

Association between Intracranial Plasmacytoma and Multiple Myeloma: Clinicopathological Outcome Study

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OBJECTIVE: Intracranial plasmacytomas are rare lesions that can arise from the calvarium, dura, or cranial base and exhibit a benign course unless associated with myeloma. Attention has recently been focused on the role of the cell adhesion molecules CD56 and CD31 in the pathogenesis of myeloma. No such information is available for intracranial plasmacytomas and myeloma-associated lesions.

METHODS: We investigated the relationship between CD56 and CD31 expression, intracranial location, and progression to myeloma for a series of nine intracranial plasmacytomas (three dural, one calvarial, and five cranial base lesions). These parameters were also correlated with proliferation indices, as assessed by MIB-1 immunostaining of the histological sections. A single pathologist (AO) performed immunohistochemical analyses and reviewed all slides.

RESULTS: Intracranial plasmacytomas presented more commonly in female patients (89%). The three dural lesions were CD56- and CD31-negative and exhibited MIB-1 staining of less than 10%; no patient developed myeloma or recurrence. Of the five cranial base lesions, three were CD56-positive, none was CD31-positive, and two exhibited MIB-1 labeling of more than 45%, with plasmablastic morphological features. Compared with other intracranial plasmacytomas, five of five patients with cranial base lesions developed bone marrow biopsy-proven myeloma ($P < 0.05$) within 8 months. The calvarial lesion was CD56- and CD31-positive, and the patient developed myeloma soon after diagnosis. Both of the two highly proliferative plasmablastic lesions recurred, one after gross total resection without radiotherapy and the other after a biopsy and 2000-cGy radiotherapy.

CONCLUSION: Among intracranial plasmacytomas, cranial base location was the strongest predictor of the development of multiple myeloma. Expression of the cell adhesion molecules CD31 and CD56 was not predictive of outcome. Extramedullary dural-based lesions were CD56-negative and were not associated with myeloma. A high proliferation index and plasmablastic morphological features were predictive of a short time to recurrence and aggressive behavior. We recommend 4050- to 5040-cGy fractionated radiotherapy for all intracranial plasma cell neoplasms and gross total resection for non-cranial base lesions. (*Neurosurgery* 49:1039–1045, 2001)

Key words: Cell adhesion molecules, Cranium, Dura, Multiple myeloma, Plasmablastoma, Plasmacytoma, Surgery

Plasma cell tumors are characterized by monoclonal proliferation of immunoglobulin-secreting plasma cells. Multiple myeloma (MM) represents the disseminated form of this disease. Isolated plasmacytomas are unusual benign lesions that are classified as either intramedullary or extramedullary on the basis of their association with bone marrow. When plasmacytomas are associated with MM, they

bear a far worse prognosis. Intracranial plasmacytomas can arise from the cranium, meninges, or brain and are quite rare, with only scattered cases having been reported in the literature.

Recent attention has focused on the role of cellular adhesion molecules in the dissemination of plasma cell neoplasms. In particular, expression of CD56 (neural cell adhesion molecule,

natural killer cell-associated antigen-1, or Leu-19) (2, 15, 21, 30, 31) and CD31 (platelet-endothelial cell adhesion molecule-1) (13, 29) has been identified in myeloma cells, suggesting an association between alterations in the density of cellular adhesion molecules and myelomatous transformation. These findings are particularly significant with respect to prognosis prediction and potential immunological and interleukin-based therapies (2, 13, 15, 21, 29–31). Data on cellular adhesion molecule expression in intracranial plasmacytomas and myeloma-related lesions, particularly extramedullary plasmacytomas, are lacking. We retrospectively examined our experience with intracranial plasmacytomas, focusing on histological and immunohistochemical markers that might facilitate the treatment of these patients.

PATIENTS AND METHODS

We reviewed the pathology records for all intracranial lesions that had been surgically treated at The Neurological Institute of New York between January 1991 and December 1998. Pathology blocks and slides with the diagnosis of plasmacytoma were recovered, and radiographic studies were reviewed (Fig. 1). Medical record reviews and telephone interviews of both patients and treating physicians were performed, to obtain demographic data and to determine clinical outcomes. The extent of resection was determined by review of the operative notes and, when available, postoperative scans. Pathology blocks and slides were reviewed by a single hematopathologist (AO) and were divided into two categories. Plasmacytic plasmacytomas contain plasma cells that appear mature, with eccentric round nuclei, condensed, coarsely clumped, nuclear chromatin, basophilic cytoplasm, and a prominent pale Golgi zone (Fig. 2A). Plasmablastic plasmacytomas contain plasma cells with large vesicular nuclei, with prominent, often centrally located nucleoli, and a moderate rim of amphophilic to basophilic cytoplasm, with a small, often indistinct Golgi zone (Fig. 2B) (33).

All patients underwent evaluations for MM, consisting of urine and serum protein electrophoresis, a skeletal survey, and a bone marrow biopsy (searching for an M-spike, lytic bone lesions, and plasma cells, respectively), at varying times

after surgery. For all cases, immunostaining results for κ and λ light chains were available. Intracranial recurrence was assessed with serial magnetic resonance imaging scans obtained at varying times, as determined by the primary oncologist.

The immunohistochemical technique used in this study for staining of paraffin-embedded tissue was previously described (6). In brief, after deparaffinization, the slides were transferred to phosphate-buffered saline. Endogenous peroxidases were quenched in a 5-minute incubation with 3% hydrogen peroxide. After two washes in phosphate-buffered saline, the slides were transferred to plastic Coplin jars filled with citrate buffer (pH 6.0) and were heated twice for 5 minutes in a microwave oven, at a power of 700 W. After being cooled at room temperature for 15 minutes, the slides were covered for 2 minutes with normal goat serum and were incubated overnight at 4°C with the following mouse antibodies: Ki-67-equivalent MIB-1 monoclonal antibody at a dilution of 1:5 (AMAC, Westbrook, ME), monoclonal anti-CD31 antibody (JC/70A; Dako, Carpinteria, CA) at a dilution of 1:30, and monoclonal anti-CD56 antibody (OB11; Sigma Chemical Co., St. Louis, MO) at a dilution of 1:1000. The slides were then stained with a biotin-conjugated goat anti-mouse antibody (Kirkegaard and Perry Laboratories, Gaithersburg, MD) for 30 min, followed by peroxidase-conjugated streptavidin (Kirkegaard and Perry Laboratories) for 30 min. The enzyme was developed with 3,3'-diaminobenzidine (Sigma) or 3-amino-9-ethylcarbazole (Sigma).

RESULTS

Nine patients were identified as having the diagnosis of intracranial plasmacytoma after a neurosurgical procedure, and the diagnoses were confirmed in histological reviews (Table 1). The seven living patients were reached for follow-up monitoring, with a mean follow-up period of 40 ± 27 months (range, 22–96 mo). The representative magnetic resonance imaging appearance of these lesions is presented in Figure 1. The mean patient age at the time of surgery was 59.8 years (range, 37–82 yr). Eight patients were female (89%). There

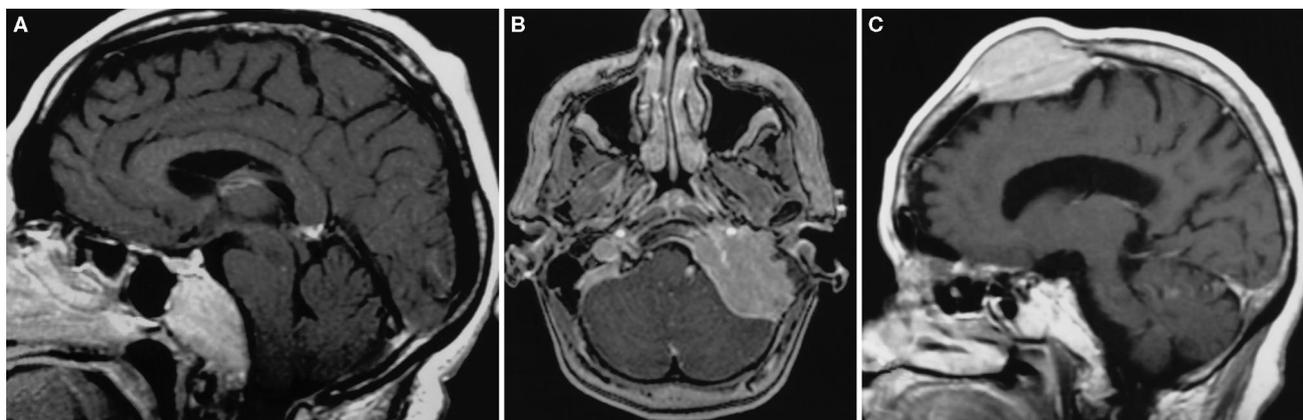


FIGURE 1. Characteristic appearance of isolated intracranial plasmacytomas on magnetic resonance imaging scans, revealing homogeneous contrast enhancement after administration of gadolinium. A, clival; B, petrous; C, calvarial.

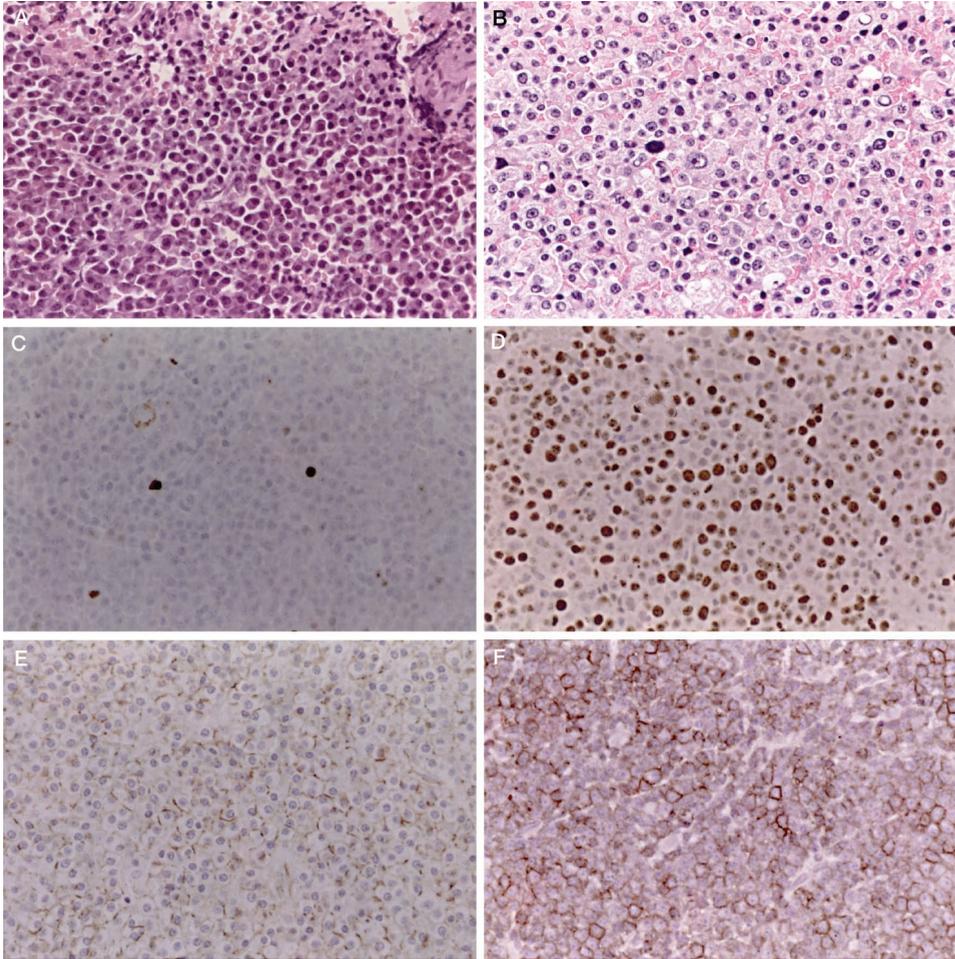


FIGURE 2. *A* and *B*, photomicrographs of tumor sections stained with hematoxylin and eosin, distinguishing between a plasmacytoma (*A*) and a plasmablastoma (*B*). The large vesicular nuclei and basophilic cytoplasm in the plasmablastoma should be noted. *C* and *D*, MIB-1 staining, revealing a low proliferation index in the plasmacytoma (*C*) and a high proliferation index in the plasmablastoma (*D*). *E* and *F*, immunohistochemical staining, demonstrating CD31 positivity (*E*) and CD56 positivity (*F*) in a plasmacytoma (original magnification, $\times 60$).

were five cranial base, one calvarial, and three dural lesions. Two patients had plasmablastic lesions located in the cranial base. Only one patient, with plasmablastic histological findings, was known to have experienced MM before surgery (Table 1). All lesions were monoclonal (five λ chain and four κ chain), with no relationship between location and light-chain type. The two plasmablastic cranial base lesions exhibited MIB-1 indices of more than 50%, whereas the indices for all other lesions were less than 10% (Fig. 2, *C* and *D*). Of the five cranial base lesions, three were CD56-positive and all were CD31-negative (Fig. 2, *E* and *F*). The one calvarial lesion was CD56- and CD31-positive. The three dural lesions were CD56- and CD31-negative.

Six patients underwent subtotal resections and three underwent gross total resections (Table 1). The extent of resection was not correlated with outcomes. Seven of nine patients underwent postoperative fractionated radiotherapy. Clival lesions were treated with the standard MM dose of 2000 cGy, whereas the other intracranial lesions were treated with the higher dose (4000 cGy) recommended for solitary plasmacytomas (17). Two patients (Patients 5 and 6) refused radiotherapy (Table 1).

All six of the patients with intramedullary plasmacytomas developed MM. Five patients had cranial base lesions and one

had a calvarial lesion. Patient 1, with a cranial base lesion, underwent two negative bone marrow biopsies (1 and 10 months after her diagnosis). However, she exhibited increasing immunoglobulin G monoclonal gammopathy and several progressive lytic bone lesions and was given the diagnosis of MM. The two patients with plasmablastic lesions and high proliferation indices both developed MM. One of these patients (Patient 5) experienced recurrence within 4 months after gross total resection and refused radiotherapy. The other patient (Patient 6) had a clival lesion and received only 2000 cGy of radiotherapy. None of the three patients with dural lesions developed MM. One died as a result of complications of cerebral aneurysm surgery and the others are alive, without recurrence or evidence of MM, at 52 and 96 months.

DISCUSSION

Intracranial plasmacytomas are infrequently encountered in neurosurgical practice, and the literature consists predominantly of isolated case reports (10). The largest single series of intracranial plasmacytomas consists of eight cases (5). We report an additional nine cases, including systematic histological and immunohistochemical characterization of these rare tumors. Extracranially, intramedullary plasmacytomas

TABLE 1. Patient Data^a

Patient No.	Age (yr)/ Sex	Location	Histological Findings	Preoperative MM	Immunological Findings	MIB-1 (%)	CD56	CD31	Postoperative MM	Surgery	XRT (cGy)	Intracranial Recurrence	Follow-up Period (mo)
1	43/F	CB, petrous	PC	No	L	<5	+	-	Yes	STR	4500	No	31
2	55/F	CB, clivus	PC	No	L	<5	-	-	Yes	Bx	2000	No	28
3	73/F	CB, petrous	PC	No	K	<5	-	-	Yes	Bx	5040	No	22
4	49/M	CB, clivus	PB	Yes	K	48	+	-	Yes	STR	2000	Yes	26
5	54/F	CB, orbital rim	PB	No	L	60	+	-	Yes	GTR		Yes	4, death
6	82/F	C, frontal	PC	No	L	<5	+	+	Yes	GTR		No	24
7	77/F	D, falx	PC	No	K	8	-	-	No	GTR	4000	No	52
8	68/F	D, frontal	PC	No	K	6	-	-	No	Bx	4000	No	4, death (unrelated)
9	37/F	D, temporal	PC	No	L	<5	-	-	No	GTR	4000	No	96

^a MM, multiple myeloma; MIB-1, MIB-1 labeling index; XRT, radiotherapy; CB, cranial base; C, calvarial; D, dural; PC, plasmacytic; PB, plasmablastic; K, κ chain; L, λ chain; Bx, biopsy; STR, subtotal resection; GTR, gross total resection; +, positive; -, negative.

progress to MM more frequently (approximately 50%) than do extramedullary plasmacytomas (approximately 30%) (8, 14). Intracranially, calvarial lesions and most cranial base lesions, being intramedullary, also have a greater chance of progressing to MM than do dura-based lesions (5, 22, 32). Nevertheless, one review of the literature demonstrated that, of 18 calvarial and 13 dura-based lesions, only 2 calvarial lesions progressed to MM (10). In contrast, our data suggest that intracranial intramedullary plasmacytomas exhibit a much higher rate of progression to MM (six of six lesions) than do intramedullary plasmacytomas in other extracranial locations. This finding was also noted by Bindal et al. (5), who presented two cranial base plasmacytomas and reviewed the literature on intracranial plasmacytomas. They observed that all cranial base-infiltrating plasmacytomas were associated with MM. Extracranially, MM may take several years to develop from a plasmacytoma (22, 37, 38). In fact, some authors recommend a minimum of 3 years without disease progression to establish the diagnosis of solitary plasmacytoma (7, 8). Bindal et al. (5) claimed that, for intracranial plasmacytomas, MM is unlikely to develop at a later time if it is not present at the initial presentation. We report a patient with a cranial base lesion (Patient 1) who underwent two negative postoperative bone marrow biopsies before ultimately manifesting MM 1 year after her diagnosis. Therefore, we recommend that a systemic search for MM should persist for at least 1 year after the discovery of an intracranial plasmacytoma, particularly if the lesion is located in the cranial base.

Histological features and proliferation indices

The differentiation between plasmacytic and plasmablastic morphological features has been well established as having prognostic significance in predictions of survival and recurrence rates for patients with MM (3, 4). This distinction, however, has been applied primarily to bone marrow biopsy specimens and not surgically resected lesions (3, 4). We identified two patients with plasmablastic histological features, both of whom had cranial base lesions associated with MM. Both patients experienced recurrence after treatment, one (Patient 5) after gross total resection and the other after a biopsy and 2000-cGy radiotherapy. These data suggest that clival

plasmacytomas should not be treated with such low doses of radiotherapy if the histological findings reveal plasmablastic histological features; such lesions may require higher doses, as recommended for plasmacytomas (17). Interestingly, both of the plasmablastic lesions exhibited very high proliferation indices. An association between plasmablastic morphological features and elevated Ki-67 fractions was previously reported for myelomatous bone marrow specimens but not intracranial surgical specimens (9).

The proliferative activity of tumors can be measured as the percentage of cells in S phase, in which DNA synthesis and preparation for mitosis occur (11). The monoclonal antibody Ki-67 recognizes a nuclear antigen present in continuously cycling cells in G₁, S, G₂, or M phase but not in G₀ phase. Proliferation indices of human bone marrow can now be determined with archival, paraffin-embedded material (6). Ki-67 has been used in previous studies to differentiate between benign monoclonal gammopathies and more aggressive myelomas (12, 27), and Ki-67 antigen expression is correlated with a tendency to relapse after therapy (9). However, there is a great deal of overlap among similarly low values for Ki-67 antigen expression in plasmacytic MM, monoclonal gammopathy of unknown significance (MGUS), and reactive plasmacytosis, supporting previous evidence that plasmacytic MM has a small growth fraction (18, 26). We also observed higher Ki-67 fractions in the two samples with plasmablastic morphological features, which were correlated with early relapse for both patients.

CD56 and CD31 expression

CD56 and CD31 are members of the immunoglobulin supergene family and share a common structure, i.e., the immunoglobulin homology unit. Molecules belonging to the family include the major histocompatibility molecules, the T cell receptor, the platelet-derived growth factor receptor, the colony-stimulating factor-1 receptor, the vascular cell adhesion molecule, intercellular adhesion molecule-1 (CD54), and carcinoembryonic antigen (35). The functions of these molecules are diverse and include both homophilic and heterophilic interactions occurring during development, inflammation, wound healing, and neoplasia (13).

CD56 is expressed on all human natural killer cells and subsets of T lymphocytes and can be detected on neurons, astrocytes, Schwann cells, and myotubes (15, 30). Roles in cell migration, embryonic development, and cellular adhesion, as both a receptor and an activator of signal transduction, have been suggested (15). Several investigators have examined the presence of CD56 in MM cells, MGUS cells, and normal plasma cells. Whereas 50 to 80% of plasma cells in MM and of monoclonal plasma cells in MGUS express CD56, normal plasma cells and polyclonal plasma cells in MGUS are CD56-negative (2, 15, 21, 25, 27, 30, 31). These findings led several investigators to hypothesize that changes in the density and nature of adhesion molecules may play an important role in the proliferation and malignant transformation of plasma cells, which are controlled via complex interactions between bone marrow stromal cells, extracellular matrix molecules, and cytokines. Although initial reports indicated a possible relationship between CD56 expression and prognosis (30), later studies demonstrated that this is not the case (21). Plasma cell leukemias, however, are CD56-negative, causing speculation that down-regulation of CD56 may permit myeloma cells to escape immune detection (2, 15, 28).

We noted CD56 positivity in none of the dural plasmacytomas, one of one calvarial myelomas, and three of five cranial base myelomas. The finding of expression in 66% of myeloma-related lesions is consistent with reports on myeloma in other locations. Both patients with high MIB-1 indices and plasmablastic lesions exhibited CD56 positivity, but patient numbers were too small to allow any definitive conclusions to be drawn; previous reports failed to link CD56 expression with prognoses, histological features, or proliferation indices (2, 21). CD56 negativity in extramedullary plasmacytomas has not been previously reported. Because normal plasma cells do not express this cell surface antigen, there may be a link between the clonal origin of extramedullary plasmacytomas and antigen expression. A larger study is required to investigate the association between CD56 negativity and the benign prognosis for these lesions.

CD31 is a transmembrane glycoprotein found on the surfaces of platelets, monocytes, granulocytes, and subsets of T and B cells and at endothelial cell intercellular junctions (13, 24). Although its precise function is not known, there is good evidence that CD31 is a key participant, both as an adhesive molecule and as a mediator of signal transduction, in the adhesion cascade that leads to extravasation of leukocytes during the inflammatory process (23). CD31 has also been found on a variety of hemopoietic progenitor cell types and on stromal macrophages from human bone marrow, indicating a possible role in early hematopoietic development (34). CD31 is also a ligand for CD38, a transmembrane receptor that is present on all plasma cells, regardless of their clonality or degree of malignancy (29). Govender et al. (13) observed that normal reactive plasmacytes expressed CD31, as did 50% of extramedullary plasmacytomas. Both extra- and intramedullary MMs, however, were CD31-negative. Those authors hypothesized a role for CD31 in inflammatory interactions that is lost during neoplastic transformation. Vallerio (29), however, reported CD31 positivity not only for normal

plasma cells and MGUS cells but also for 100% of plasmacytic MMs. CD31 negativity was observed for the majority of plasmablastic MM cases, as well as plasma cell leukemia. Our results add little to these previous conflicting reports. We observed CD31 negativity for both intramedullary MM and extramedullary plasmacytoma specimens. One calvarial specimen exhibited positive results. Additional data on the role of CD31 in plasma cell neoplasms are clearly needed.

Treatment recommendations

The literature on intracranial plasmacytomas suggests that the optimal therapy is complete surgical resection followed by at least 5000 cGy of radiotherapy (5, 32). This recommendation seems to be based on two cases in which disease recurred after subtotal resection and 5000-cGy fractionated radiotherapy (5, 20). Cure is achievable, however, with complete surgical resection alone (1) or with a biopsy and radiotherapy, because plasma cell neoplasms are exquisitely radiosensitive (16, 19). For calvarial, dural, or sinus-based lesions for which complete resection is easily achieved, we concur with a management strategy of complete resection followed by radiotherapy. Nevertheless, radiotherapy after a diagnostic biopsy is always a reasonable alternative for treatment of these lesions, particularly for patients with any medical comorbidity.

In light of the overwhelming evidence that cranial base plasma cell neoplasms are universally associated with systemic MM, which bears a 3-year median life expectancy, we prefer to treat these lesions with biopsy or conservative subtotal resection, followed by aggressive radiotherapy (5040 cGy) for control of local disease. Our data indicate that treatment of clival lesions with lower doses may be acceptable, if the histological findings do not reveal plasmablastoma. Whether a higher radiation dose will be more successful in achieving local control of intracranial plasmablastomas is not clear. Our data indicate that much more aggressive attempts at local control with higher doses of radiation are warranted.

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COMMENTS

The authors have attempted to find objective data to predict which cranial plasmacytomas are more likely to be associated with progression to multiple myeloma (MM). Their attempt to use adhesion molecules as a marker was a nice try; unfortunately, it did not work. The association of location (cranial base) with development of systemic disease is interesting; however, the reasons for this connection remain obscure. More primitive histology and a history-labeling index are predictors of MM, so these findings are not surprising. Regardless, these tumors are uncommon in a general neurosurgical practice, and this report contains some interesting data.

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In appreciating this report, readers should bear in mind that the authors' conclusion that "cranial base location was

the strongest predictor of the development of multiple myeloma" in patients with intracranial plasmacytoma is made on the basis of a very small number of patients and ignores that the other bone-based tumor, the calvarial case, also developed MM.

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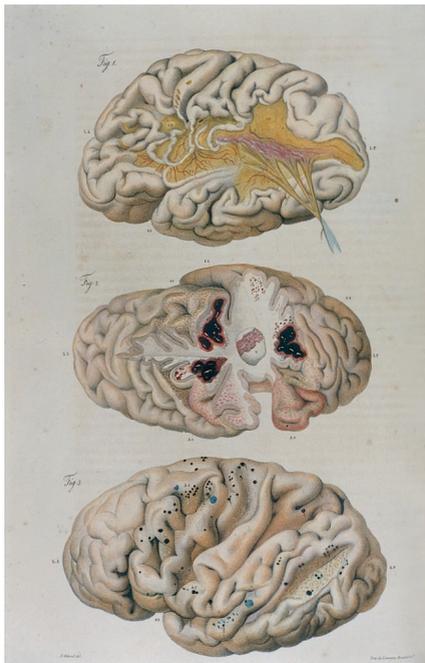
This report by Schwartz et al. introduces a few interesting observations regarding a relatively rare tumor type. The correlations noted in this report, coupled with others described in the literature, suggest that intramedullary lesions, especially those at the cranial base, require aggressive treatment. The discussion regarding histology, proliferation rates, and treatment, although based on a small number of patient observations, will be useful to clinicians.

Jack P. Rock
Detroit, Michigan

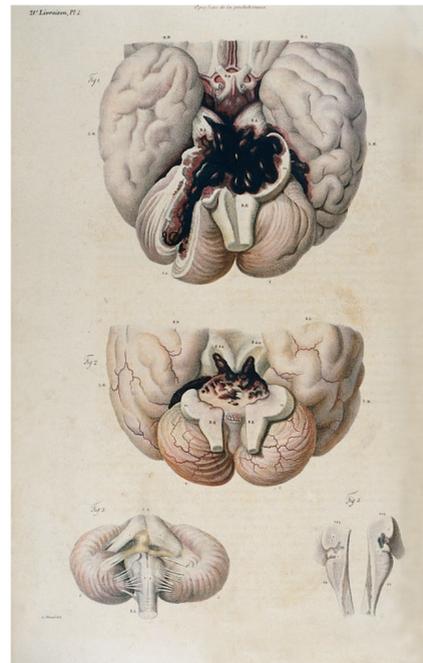
Plasma cell tumors are characterized by a monoclonal proliferation of immunoglobulin-secreting plasma cells. MM represents the disseminated form of this disease. Although iso-

lated plasmacytomas are usually benign lesions, on occasion they can be associated with MM, which also correlates with a much worse prognosis. Expression of various adhesion molecules has been documented in myeloma cells, and this expression is particularly important as one of the indicators of prognosis. Data on cellular adhesion molecules in intracranial plasmacytomas are lacking, and the goal of this study was to examine the expression of these markers in this relatively rare group of intracranial tumors. The results of this relatively small series demonstrate that the expression of various cell adhesion molecules CD31 and CD56 was not predictive of outcome. The authors do demonstrate, however, that a high proliferation index and plasmablastic morphology was predictive of recurrence. In addition, the cranial base location of a plasma cell tumor is the strongest predictor of the development of MM. Perhaps the differences in the cellular development and physiology of the cranial bones versus the peripheral skeletal bones, especially at the cranial base, may play a role in the pathogenesis of this tumor.

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Illustrations of gross pathology of various disease processes of the brain. From, Jean Cruveilhier, *Anatomie pathologique du corps humain, ou Descriptions, avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible*. Paris, Baillière, 1829–1842, vol. 2. (Courtesy, Rare Book Room, Norris Medical Library, Keck School of Medicine, University of Southern California, Los Angeles, California.)



Illustrations of brainstem vascular malformations resulting in apoplexy. From, Jean Cruveilhier, *Anatomie pathologique du corps humain, ou Descriptions, avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible*. Paris, Baillière, 1829–1842, vol. 2. (Courtesy, Rare Book Room, Norris Medical Library, Keck School of Medicine, University of Southern California, Los Angeles, California.)