Anaplastic meningiomas that resemble sarcomas often reveal clues to their meningothelial differentiation or develop in a plausible setting that confirms their meningothelial origin. Malignant mesenchymal neoplasms without obvious evidence of meningothelial differentiation or origin are more likely to be true primary or metastatic sarcomas. Because of their clinical and biological differences, it is important to distinguish anaplastic meningioma from a sarcoma. We present a 67-year-old woman with multiple meningiomas, who developed a high-grade spindle cell tumor 6 months after the resection of a World Health Organization grade I meningioma. It was not clear whether this tumor represented a malignant transformation of meningioma or a primary sarcoma. Malignant transformation of a meningioma is exceptional within this short period and a coexisting sarcoma and meningioma are equally uncommon. Even though these malignant neoplasms are rare in general, they appear to be more prevalent in patients with multiple meningiomas including those with neurofibromatosis type 2.

Emergence of a High-Grade Sarcoma in a Recurrent Meningioma

Malignant Progression or Collision Tumor?

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Meningiomas are presumed to originate from arachnoid cells and constitute approximately 30% of all primary intracranial tumors. Multiple meningiomas comprise 2.3% to 8.9% of all intracranial meningiomas that occur outside the setting of neurofibromatosis type 2. Previous studies reported no significant difference between multiple and solitary meningiomas in overall prognosis. However, there is no study matching the histologic type, grade, extent of resection, and adjuvant therapies to determine impact on the outcome.

Anaplastic meningiomas account for 1% to 2.8% of all meningothelial neoplasms and are associated with a median survival time of less than 2 years. There have been considerable changes in the criteria for anaplastic meningiomas, and because of the rarity of such examples, accurate characterization has been difficult. Studies prior to the 2000 World Health Organization (WHO) classification scheme have considered brain invasion as a criterion for anaplasia. Currently, meningiomas are considered anaplastic by virtue of their histologic features or very high mitotic rate. The WHO 2007 definition of anaplastic meningioma includes “high mitotic index in excess of 20 per 10 high power fields or histological features of frank malignancy.” Although the former is quite reproducible, the latter is subject to different interpretations. Two histologic subtypes, papillary and rhabdoid variants, constitute a significant component of anaplastic meningiomas. These 2 subtypes have aggressive clinical course and fatal outcomes.

Anaplastic meningiomas may show carcinoma, sarcoma, or even melanoma-like morphologic patterns, and other primary central nervous system tumors and metastatic malignancies should be excluded in the presence of such poorly differentiated malignant neoplasms. Historically, many meningiomas with sarcomatous morphology have been high grade from the onset, but malignant progression of meningiomas is well recognized. A small case series in the literature suggests that 33% to 70% of the anaplastic meningiomas progressed from low-grade tumors.

There are rare case reports of high-grade sarcomas following a benign meningioma in the literature. One case was reported to recur as a sarcoma among 936 meningiomas. This tumor was considered to have undergone a “Grade IV sarcomatous transformation.” There are also few reports of synchronous meningiomas and sarcomas.

Malignant stromal neoplasms that develop in the absence of a precursor meningioma or without obvious evidence of meningothelial origin represent true sarcomas. Primary sarcomas of the central nervous system are exceedingly rare, and undifferentiated sarcoma, chondrosarcoma, and fibrosarcoma are the most common types. The prognosis largely depends on the type and grade of sarcoma, and 5-year survival rate for high-grade sarcomas was reported to be 28%.

Dedifferentiated anaplastic meningiomas are difficult to separate from primary meningiomas and the

Accepted for publication September 20, 2010.

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The authors have no relevant financial interest in the products or companies described in this article.

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analysis often requires special studies. In this report, we present a patient with multiple meningiomas who developed a poorly differentiated sarcoma 6 months after complete resection of a grade I meningioma.

**CASE REPORT**

A 67-year-old woman was admitted with complaints of memory loss, cognitive difficulties, and difficulty in her movements. She had difficulty recognizing her family members. Neurologic examination revealed loss of orientation to time and place, depressed mental functions, and dysphasia. Her motor and sensory functions were essentially intact. There was bilateral papilledema. The findings suggested a space-occupying lesion. The patient had a history of breast carcinoma that was treated with right mastectomy and local radiotherapy 15 years ago. There was no information regarding the pathologic diagnosis and stage of the breast carcinoma.

Magnetic resonance imaging examination revealed a 7 × 6 × 4.5 cm extra-axial parasagittal mass near the right frontal lobe with extension into the interhemispheric fissure. Another extra-axial mass 7.5 × 3 × 4 cm was present in the left parietal region near the left sylvian fissure extending toward the vertex and involving the left insular cortex. Fluid-attenuated inversion recovery images demonstrated marked peritumoral as well as periventricular edema with mass effect. Both tumors were isointense to gray matter on T1 images and demonstrated strong but heterogeneous contrast enhancement. A third mass, measuring 4 × 3 × 2.5 cm, was located at the anterior part of left temporal lobe near the sphenoid wing. Finally, a fourth lesion measuring 1 cm in greatest dimension was located at the right parieto-occipital lobe (Figure 1, A through D).

The patient underwent bifrontal craniotomy and microsurgical resection of the large tumors involving the frontal lobes. Both tumors were adherent to the underlying brain parenchyma as well as to the falk cerebri. Complete resection was achieved for both tumors and postoperative scans showed no evidence of residual tumor in the frontal lobes (Figure 1, E). A second operation was planned for the smaller tumors in the left temporal and right parieto-occipital lobes, and radiotherapy was suggested. However, the patient refused further treatment and was discharged with close follow-up and interval scans. Her first interval scan revealed encephalomalacia in both frontal lobes superiorly and minimal linear extra-axial contrast enhancement.

![Figure 1](image-url). Contrast-enhanced T1-weighted images of the tumors. A, Sagittal image showing right frontal meningioma (white arrow). B, Coronal image showing right frontal meningioma (white arrow). C, Coronal image showing the posterior aspect of the right frontal meningioma (white arrow), left frontal meningioma (white arrowhead), and the left temporal lobe meningioma (black asterisk). D, Axial image showing right frontal meningioma (white arrow). E, Postoperative axial image following resection of both frontal meningiomas. White asterisk shows the resection cavity of the right frontal meningioma. There is in addition the small right parieto-occipital meningioma (black arrow). F, Axial images 6 months after gross total resection of the meningioma showing markedly enhancing sarcoma (black arrowhead) filling the resection cavity with associated midline shift and ventricular compression.
Six months after the initial operation, the patient was readmitted with similar complaints. Magnetic resonance imaging examination revealed a new heterogeneously enhancing parafalcine mass in the right frontal lobe. The recurrent tumor measured 6 cm and was associated with ventricular compression and midline shift (Figure 1, F). There were no significant changes in the preexisting right parieto-occipital and left temporal masses. Fluorodeoxyglucose positron emission tomography/computed tomography scan showed marked hypermetabolic activity in the recurrent tumor, but the metabolic imaging characteristics of the left temporal meningioma were similar to the gray matter.

The patient underwent a second surgery to remove the recurrent tumor in the right frontal lobe and the existing tumor in the left temporal lobe. Postoperative images confirmed total resection in both sites. She had full-body scan as a part of her metastatic workup and no other malignancy was identified. The patient was discharged home with a Karnofsky performance score of 70 and minimal residual neurologic deficits. She refused further treatment and 2 months following the second surgery suddenly died at home. Unfortunately, the family declined an autopsy.

**HISTOLOGIC FINDINGS**

The pathologic specimen from the initial resection of the right frontal tumor consisted of multiple rubbery fragments that demonstrated a meningioma with meningothelial and chordoid patterns (Figure 2, A and C). The tumors predominantly consisted of meningothelial meningioma with less than a third of the mass showing chordoid features. There was no evidence of small cell change, necrosis, or brain parenchymal invasion or chondromatous metaplasia. The mitotic rate was less than 4 per 10 high-power fields. Presence of focal chordoid pattern was not considered sufficient to represent WHO grade II meningioma (chordoid variant) because it was not the predominant pattern in this neoplasm. Immunohistochemically, both the meningothelial and the chordoid patterns demonstrated strong and diffuse epithelial membrane antigen positivity as well as nuclear positivity for progesterone receptor antibody in almost all tumor cells (Figure 2, E). There was focal strong positivity for CD34 antibody in the chordoid component. Staining for S100 protein, smooth muscle actin, bcl-2, and p53 protein was negative. MIB-1 staining revealed a labeling index less than 4% in the sections stained (Figure 2, G). Ultrastructural analysis of the meningioma revealed typical cell junctions and conspicuous interdigitating cell membranes with focal basement membrane-like deposits.

Surgical material from the second resection consisted of 2 specimens. The first specimen was obtained from the frontal lobe and was composed of multiple fragments of rubbery to firm hemorrhagic tissue. Microscopically, the specimen exhibited a poorly differentiated malignant spindle cell neoplasm with marked increased cellularity, haphazard growth pattern, and foci of fascicular and chondromatous differentiation (Figure 2, B). There were many areas of necrosis and hemorrhage as well as fibrin thrombi. Many areas exhibited a myxoid background with chondromatous matrix, but this was distinct from the chordoid pattern seen in the meningioma. The tumor appeared to be separate from the brain parenchyma, but focally invaded the Virchow-Robin spaces. The tumor was composed of highly pleomorphic spindle cells with marked nuclear hyperchromasia and numerous apoptotic and mitotic figures with abnormal forms (Figure 2, D). Immunohistochemically, the tumor was negative for epithelial membrane antigen, progesterone receptor, CD34, smooth muscle actin, and p53 protein. There was diffuse strong staining with bcl-2 (Figure 2, F), and focal staining with S100 protein. MIB-1 staining revealed a labeling index in excess of 50% (Figure 2, H). Ultrastructural evaluation of the tumor demonstrated a highly undifferentiated spindle cell neoplasm without any evidence of meningothelial differentiation.

The second specimen from the left temporal lobe was a large rubbery mass, quite distinct in texture and color in comparison to the first specimen. Histologically, the tumor was a classical WHO grade I meningioma without a chordoid component, high mitotic rate, or brain invasion. Immunohistochemical profile of this tumor was identical to the meningioma removed from the frontal lobe.

**COMMENT**

This case presents an intriguing challenge but provides us with limited clues to decide whether the high-grade sarcoma is a progression from a preexistent meningioma or a synchronous but different neoplasm. Immunohistochemical and ultrastructural evidence point to 2 distinct lesions, and there is no evidence for a common origin other than the physical proximity of the 2 neoplasms. Yet the phenotypical differences between a primary neoplasm and its metastases are well recognized, and it is almost impossible to exclude this with absolute certainty. Another remote possibility is the existence of an unsampled sarcoma within the meningioma. This is highly unlikely because radiologic studies showed a homogeneous tumor and the resection was entirely submitted for pathologic evaluation. Even if we consider this suggestion to be true, the question of whether the tumor is a malignant meningioma or a collision tumor still remains unanswered.

We have not considered the original meningioma a “chordoid meningioma” based on our interpretation of the WHO classification scheme and our extensive correspondence with the members of the WHO working group (Drs. Arie Perry and Bernd W. Scheithauer, personal communications). Currently, a chordoid meningioma is considered to be a “meningioma variant consisting predominantly of tissue histologically similar to chordoma.”

We consider predominant to be the majority (> 50%) of the tumor tissue even though some may consider a tumor with as low as 10% chordoid component within this category.

In our patient, the period between the initial resection of typical meningioma and the emergence of the high-grade sarcoma was 6 months. Although this period can be considered short for anaplastic transformation of a meningioma, this possibility cannot be excluded. The aggressive clinical course and short survival are consistent with both anaplastic meningioma and a high-grade sarcoma. The possibility of anaplastic transformation can be a plausible explanation if the sarcoma reveals clues to its meningothelial origin or the 2 tumors share some histologic, immunohistochemical, or genetic features. The high-grade sarcoma in our patient did not have any meningothelial features and had a distinctly different
Figure 2. Histologic features. A, The first tumor resection from the frontal lobe showing a typical World Health Organization grade I meningothelial meningioma (hematoxylin-eosin, original magnification ×200). B, Histologic features of the sarcomatous neoplasm arising in the frontal lobe meningioma (hematoxylin-eosin, original magnification ×200). C, Focal (< 30%) chordoid pattern within the frontal lobe meningioma (hematoxylin-eosin, original magnification ×200). D, High-power magnification of the sarcoma showing numerous mitoses and apoptotic bodies (hematoxylin-eosin, original magnification ×400). E, Immunohistochemical staining for progesterone receptor showing diffuse nuclear positivity in tumor cells in the meningioma (original magnification ×400). F, Immunohistochemical staining for bcl-2 in the sarcoma showing diffuse positivity.
immunohistochemical profile. Ultrastructural examination also demonstrated distinct differences between the meningiomas and the sarcoma. In addition, we did not find any chordoid features in the sarcoma or chordomatous features in any of the meningiomas. Therefore, it is not possible to speculate if any of the histologic patterns in the meningioma may be suggested as a precursor to the sarcoma.

Alternatively, the tumors in our patient could be considered 2 metachronous primaries. Presence of metachronous meningiomas with other malignant tumors is well recognized. For example, neurofibromatosis patients can develop multiple meningiomas in addition to malignant peripheral nerve sheath tumors. Even in the absence of a dysgenetic syndrome, patients develop meningiomas following radiotherapy for treatment of high-grade tumors such as medulloblastomas, high-grade gliomas, and leukemias. Furthermore, development of meningioma long after the radiotherapy of simple disorders such as tinea capitis is a well-documented phenomenon. Similarly, there are reports of sarcomas following radiation treatment of a meningioma. Although some authors considered these emerging sarcomas as dedifferentiated meningiomas, there is little evidence and no proof that such tumors are actually sarcomatous transformation of typical meningiomas. A classical radiation-induced sarcoma is expected to occur a decade or longer following treatment, and the short duration in some of these case reports is intriguing. The possibilities of metachronous tumors due to a known dysgenetic syndrome or due to radiotherapy are excluded in our patient.

It is possible that multiple meningiomas and high-grade sarcomas can occur in the same patient because of a yet undiscovered genetic tendency or pure coincidence not unlike neurofibromatosis type 2 patients. We were unable to identify any report of distinct and metachronous meningioma and sarcoma in the absence of a dysgenetic syndrome or radiation treatment. The overwhelming majority of cases reported in the literature can be considered malignant transformation of an existing meningioma. These transformations were reported to be years after the meningioma even in cases without radiotherapy. Yet it is quite possible that our patient has an increased predisposition of developing both tumors because of a hitherto undiscovered genetic predisposition syndrome.

There are also reports of high-grade tumors synchronous with benign meningiomas. Heimberger et al reported a carcinoma-like component within a histologically benign fibroblastic meningioma, and comparative genomic hybridization analysis confirmed that, despite different histologic phenotypes, 2 components were genetically related suggesting a malignant transformation. Other case reports of synchronous meningiomas and sarcomas also suggested either coincidental tumors or sarcomatous transformation of a preexisting meningioma, but no definitive evidence was reported to prove these theories. Thus, most tumors reported as synchronous could be classified under de novo anaplastic meningiomas or anaplastic transformation of lower grade meningiomas.

We have also considered a metastatic sarcoma to a prior surgical site because it is plausible to conceive a metastasis to a brain site with altered anatomic integrity and increased vascularity. Meningiomas are reportedly the most common primary intracranial tumors to receive metastases. Most of such metastases arise from breast and lung carcinomas. Sarcoma metastasis to central nervous system is very rare, and to our knowledge there is no previous report of a sarcoma metastasis to a meningioma. Although our patient had a history of metastatic breast carcinoma, she was free of this tumor locally and a metastatic workup did not identify any other tumor elsewhere.

Another important question is whether having multiple meningiomas can be due to an underlying propensity for developing benign and malignant tumors. Currently, we are not aware of a tumor predisposition syndrome other than neurofibromatosis type 2. Sporadic multiple meningiomas are rare and their management is often complicated with multiple operations and radiotherapy. Although most of the previous reports suggested good prognosis, occasional progression of such lesions is documented. There is one previous report of malignant transformation after multiple recurrences. In a recent study, Shen et al reported that, in contrast to familial tumors, sporadic multiple meningiomas showed significant genomic imbalance events comparable to the atypical solitary tumors, suggesting a potential for higher aggressiveness and a worse prognosis.

It can be argued that the distinction between a sarcoma and a malignant meningioma is trivial because of the poor prognosis portended in both diagnoses. However, adverse outcomes are hardly sufficient enough rationale to consider this distinction to be trivial. There is little doubt that pathologists need to be as accurate as possible in defining the nature of the disease because even most malignant neoplasms have differences in biological behavior, recurrence patterns, and treatment response. In the case of a sarcoma, it is also important to consider a metastatic neoplasm, which should prompt evaluation of a patient for a possible primary site. This attempt can be avoided in tumors recognized as malignant meningiomas, saving the patient substantial expense and discomfort in an attempt to search for a primary tumor. There are also distinct differences between malignant meningiomas and sarcomas in their metastatic potential.

In summary, it is quite difficult to determine whether our case actually represents 2 primary neoplasms or malignant progression of a low-grade meningioma. It is critical to recognize the background in which such tumors can develop and to determine whether the predilection is due to the individual (an inherent tendency to develop malignant meningiomas and/or sarcomas) or due to the tumor (tendency for malignant transformation). More experience is required for better understanding on how to approach and treat such neoplasms.
References