Meningiomas in Pregnancy: A Clinicopathologic Study of 17 Cases

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BACKGROUND: Dramatic growth of meningiomas is occasionally encountered during pregnancy. While cell proliferation is often assumed, hemodynamic changes have also been touted as a cause.

OBJECTIVE: We identified 17 meningiomas resected during pregnancy or within 3 weeks post-partum and characterized them to determine the cause of occasional rapid growth in pregnancy.

METHODS: Seventeen tumors were identified from searches at 4 university centers. All available clinical records, radiology images, and tissue specimens were reviewed, with immunohistochemical studies performed as needed.

RESULTS: Sixteen patients underwent tumor resection and 1 died of complications prior to surgery. Average patient age was 32 years. Nine experienced onset of symptoms in the third trimester or within 8 days post-partum. Principle physical findings included visual complaints (59%) and cranial nerve palsies (29%). Ten tumors (59%) were located in the skull base region. The Ki-67 labeling index was low (0.5-3.6%) in 11 of 13 benign (grade I) tumors and elevated (11-23.2%) in 3 of 4 atypical (grade II) meningiomas. Eight (50%) tumors featured hypervascularity with at least focal CD34-positive hemangioma-like microvasculature. Fourteen (82%) showed evidence of intra- and/or extracellular edema, 1 so extensive that its meningothelial nature was not apparent. Five tumors (29%) exhibited intratumoral hemorrhage and/or necrosis.

CONCLUSION: Our series suggests that pregnancy-associated meningiomas located in the skull base are likely to require surgical intervention for visual complaints and cranial nerve palsies. The rapid tumor growth is more often due to potentially reversible hemodynamic changes rather than hormone-induced cellular proliferation.

KEY WORDS: Meningioma, Pathology, Pregnancy

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Meningiomas are common tumors comprising over 30% of all primary central nervous system (CNS) tumors.[1] Although most are benign and curable by surgery, roughly 20% are clinically aggressive and require adjuvant therapy, usually irradiation.[2] The female gender predilection of meningiomas is 2:1, a ratio that increases to 7:1 when considering only spinal lesions of the spine.[1,3,4] Given this strong gender bias, some have suggested that the origin and growth of meningiomas may be related to female sex steroid production. Although the vast majority of meningiomas lack estrogen receptor, up to 80% of benign meningiomas express progesterone receptor (PR). The latter is decreased in high-grade tumors, with levels being roughly inversely related to progression-free survival.[5-7] Some epidemiologic studies suggest an association between breast cancer and meningioma,[8,9] while others suggest an association between exogenous or endogenous hormones and meningioma risk.[10-12] Menopausal women have very low levels of circulating progesterone and perhaps a reduced risk of developing meningioma.[13] All of these associations are relatively weak and remain controversial, particularly since the meningiomas of both children and men, having little circulating progesterone, are nearly as often PR positive as those of 5 women of childbearing age.[14,15]

ABBREVIATION: CI, confidence interval

In 1929, Cushing and Eisenhardt described the case of a 52-year-old woman who at age 38

presented with progressive left visual loss during pregnancy. It improved after delivery only to recur with the next pregnancy 6 years later and progress to blindness in the left eye; this proved to be due to a very large tuberculum sellae meningioma.[16] Since that time, there have been a number of reports of meningiomas enlarging or becoming symptomatic during pregnancy or even the luteal phase of the menstrual cycle. In pregnancy-associated cases, regression in tumor size and severity of symptoms often follows delivery, but relapses are noted during subsequent pregnancies.[17-22] Several authors have hypothesized about the causes of increased growth during pregnancy. One of the most common assumptions, even today, is that tumor growth is the result of hormone-induced cell proliferation,[21,23,24] an unlikely suggestion since one would not expect cellular expansion to be reversible upon delivery. In 1950, Rand and Andler reported a series of brain tumors presenting during pregnancy, including 1 meningioma, and stated that "pregnancy hastens the growth of tumor . . . it is our impression that the altered metabolism of the body at this time may accelerate tumor growth."[21] In that same year, King postulated that dramatic growth of meningiomas during pregnancy is probably due to "engorgement of the blood vessels" and that "the usual rate of growth is not materially increased.[20] In 1951, Weyand et al reported a series of pregnancy-associated changes in 10 patients with meningiomas occurring near the optic chiasm. While only 2 tumors were resected during pregnancy, the authors noted that, microscopically, the cells featured "foamy and swollen" cytoplasm. They concluded that the change observed could be caused by an increase in intracellular fluid.[22] Since such cases have been largely case reports or small series focusing mainly upon clinical features, this mechanistic question has not been adequately addressed. In the current study, we examined 17 meningiomas resected during pregnancy or within 3 weeks postpartum to identify clinicopathologic features elucidating the mechanism of pregnancy-associated tumoral growth.

PATIENTS AND METHODS

Clinical Cases

With IRB approval, the pathology reports from 1955 to 2010 at 4 university centers were searched for the diagnosis of meningioma and the terms "pregnancy," "pregnant," or "post-partum" in the submitted clinical history. Seventeen tumors were identified: 10 from the Mayo Clinic, 3 from Washington University, 3 from Muenster University, and 1 from the University of Florida. Those resected during pregnancy or after a short post partum interval, defined as 3 weeks, were retrieved for further study. All available clinical records, radiology images, and tissue specimens were reviewed, with immunohistochemical studies being performed as needed. The tumors were compared with a control group of 18 age-matched, non-pregnant female patients with spheno-orbital (SO) meningiomas; this control group of women with meningiomas in skull base locations was selected given that the majority (59%) of the study cohort of women similarly had tumors in this location.

Pathology

Each meningioma was graded and subtyped based upon the most recent World Health Organization (WHO) classification scheme.[25] Their degree of tumoral vascularity was scored subjectively on both H&E and CD34 immunostained sections (see below). Comparisons with the control group were based upon the same criteria. Hypervascularity was defined by the presence of regions wherein blood vessels either a) comprised over half of the tumoral area or b) formed tight clusters of angioma-like microvasculature. The presence of intracellular or stromal edema was also recorded, the former consisting of clear, foamy or vacuolated tumor cells and the latter of loose, clear to myxoid/mucoid extracellular fluid. In some cases, the changes bore a resemblance to microcystic or chordoid morphology, although in most they lacked the degenerative changes typically seen in the former and the trabecular architecture of the latter. As additional evidence of hemodynamic changes, the presence of spontaneous hemorrhage and/or necrosis was also recorded. In terms of estimating cell proliferation, both mitotic indices and Ki-67 labeling indices were recorded and compared to control group values (see below). The mitotic index was based upon the highest mitotic count obtainable over any 10 consecutive high power (40×) fields within each tumor. The Ki-67 labeling index (LI) was similarly based upon assessment of "hot spots," being expressed as a percentage of positive nuclei among 500 to 1000 consecutive nuclei counted in maximally active portions of the specimen. Based on a prior clinicopathological study by 2 of the authors, a high Ki-67 LI was defined as being greater than 4.2%.[26]

Immunohistochemistry

Immunohistochemical studies were performed utilizing antibodies directed against epithelial membrane antigen (EMA) (Ventana, Tucson, Arizona; clone 30-9, prediluted), progesterone receptor (PR) (Ventana, clone 1E2, prediluted), estrogen receptor (ER) (Ventana, clone SP1, prediluted), CD34 (Ventana, clone QBEnd/10, prediluted), and MIB-1 (Ki-67) (Ventana, clone 30-9, prediluted) and are summarized in Table 1. As previously described,[27] a Ventana Benchmark XT immunostainer (Ventana Medical Systems; Tucson, Arizona) was utilized. All slides were counterstained with hematoxylin. Omission of the primary antibody

TABLE 1. Antibody Dilutions and Sources[a]

Antibody	Host	Clone	Manufacturer	Location	Dilution
Ki-67	Rabbit	30-9	Ventana	Tucson, Arizona	Prediluted
EMA	Mouse	E29	Ventana	Tucson, Arizona	Prediluted
ER	Rabbit	SP1	Ventana	Tucson, Arizona	Prediluted
PR	Rabbit	1E2	Ventana	Tucson, Arizona	Prediluted
CD 34	Mouse	QB End/10	Ventana	Tucson, Arizona	Prediluted

[a]EMA, epithelial membrane antigen; ER, estrogen receptor; PR, progesterone receptor.

served a negative control. Appropriate positive controls were utilized as recommended by the manufacturer. The scoring scale used for PR, ER and EMA reactivity was as follows: 0 = <5% cellular staining, 1+ = 5 to 20%, 2+ = 20 to 90% and 3+ = >90%. CD34 immunostaining was compared to that of the SO non-pregnant meningioma cohort. Vascularity was recorded as normal, focally increased, or markedly/diffusely increased.

Statistical Analysis

Statistical analysis was done using Graph Pad Prism 5 (La Jolla, California). Fisher's exact test was used in the analysis 2×2 contingency tables. This was used to compare the meningioma pregnancy group and the control group in the different histological and immunohistochemical variables. Non-informative results were not included in the calculation and results were considered significant with a P value $< .05$.

RESULTS

Clinical Presentation

Of the 17 patients with meningioma during pregnancy or within 3 weeks post-partum, 16 underwent a surgical resection and 1 died preoperatively of complications of mass effect. We reviewed imaging studies in only 3 cases. Figures 1 and 2 are representative computed tomography (CT) and magnetic resonance (MR) images respectively, from patient 2 with an intracranial meningioma that had become acutely symptomatic, developing headache and right VIIth cranial nerve palsy. A non-contrast CT revealed a right-sided lesion with peritumoral edema (Figure 1A). An MRI scan performed the next day showed a large right sphenoid wing meningioma with cavernous sinus extension (Figure 2). The following day, worsening headache and new left-sided hemiparesis prompted an interval head CT scan (Figure 1B), which showed a dramatic increase in peritumoral edema, increase in the size of the meningioma, and possible intratumoral hemorrhage. The only patient not undergoing surgery (case 5) developed acute headache 8 days post partum. Before surgery could be performed, she died. An autopsy revealed a large (6×3.5 cm) edematous-appearing olfactory groove/tuberculum sellae meningioma with associated diffuse cerebral edema and bilateral uncal as well as tonsillar herniation.

Table 2 describes the demographics, presentation and location of the meningiomas presenting during pregnancy, in comparison to the control group of SO meningiomas in non-pregnant women (Table 3). Ten (59%) were located at the skull base. Three (18%) involved eloquent regions overlying the motor cortex (n = 2) or the occipital lobe (n = 1), and caused rapidly progressive hemiparesis or visual loss, respectively. The other 4 patients developed new onset of seizures, increasing frequency of seizures, or massive cerebral edema requiring urgent neurosurgical attention. Principle physical findings in these patients included visual complaints in 10 cases (59%) and cranial nerve palsy in 5 (29%).

The mean and median ages of the patients were 32 and 33 years, respectively. Only 1 patient presenting to neurosurgical attention was less than age 20. Five patients (29%) presented from 21 to 30 years of age, and 11 (65%) between 31 and 40. Most patients became neurologically symptomatic at the mid to latter stages of pregnancy. Three patients (18%) presented in their first trimester, 5 (29%) during the second, and 7 (41%) during the third. Two patients became neurologically symptomatic post partum, all within 8 days of delivery. Two patients became symptomatic during their first pregnancy, while 4 each presented during pregnancies number 2, 3, and greater. Parity was unknown in 3 patients.

Pathology

Histological characteristics are summarized in Table 4 for the study cohort and Table 5 for the control group, with corresponding immunohistochemical data listed in Tables 6 and 7 representative histopathologic images are shown (Figures 3 and 4). There were 13 WHO grade I (76%) and 4 WHO grade II (24%) tumors. The Ki-67 labeling index was low in all but 2 WHO grade I meningiomas and was >4.2% in 3 of 4 WHO grade II lesions (3.5%, 11%, 11.6%, and 23.2%). Of the 2 grade I meningiomas with elevated indices, 1 was borderline (4.5%), and the other clearly high (8.4%; case 13), although the latter specimen included a significant inflammatory infiltrate that likely inflated the labeling index. Fourteen of the tumors (82%) showed evidence of intracellular and/or intercellular edema, 1 (patient 2) so extensive that meningioma features were obscured (Figure 3A). The tumor was, however, strongly immunoreactive for both EMA and PR (Figure 3B). The latter stain highlighted cells with large, clear cytoplasmic vacuoles peripherally displacing the nucleus and imparting a signet-ring cytology (Figure 3B arrows). Five of the tumors exhibited spontaneous intratumoral hemorrhage and/or necrosis (Figure 3C-D). None of the spheno-orbital control meningiomas derived from non-pregnant patients showed similar foci of edema, spontaneous necrosis, or hemorrhage, which were both statistically significant (Edema- $P < .001$; Fisher's exact test, necrosis and/or hemorrhage; <0.0191; Fisher's exact test). There were, however, no significant statistical differences in grade distribution or proliferative indices. These results are summarized in Table 8.

Immunohistochemistry

Tables 6 and 7 summarize the immunostaining results in meningiomas of pregnancy and control meningiomas, respectively. All but 2 study tumors were extensively (2-3+) progesterone receptor-positive (Figure 3B), a similar proportion to that of the control group. Only 1 of the meningiomas demonstrated weak estrogen receptor positivity; the remainder were negative. Eleven meningiomas demonstrated extensive EMA positivity, a figure similar to that of the control group. In 1 extensively vascular, angioma-like tumor (Figure 4A-B), the

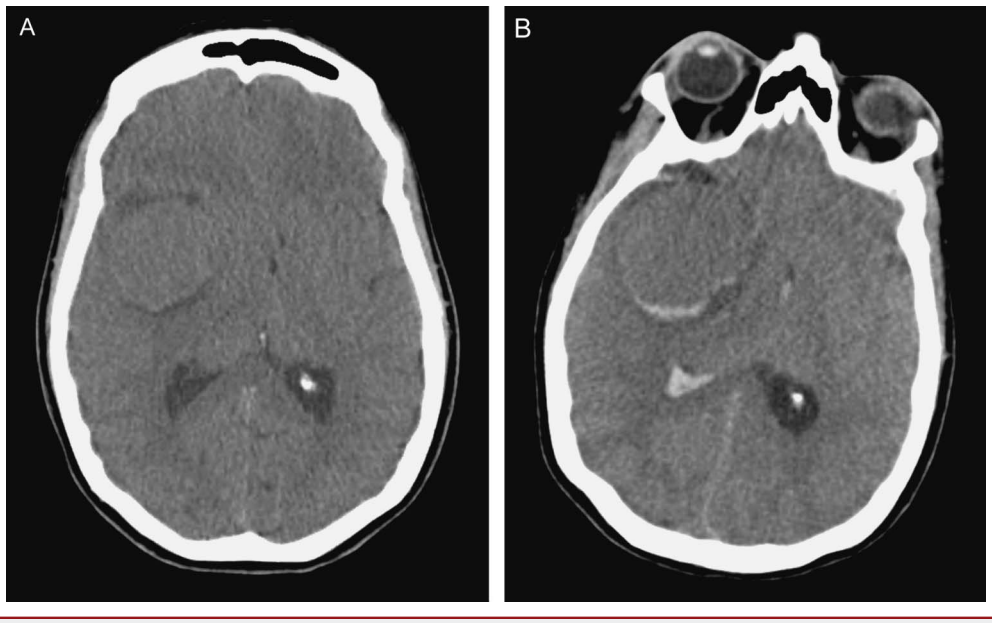

FIGURE 1. *Case z. Noncontrast computed tomography scans at initial presentation (A) and 2 days later (B) demonstrating a dramatic increase in tumor size, peritumoral edema, and possible lesional hemorrhage.*

stain highlighted small clusters of meningothelial cells between blood vessels, not readily evident on H&E sections (Figure 4C). On CD34 stain, 8 (50%) tumors featured hypervascularity, which was either extensive (Figure 4B) or formed focal hemangioma-like microvascular aggregates (Figure 4D), a rate greater than that of the control group (24%), although the difference did not meet statistical significance (P = .16; Fisher's exact test). These results are summarized in Table 8.

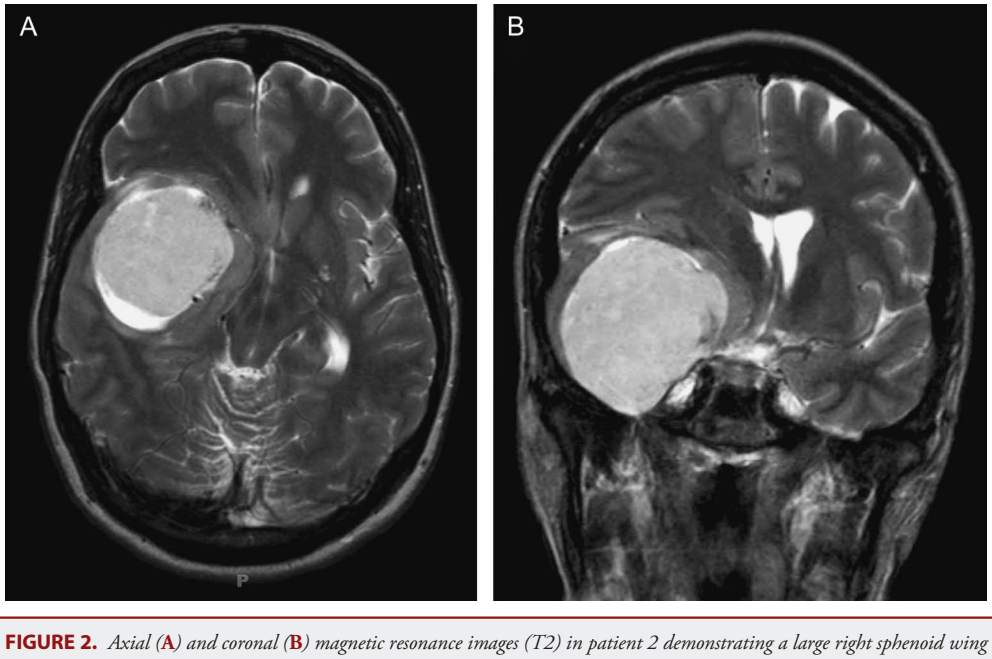

FIGURE 2. *Axial (A) and coronal (B) magnetic resonance images (T2) in patient 2 demonstrating a large right sphenoid wing meningioma with cavernous sinus extension. Histology revealed an atypical meningioma with marked intratumoral edema (Figure 3A and 3B).*

TABLE 2. Clinical Information: Pregnancy Group[a]

Patient	Age, y	Pregnancy	Trimester Symptoms Began	Timing of Surgery to Delivery	Similar Symptoms in Previous Pregnancies	Neurological Presentation	Skull Base?	Anatomic Location
1	39	Unknown	Third	3 d PP	Unknown	Vision loss	Y	Tuberculum sellae
2	40	G8P6	Third	Same day	No	CN VII palsy, L HP	Y	R sphenoid wing, cavernous sinus extension
3	39	G3P2	Second	3 wk PP	Yes	Diplopia, ptosis/ vision loss R eye, HA	Y	Dorsum sellae, cavernous sinus extension, petrous pyramid
4	33	G2P1	Third	15 d after CS	No	Diplopia, R CN VI, VII, and XII palsy	Y	R CPA, cavernous sinus extension, petrous apex
5	34	Unknown	PP	No surgery	Unknown	HA, cerebral edema	Y	Tuberculum sellae, olfactory groove
6	28	G1P0	PP	10 d PP	. . .	HA, R CN III palsy, ptosis	Y	R anterior clinoid, tuberculum sellae
7	32	G3P2	Third	2 d PP	No	L HP, L dysmetria	N	R parafalcine at precentral gyrus
8	19	unk	Second	13 wk pregnant	Unknown	HA, R vision loss	N	R tentorium with transverse sinus invasion
9	29	G3P1	Second	25 wk pregnant	No	HA, R vision loss	Y	R anterior clinoid
10	35	G2P1	First	10 wk pregnant	No	HA, R CN VI palsy, B papilledema	N	R frontal parasagittal
11	36	G4P1	Second	24 wk pregnant	No	L vision loss, ocular pain	Y	Olfactory groove, planum sphenoidale, L cavernous sinus invasion
12	38	G3P2	Third	34 wk pregnant	No	R HP	N	L parasagittal at precentral gyrus
13	22	Unknown	Third	2 wk PP	Unknown	HA, multiple GTC seizures	N	R frontal parasagittal
14	33	G2P1	Second	34 wk pregnant	Unknown	R vision loss, L eye hemianopsia	Y	Tuberculum sellae
15	37	G5P3	Third	3 d PP	Unknown	Seizures	N	L parietal parasagittal
16	25	G4P3	First	12 wk pregnant	Unknown	Seizures	N	R parasagittal
17	25	G2P1	First	12 wk pregnant	Yes	B decreased vision, HA/vomiting	Y	Tuberculum sellae and olfactory groove

[a]B, bilateral; CN, cranial nerve; CPA, cerebellopontine angle; CS, cesarean section; Dec, decreased; GTC, generalized tonic clonic seizure; HA, headache; HP, hemiparesis; PP, postpartum.

DISCUSSION

The association between pregnancy and rapid growth of meningioma has long been appreciated, but its basis remains disputed.[20-22] To address this issue, we report the clinicopathologic features of 17 meningiomas resected in pregnancy. Nevertheless, it is important to note that such series represent a biased study cohort, since both meningiomas and pregnancy are common, but surgery for meningiomas during pregnancy is rare. As such, it is likely that most meningiomas are clinicopathologically indistinguishable from ones unassociated with pregnancy, while only the most problematic tumors are resected and pathologically examined. With that in mind, meningiomas in pregnancy remain of interest given their potential for sudden, occasionally life-threatening growth, which was the case in patient 5 of our series.

The majority of our pregnancy-associated meningiomas were located at the skull base (59%), a finding in keeping with the report by Roelvink et al[28] who reviewed 86 published pregnancy-associated meningiomas, with 62 (60%) being similarly situated. This is considerably higher than the 35% frequency of skull base meningiomas in the general population.[29,30] Roelvink felt this was unexpected in pregnancy since basal meningiomas, more prone to interfere with hypothalamic function, should decrease fertility. However, it seems more probable that such cases are over-represented in a surgical series because rapidly growing basal meningiomas are more likely to present with severe clinical problems, given their proximity to eloquent structures, such as the optic pathway and several cranial nerves. The urgency of complications increases the likelihood of surgical intervention during pregnancy. Although it was possible that these meningiomas are biologically different, with the exception of the

TABLE 3. Clinical Summary: Control Group

Patient	Age, y	Neurological Presentation	Skull Base?	Anatomic Location
1	15	Proptosis	Y	R spheno-orbital
2	56	Retro-orbital pain/pressure	Y	R frontotemporal spheno-orbital
3	43	R visual deterioration	Y	R lateral sphenoid wing/anterior clinoid
4	43	Proptosis/visual acuity decline	Y	L lateral sphenoid wing
5	66	Proptosis and increased lacrimation	Y	R orbital sphenoid
6	49	Proptosis and increased lacrimation/retro-orbital pain	Y	R anterior sphenoid wing/spheno-orbital
7	53	Proptosis	Y	L spheno-orbital
8	50	Proptosis/visual acuity decline	Y	R lateral sphenoid wing/spheno-orbital
9	51	Proptosis/visual acuity decline	Y	L spheno-orbital
10	34	R visual deterioration	Y	R spheno-orbital
11	70	Proptosis	Y	L spheno-orbital
12	50	Proptosis	Y	L spheno-orbital/sphenoid wing
13	42	Proptosis/headache	Y	L spheno-orbital
14	45	Proptosis/vision loss	Y	L lateral sphenoid wing
15	39	Proptosis	Y	L orbital sphenoid
16	44	Proptosis/visual acuity decline	Y	R lateral sphenoid wing/spheno-orbital
17	49	Visual acuity decline	Y	L medial sphenoid wing/convexity
18	45	Peri-orbital pain, proptosis	Y	L lateral sphenoid wing

hemodynamic changes, we otherwise observed features similar to those of conventional meningiomas.

Another location where very little growth could cause profound neurological findings is with spinal meningiomas. While none of our cohort was spinal meningiomas there is some discussion of these in the literature. In a large review of brain and spinal tumors in pregnancy,[28] 5 of 62 (8%) meningiomas presenting in pregnancy were spinal. In another paper, reporting 122 spinal meningiomas operated on at 1 institution, 2 (1.5%) presented during pregnancy. There were 4 other spinal meningiomas included in their literature review.[31] It was hypothesized that, like meningiomas in the parasellar region, in spinal meningiomas "...only a small increase in size is required to produce quite a dramatic increase in symptoms..., room for expansion being limited."

Also of note in our series is that a) the study population was older than is typical for child-bearing years and b) the majority of

TABLE 4. Histological Characteristics: Pregnancy Group[a]

Case	WHO Grade	Subtype	Mitoses	Whorls	Psammoma	Vascularity	Edema	Hemorrhage or Necrosis
1	I	Men	Rare	Yes	Yes	Marked	Focal IC	No
2	II	...	8/10 HPF	No	No	Marked	EC	No
3	I	Men	Rare	Yes	No	Avg	Mild EC	No
4	I	Men	Rare	Yes	Yes	Avg	EC	Yes
5	I	Fib	Rare	Yes	No	Avg	EC	No
6	I	Men	Rare	Yes	Yes	Avg	Mild EC	No
7	II	...	5/10 HPF	No	No	Avg	EC	Yes
8	I	Trans	Rare	Yes	Yes	Avg	Mild EC	Yes
9	I	Trans	Rare	Yes	Yes	Avg	Focal EC	No
10	I	Men	1/10 HPF	Yes	No	Avg	None	Yes
11	I	Trans	2/10 HPF	Yes	Yes	Avg	Focal EC	No
12	II	...	4/10 HPF	No	No	Avg	Marked EC	No
13	I	Fib	1/10 HPF	No	No	Avg	Marked EC	No
14	I	Men/Mic	Rare	Yes	Yes	Marked	EC	No
15	I	Trans	Rare	Yes	Yes	Avg	None	No
16	II	...	4/10 HPF	Yes	Yes	Avg	Patchy EC	Yes
17	I	Men	Rare	Yes	Yes	Avg	None	No

[a]Aty, atypical; Avg, average; Chord, chordoid; EC, extracellular (loose, microcystic appearance with clear to myxoid appearance); Fib, fibrous; Focal IC, focal intracellular (clear to vacuolated cytoplasm); HPF, high-powered field; Marked, marked hypervascularity on routine hematoxylin and eosin stains; Men, meningothelial; Mic, microcystic; Trans, transitional; WHO, World Health Organization.

TABLE 5. Histological Characteristics: Control Group[a]

Case	WHO Grade	Subtype	Mitoses	Whorls	Psammoma	Vascularity	Edema	Hemorrhage or Necrosis
1	II	. . .	Rare	No	No	Avg	None	No
2	I	Trans	Rare	Yes	No	Avg	None	No
3	I	Men	Rare	Yes	Yes	Avg	None	No
4	I	Men	Rare	Yes	No	Avg	None	No
5	I	Sec	Rare	Yes	Yes	Avg	None	No
6	I	Men	Rare	No	Yes	Avg	None	No
7	I	Trans	Rare	Yes	No	Avg	None	No
8	I	Sec	Rare	Yes	No	Avg	None	No
9	I	Men	Rare	No	No	Avg	None	No
10	I	Trans	Rare	No	No	Avg	None	No
11	II	. . .	Rare	Yes	No	Avg	None	No
12	II	. . .	8/10 HPF	Yes	No	Avg	None	No
13	I	Trans	Rare	Yes	Yes	Avg	None	No
14	II	. . .	Rare	No	No	Avg	None	No
15	I	Trans	Rare	Yes	Yes	Avg	None	No
16	II	. . .	Rare	Yes	No	Avg	None	No
17	I	Trans	Rare	Yes	No	Avg	None	No
18	I	Men	Rare	No	No	Avg	None	No

[a]Avg, average; HPF, high-powered field; Marked, marked hypervascularity on routine hematoxylin and eosin stains; Men, meningothelial; Sec, secretory; Trans, transitional; WHO, World Health Organization.

patients presented late in pregnancy. In addition, all but 2 tumors were extensively progesterone receptor immunopositive, while only 1 was minimally estrogen positive. This is typical of meningiomas in general and similar to the results of a recent study of sex hormone receptor expression in pregnancy-associated giant meningiomas, where all 3 tumors were progesterone receptor-positive, none expressing estrogen receptor.[32] Like our series, the review of Roelvink[28] also found that presentation with meningioma increased gradually in the second and third trimesters. In 1 clinical study of meningioma management during pregnancy, all

TABLE 6. Immunohistochemical Results: Pregnancy Group[a]

Case	EMA	PR	ER	CD34	Ki-67 LI, %
1	3+	3+	0	Marked	1
2	3+	3+	1+	Marked	23.2
3	3+	3+	0	Normal	2.8
4	2+	3+	0	Focal	0.8
5	2+	2+	0	Normal	NI
6	2+	3+	0	Focal	4.5
7	3+	2+	0	Focal	11.6
8	1+	2+	0	Focal	2.7
9	2+	3+	0	Normal	2.3
10	3+	1+	0	NI	1.9
11	1+	2+	0	Focal	3.6
12	3+	3+	0	Normal	11.0
13	1+	1+	0	Normal	8.4
14	3+	2+	0	Focal	1.6
15	1+	2+	0	Normal	0.7
16	1+	2+	0	Normal	3.5
17	1+	2+	0	Normal	1.9

[a]CD34, endothelial marker allowing measure of tumor vascularity; EMA, epithelial membrane antigen; ER, estrogen receptor; Focal, focally increased microvasculature; Ki-67 LI, Ki-67 labeling index; NI, noninformative; PR, progesterone receptor.

TABLE 7. Immunohistochemical Results: Control Group[a]

Case	EMA	PR	CD34	Ki-67 LI, %
1	. . .	. . .	. . .	12.5
2	. . .	3+	Normal	1
3	2+	3+	Normal	NI
4	2+	2+	Marked	1.9
5	1+	3+	Normal	NI
6	3+	3+	Normal	NI
7	. . .	3+	Focal	1.5
8	2+	3+	Normal	NI
9	3+	3+	Normal	2.5
10	3+	3+	Normal	3.1
11	. . .	3+	NI	2.5
12	2+	2+	Focal	NI
13	1+	3+	Normal	1
14	3+	3+	Normal	1.5
15	3+	3+	Normal	2.9
16	. . .	3+	NI	6
17	3+	3+	Normal	NI
18	2+	3+	Focal	2.3

[a]CD34, endothelial marker allowing measure of tumor vascularity; EMA, epithelial membrane antigen; Focal, focally increased microvasculature; Ki-67 LI, Ki-67 labeling index; NI, noninformative; PR, progesterone receptor.

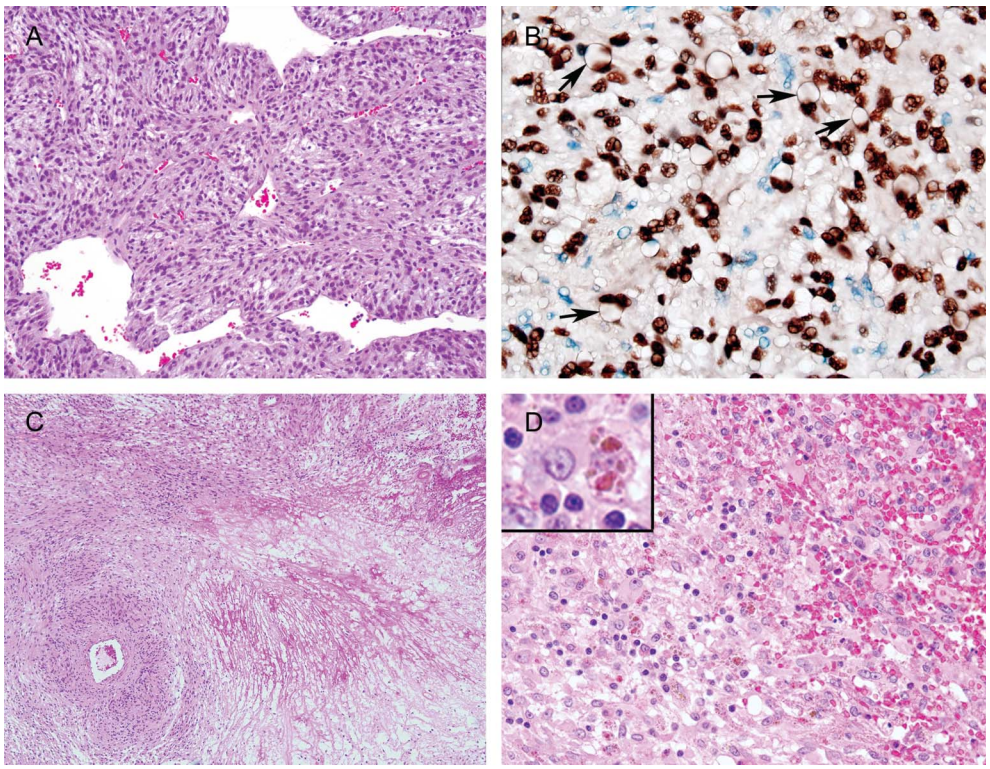

FIGURE 3. *Photomicrographs of representative pregnancy-associated meningiomas. Case 2 was striking for loose edematous stroma throughout the tumor (**A**) and focally increased, staghornlike vasculature reminiscent of hemangiopericytoma. The meningothelial nature of this tumor was confirmed by the presence of strong epithelial membrane antigen expression and (**B**) diffuse progesterone receptor nuclear staining, which highlighted signet ring-like cells containing large, clear, perinuclear cytoplasmic vacuoles (arrows), a finding interpreted as intracellular edema. Case 7 showed foci of both spontaneous intratumoral necrosis (**C**, right half) and remote hemorrhage (**D**, top right) characterized by hemosiderin deposition (inset).*

18 patients presented during the last 2 trimesters.[33] Since progesterone levels increase at least 5-fold over the course of pregnancy,[13] it has been hypothesized that the rapid growth of meningioma may be more progesterone- than estrogen-related.[34] This is in keeping with the fact that meningiomas do not enlarge during the follicular phase of menstruation when estrogen levels are highest but during the luteal phase when progesterone levels peak.[13,34] In addition, exogenous estrogen therapy does not increase meningioma risk.[10,11] We also found that parity had no significant effect upon the development of symptomatic meningiomas during pregnancy, a finding also noted by others.[35] Nonetheless, progesterone "stimulation," be it through increased cell proliferation or by the induction of hemodynamic changes, may be an oversimplification. The frequency of PR positivity was similar in our pregnancy-associated and control group tumors. As previously stated, PR is expressed in meningiomas of children and of men, patients in whom circulating progesterone levels are minimal. Thus, it seems unlikely that progesterone levels alone explain meningioma growth. Since the hormonal and growth factor milieu of pregnancy is complex, further studies are needed to evaluate the potential roles of other factors. Another consideration is the association of progesterone levels and vascular changes. Relatively little is known about progesterone's effects on normal cerebral blood vessels, much less about tumor-associated vessels. Nonetheless, there is some evidence to suggest that progesterone increases cerebrovascular inflammation and vascular dilatation[36]; this could contribute to reversible growth, although further studies are needed to further address this question.

In exploring the basis of rapid tumor growth during pregnancy, several mechanisms have been postulated, including accelerated cellular proliferation,[21] dramatic increase in tumor-associated vascularity,[20] and increases in intracellular fluid.[22] Our case series provides evidence against cell division as a factor in rapid tumor growth in most cases, since neither grade nor proliferation indices differed significantly between study and control cases. If we combine 3 recent studies[32,33,37] of meningiomas resected during pregnancy (n = 22), the frequency of high-grade tumors is even lower than in our series, 20 (91%) being WHO grade I meningiomas and only 2 (9%) atypical (WHO grade II). Thus, while we cannot exclude the rare occurrence of pregnancy-induced

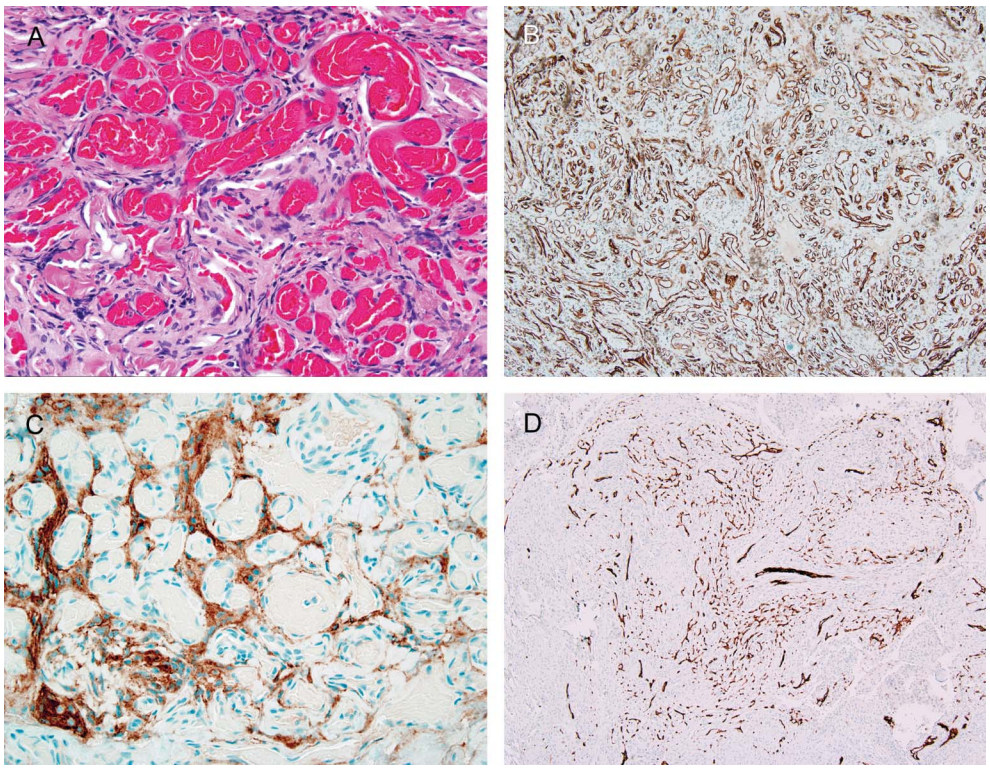

FIGURE 4. *Photomicrographs of representative cases demonstrating hypervascularity. Case 1 showed large foci of hemangiomalike vascular proliferation (A), markedly increased vascularity on CD34 immunostaining (B), and small epithelial membrane antigen-positive meningothelial clusters between blood vessels (C). In contrast, case 8 showed only focal evidence of hypervascularity on CD34 stain (D).*

cellular proliferation in individual cases, it does not appear to play a significant role in most.

On both H&E stain as well as on CD34 stain for endothelial cells, a significant fraction (50%) of our meningiomas in pregnancy exhibited increased vascularity. The same could be seen in 24% of the non-pregnancy-associated meningiomas. Perhaps due to insufficient case numbers, this trend towards increased vascularity in the latter fell short of statistical

TABLE 8. Pregnancy vs Control Characteristics Summary and *P* Values[a]

Characteristic	Pregnancy Group, n (%)	Control Group, n (%)	*P*
Grade I vs II	13 (76)	13 (72)	1.00
Whorls	13 (76)	12 (67)	.71
Psammoma bodies	10 (59)	5 (28)	.09
Vascularity	3 (18)	0 (0)	.10
Edema	14 (82)	0 (0)	<.001[b]
Hemorrhage/necrosis	5 (29)	0 (0)	.02
EMA (2-3+)	11 (65)	11 (85)	.41
PR (2-3+)	15 (88)	17 (100)	.48
Ki-67 LI (>4.2%)	5 (32)	2 (17)	.66
CD34 (increased)	8 (50)	4 (24)	.16

[a]CD34, endothelial marker allowing measure of tumor vascularity; EMA, epithelial membrane antigen; ER, estrogen receptor; Ki-67 LI, Ki-67 labeling index; PR, progesterone receptor. *P* value is by the Fisher exact test.
[b]Significant.

significance. However, even more tumors (82%) displayed at least focal intra- and/or extracellular edema, a finding not seen in tumors of the control cohort ($P < .001$; Fisher's Exact test). This had first been noted in a 1951 study of 10 symptomatic, pregnancy-associated meningiomas near the optic chiasm.[22] Both of the histologically examined tumors featured cytoplasm that "appeared foamy and swollen." In our cases, stromal edema was the more common of the 2 patterns, often creating either a vaguely microcystic or somewhat chordoid appearance depending upon whether the fluid was mostly clear or myxoid/mucoid. In 1 example, it was so extensive that the meningothelial nature of the tumor was obscured on routine stains, necessitating ancillary stains to establish the diagnosis. It is unclear of the mechanism for this, but 1 study showed that during pregnancy in rats there is an increase in aquaporin 4, a water channel associated with brain edema, around intracerebral blood vessels.[38] Whether this is similarly true in the blood vessels of human meningioma during pregnancy would require further studies.

In addition to the increased edema, 5 cases (29%) were found to exhibit at least minor spontaneous intratumoral hemorrhage and/or necrosis. All 3 of these findings, tumoral hypervascularity, edema, and hemorrhage/necrosis, suggest vascular/hemodynamic effects that could potentially explain both the rapid increase in tumor size during pregnancy as well as the frequent partial regression post-partum. Of further interest is the fact that these potentially reversible hemodynamic changes appear to recur during subsequent pregnancies. In considering this we looked whether there was also an association with posterior reversible encephalopathy syndrome (PRES), a syndrome thought to be caused by altered hemodynamics, but were not able to find such an association, either sporadically or pregnancy related.

We feel that this study is particularly important because there is currently a common misconception by physicians that progesterone stimulates cellular proliferation in meningiomas during pregnancy or during hormonal therapy/contraceptive use, a misconception which has even led to occasional malpractice claims. However, our study does not support this conclusion and elucidates other potential mechanisms of growth during pregnancy, most of which seem reversible.

Based on our data and the available literature, for the vast majority of women of child bearing age, we would not consider the presence of residual or unresected meningioma to be a contraindication to pregnancy. However, for those where further increases in tumor size or associated edema could be associated with significant morbidity or even mortality, this decision should probably be carefully discussed ahead of time with the patient's neurosurgeon, including considerations of aggressive surgical or radiosurgical therapy prior to the patient's attempts at getting pregnant.

CONCLUSION

Our clinicopathologic study suggests that pregnancy-associated meningiomas becoming sufficiently symptomatic to warrant surgical intervention often 1) occur in skull base locations or near eloquent cortex, 2) present with cranial nerve palsy or visual disturbance, 3) present in late stages of pregnancy, 4) represent low-grade meningiomas with diffuse PR positivity, and 5) display potentially reversible hemodynamic changes such as intratumoral hypervascularity, edema, and spontaneous hemorrhage or necrosis.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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