findings, however, these indices denote something that is already happening in the tumor cells more than they predict the tumor’s potential behavior. As defined by the WHO, human neoplasms are the histological, phenotypical expression of an intriguing process involving the accumulation of successive genetic abnormalities implicated in the normal regulation of cell proliferation, differentiation, and death.\(^{98}\) Therefore, it seems logical that before a tumor cell emerges a genetic alteration is present, even in the so-called initial diploid stage of a meningioma. Such phenomena can be explained by the limitation of the techniques in which in vitro cultured cells are used; nontumor cells, such as fibroblasts, may dominate these cultures. Only the few most active cells may be cytogenetically analyzed, or chromosomal changes may be the result of the in vitro propagation of a cell culture.\(^{98}\) These facts could explain the results of the standard genetic studies performed in our cases.

New techniques have been developed in answer to the criticism of the classic process for the culture of cells.\(^{22,36,86}\) Fluorescence in situ hybridization is not time consuming and can be applied to various clinical materials, including paraffin-embedded tumor samples or biopsy samples.\(^{22}\) Fluorescence in situ hybridization has been shown to be as or
even more sensitive than the standard cytogenetic models. This finding was confirmed in our series, in which the FISH analyses were more sensitive than the standard technique. Unfortunately, we were limited to the probes we chose to study and may have lost the ability to detect a stepwise progression. Nonetheless, it is possible to analyze previous samples allows for the possibility of recognizing the presence of a complex karyotype years before any histopathological manifestation of malignancy. This analysis is what can predict the clinical behavior of a meningioma.

**Conclusions**

We present a series of meningiomas with histopathologically documented malignant progression, a phenomenon that probably occurs more often than is recognized. Reports in the literature indicate a stepwise genetic progression, with the deletion of chromosome 22 as the fundamental alteration and deletions in other chromosomes (1p, 14q, and 10q among others) in the progression of these tumors toward a more malignant type. In our study, the presence of a complex karyotype in the benign tumor preceded the histopathologically confirmed progression. This finding raises the possibility that these tumors were already intrinsically malignant and that they were destined to progress rather than evolve in a stepwise cytogenetic fashion corresponding to their histopathological progression. Thus, a complex karyotype should be considered in the classification of these tumors and used as a predictor of meningioma behavior.

**Acknowledgment**

We thank Mrs. Julie Yamamoto for her editorial assistance.

**References**

12. Cushing H: Meningiomas, Their Classification, Regional Behavior, Life History and Surgical End Results. Springfield, IL: Charles C Thomas, 1938
33. Lemaid RD, Bucci MN, Farhat SM, et al: Malignant transforma-
Malignant progression in meningioma: cytogenetic findings


**Manuscript received October 23, 2003. Accepted in final form March 24, 2004.**

This work was supported in part by the Chancellor’s Circle at the University of Arkansas for Medical Sciences and the William P. Williamson Research Fund.

Address reprint requests to: Ossama Al-Mefty, M.D., 4301 West Markham, #507, Little Rock, Arkansas 72205, e-mail: aekeeland@uams.edu.