Meningioma

Last updated: September 5, 2017

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MENINGIOMAS OF SPINAL CANAL — see p. Onc54

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EPIDEMIOLOGY

1. 13-30% of all primary intracranial neoplasms (only 1.5% in children); 30% in Africa!

2. at autopsy: 1.4-2.3% people have undiagnosed asymptomatic meningiomas.

3. Increased incidence of meningiomas over time:

- 0-19 years: 0.12 per 100,000 individuals - occur in children (more aggressive forms)
- 20-34 years: 0.74
- 35-44 years: 2.62
- 45-54 years: 4.89
- 55-64 years: 7.89
- 65-74 years: 12.79
- 75-84 years: 17.04

4. male-to-female ratio = 1.4:4.2:8 (peaks to 1:3.5: in patients 40-44 years);

- ratio increased over time - use of hormonal medications (hypothesis has not been proven in men),

- meningiomas associated with HEREDITARY tumor syndromes occur in younger patients, and more equally in men and women.

- ATYPICAL and ANAPLASTIC meningiomas show male predominance.

- SPINAL meningiomas — 90% women.

5. in Scandinavia, incidence has increased between 1968 and 1997 from 2.6 to 4.5 per 100,000 people, and from 1.4 to 1.9 in men.

6. in one Italian study, numbers have remained stable for decades.

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ETIOLOGY

1. Radiation

- meningiomas are known to be induced by low-, moderate-, and high-dose radiation (average time interval to tumor appearance of 35, 26 and 19-24 years, respectively)

1) history of low-dose irradiation (800 rad) to scalp for tinea capitis — 4-fold increased risk for multiple meningiomas decades later,

2) high-dose radiation (> 2000 rad) for primary brain tumors

N.B. radiation-induced meningiomas tend to be more atypical or aggressive, multifocal, highly proliferative, and occur in younger age groups.

2. Genetic causes

- familial meningiomas are rare (unless associated with neurofibromatosis-2).

- most common (60% of sporadic meningiomas) - loss of NF-2 gene (22q12), meningioma locus is close to but probably different from gene responsible for NF-2.

- others - chromosomal loss of 1p, 3p, 6q, 14q, 8p12 (Werner's syndrome).

- chromosome 7 monosomy - frequent in radiation-induced meningiomas.

- events associated with higher grades of meningioma:

- loss of chromosome 10:

- loss of tumor suppressor in lung cancer-1 gene (TSLC-1).

- loss of progesterone receptors.

- increased expression of cyclooxygenase-2 and ornithine decarboxylase.

- 17q - associated with progression to anaplastic meningioma.

- association between sex hormones (estrogens, progesterone, androgens) and risk for meningiomas remains under investigation.

- meningiomas may wax and wane with pregnancy, and they are positively associated with breast cancer

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PATHOLOGY

Benign extra-axial neoplasm of arachnoidal (meningothelial) cells in arachnoidal cap (component of arachnoidal villi in dura); typically attached to inner surface of dura mater:

- globular, well-demarcated (MENINGIOMA EN MASSE).

- MENINGIOMA EN PLAQUE — sheet-like extension that covers dura (may not invaginate parenchyma);

- when biopsy is taken from macroscopically uninvolved dura, abnormal cells are found there.

- CAVERNOUS SINUS MENINGIOMA — infiltrates cavernous sinus and becomes interdigitated with its contents.

- firm to soft.

- wide dural attachment.

- cut surface is either translucent pale or homogeneously reddish brown (may be gritty on cutting).

- calcification (small punctate calcium deposits) within meningiomas is found in 10-20% cases.

- necrosis or extensive hemorrhage are not present.

- grow very slowly (∼0.24 cm in diameter per year).

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Meningioma

- invaginate into underlying brain without invading it (i.e., well demarcated from surrounding brain);
- degree of edema around tumor is variable (may be massive);
- true brain invasion upgrades to grade II (even if histology is benign);
- can invade skull bones → hyperostosis or bone destruction; sometimes causes reactive hyperostosis without invasion;
- bone invasion has been reported in 20-68% of studies with histopathologically confirmed data;
- degree of edema around tumor is variable (may be massive).

- can invade skull bone → hyperostosis or bone destruction; sometimes causes reactive hyperostosis without invasion!
- bone invasion has been described in 10%–40% of cases with no hyperostosis (imaging is insufficient to predict bone invasion!!)
- blood supply: from dura.
- over long term, parasitization (recruitment) of cortical vessels by malignant tumors over cerebral convexity or of branches of ophthalmic artery by subfrontal masses is not rare—which makes tumor resection much more difficult.

- encased vessels: if not circular, vessel is not invaded; if circular, vessel wall may be invaded (esp. if lumen is abnormal on MRI flow voids).
- malignant potential is extremely rare (features as clear signs of malignancy: cortical invasion by tumor and dural metastasis).

- immunohistologic stains for mitotic activity used to predict malignant behavior of meningiomas:
  a) bromodeoxyuridine labeling (IV injection before tumor removal) – tumors with indices > 5% have recurrence rate ≈ 100%.
  b) proliferating cell nuclear antigen PCNA (can be performed on fixed specimens).
  c) Ki-67 (Ki-67 antigen is present in nuclei of cells in G1, S, G2 and M phases, while, resting cells in G0 phase do not express it).

MULTIPLE MENINGIOMAS

1. neurofibromatosis type 2 (NF2)
2. families with hereditary predisposition to meningioma
3. < 10% of cases of sporadic meningiomas

LOCATION

- brain surface: wherever there is dura (over convexity or at skull base).
- 2% meningiomas occur in intraventricular location (presumably from cells migrating in with choroid plexus; 75% are located in left occipital horn).
- rarely in intravascular location.
- meningiomas in spine are almost always found in women (10:1).

Site of Tumor

<table>
<thead>
<tr>
<th>Site of Tumor</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasagittal zone (from occipitocerebral suture)</td>
<td>15</td>
</tr>
<tr>
<td>Convexity usually around coronal suture</td>
<td>20</td>
</tr>
<tr>
<td>Sphenoidal ridge</td>
<td>20</td>
</tr>
<tr>
<td>Olfactory groove zone from lamina (rostrum)</td>
<td>10</td>
</tr>
<tr>
<td>Suprasellar (region of hypothalamic sulcus)</td>
<td>10</td>
</tr>
<tr>
<td>Posterior fossa (con convex or foramen magnum)</td>
<td>10</td>
</tr>
<tr>
<td>Middle fossa</td>
<td>2</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>2</td>
</tr>
</tbody>
</table>

N.B. 90% meningiomas are supratentorial!

Source of picture: WebPath—The Internet Pathology Laboratory for Medical Education (by Edward C. Klatt, MD)
Note how this meningioma beneath dura has compressed underlying cerebral hemisphere.

Incidental finding at autopsy - meningioma of sphenoid ridge: base of sella is at bottom center, above which is tan pituitary. Above and lateral to pituitary are common carotid and anterior cerebral arteries, above which slightly medially are optic nerves. To upper right is light tan meningioma.

Bone flap was removed. Note tumor breach of dura.
Here is resected meningioma:

**HISTOLOGY**

WHO 2007 Classification of Meningiomas:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I - benign meningioma (90-94%)</td>
<td>meningothelial, fibrous, transitional, psammomatous, angiomatic, microcystic, secretory, lymphangio-myocyte-rich, metaplastic</td>
</tr>
<tr>
<td>Grade II - atypical meningioma (5-20%)</td>
<td>Atypical, clear cell (intracranial), chordoid II</td>
</tr>
<tr>
<td>Grade III - anaplastic meningioma (1-5%)</td>
<td>Rhabdoid, papillary, any meningioma with brain invasion</td>
</tr>
</tbody>
</table>

Many previously called ‘angioblastic’ meningiomas have now been reclassified as intracranial HEMANGIOPERICYTOMA.

N.B. tumor type that closely resembles meningioma is HEMANGIOPERICYTOMA.

Full WHO 2007 criteria for atypical meningioma - 1 or more of the following:

1. 4-19 mitoses per 10 high-power fields
2. At least 3 of the following 5 atypical features: spontaneous necrosis, macronucleoli, loss of architecture (sheeting), hypercellularity, small-cell change.
3. Brain invasion
4. Predominant (> 50% of tumor volume) clear-cell or chordoid morphology

- Certain histological subtypes or meningiomas with specific combinations of morphologic parameters are associated with less favorable clinical outcomes and correspond to WHO grades II (atypical) and III (anaplastic or malignant).
- Can have nuclear polymorphism.

Most common histologic subtypes:

1. meningothelial (syncytial) - densely packed polygonal cells with no clearly visible cell membranes arranged in solid sheets and whorled nests; characteristic calcified foci (psammoma bodies).
2. fibroblastic (fibrous) - sheets of interlacing long spindle cells; intercellular stroma is composed of reticulin and abundant collagen.
3. transitional (mixed) - features common to both meningothelial and fibroblastic varieties.

Meningiomas grouped by likelihood of recurrence and grade:

- Immunohistochemistry:
  - 80% stain positive for epithelial membrane antigen (EMA).
  - Stain negative for anti-Leu 7 antibodies (positive in SCHWANNOMAS) and for glial fibrillary acidic protein (GFAP).
  - Progesterone receptors present consistently in cytosol of meningiomas; presence of other sex hormone (estrogen, androgen) receptors is much less consistent. 88% of meningiomas have progesterone, 40% have estrogen and 39% have androgen receptors.
  - Somatostatin receptors present consistently.

Meningioma at low magnification – cells have abundant pink cytoplasm; dura at right:
Meningioma

Parasagittal multilobular meningioma attached to dura with compression of underlying brain.

A.
**CLINICAL FEATURES**

- **may be asymptomatic** (very slow growth sometimes permits brain to accommodate tumors even when they reach large size).
- **signs & symptoms** become exacerbated during **pregnancy** (but usually improve postpartum).

1. **Irritation of underlying cortex** *(**CONVEXITY MENINGIOMAS**) → seizures *(risk of recurrent seizures after surgery) increases from low after one seizure to high with every repeat seizure – indication for early surgery even for small meningiomas that cause seizures)*

2. **Compression of brain / cranial nerves** *(focal or more generalized cerebral dysfunction, cranial nerve paresis)*

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasagittal</td>
<td>Contralateral leg monoparesis/hemiparesis or paraparesis, dementia-like loss of cognition</td>
</tr>
<tr>
<td>Multifocal</td>
<td>Change in memory, gait, development behavior, urinary incontinence</td>
</tr>
<tr>
<td>Intracranial pressure</td>
<td>Seizures with possible Kernohan-Foster syndrome, frontal syndrome (late)</td>
</tr>
<tr>
<td>Cranial sinus</td>
<td>Multiple cranial nerve deficits (III, IV, V, VI)</td>
</tr>
<tr>
<td>Optic nerve sheath</td>
<td>Compressive, inflammatory with loss of vision, active stretching &amp; optic-ocular shear symptoms (optic atrophy occurs before loss of vision is complete?!)</td>
</tr>
<tr>
<td>Sphenoid wing</td>
<td>Medial/middle/lateral: Grow into cavernous sinus, carotid artery, optic nerve</td>
</tr>
<tr>
<td>Parasellar</td>
<td>Grow anastomosis into orbit (papilloma)</td>
</tr>
<tr>
<td>Tentorial</td>
<td>Grow into infratemporal fossa; hydrocephalus</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>Contralateral hemiparesis, visual field defects</td>
</tr>
<tr>
<td>Cerebellopontine angle</td>
<td>Decreased hearing, facial weakness and numbness</td>
</tr>
<tr>
<td>Spinal canal</td>
<td>Pachyphyicytosis, unusual field deficits</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>Obstructive hydrocephalus</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Localized spinal pain; Brown-Sequard syndrome → quadriparesis or paraparesis</td>
</tr>
</tbody>
</table>

3. **Vascular injuries**

- **PARASAGITTAL MENINGIOMAS** frequently involve sagittal sinus and important cortical veins that drain into this sinus (middle and posterior thirds of sagittal sinus, if involved but patent, cannot be sacrificed without severe neurologic sequelae, therefore, total resection of these tumors is often impossible!)

- **SKULL BASE MENINGIOMAS** may narrow cerebral arteries → TIAs, stroke.

4. **Involvement of bone & subcutaneous** tissues → hydrocystoma.

* i.e. tumor may breach sanctity of dura and bone, thus appearing subcutaneously.
DIAGNOSIS

Imaging is mainstay of diagnosis (typical features and location do offer reasonable amount of certainty in diagnosis).

Plain skull radiograph - hyperostosis, bone invasion, calcifications within tumor (10-20%), enlarged vascular channels over skull vault (convexity meningiomas are heavily supplied by meningeal arteries).

- ‘blistering’ (expansion of sphenoid sinus, with elevation of its roof) is extremely suggestive of meningioma of planum sphenoidale.
- CT – dural-based extraxial tumor with well-defined borders; compresses brain without invading it (white matter buckling!!)
  - isodense or hyperdense (60%)
  - enhance homogeneously and intensely (multiple meningiomas may be difficult to differentiate from metastasis).
  - perilesional edema may be extensive.

MRI - many are isointense on all image sequences to cortex.

- enhance homogeneously and intensely.
- “dural tail” (streak of dural enhancement flanking main tumor mass) may be apparent; not pathognomonic for meningioma!
- Fat suppression images are used for tumors adjacent to orbit or infratemporal fossa or after previous skull base approach.
- Image fusion with bone-window CT scan may be helpful for meningiomas in cranial base locations.
- Look at T2 - if edema in surrounding brain – higher risk of seizures.

Angiography (preoperatively* - tumor vascularization [characteristically extracerebral] and encroachment on vital vascular structures) - both internal (or vertebral) and external carotid arteries should be selectively injected!

- supply from external circulation (sunburst or radial appearance of feeding arteries).
- cortical vessels are displaced away from tumor.
- “mother-in-law” blush (prolonged homogeneous vascular stain that comes early and leaves late).
- late venous images are important to determine patency of involved dural sinuses (esp. sagittal).
- Tumor embolization is possible.

Somatostatin receptor scintigraphy with 111In octreotide can confirm diagnosis + detect residual or recurrent tumor.

Bone-window CT reveals calcification of meningioma

Bone-window CT scan reveals skull involvement; absence of tumoral calcification

Sphenoid ridge meningioma (contrast T1-MRI): extensive tumor with bilateral cavernous sinus invasion and encasement of both carotid arteries

Parasagittal meningioma (contrast MRI).

Cerebellopontine angle meningioma (MRI and angiogram):
Falx meningioma (contrast T1-MRI) - enhancing extracranial mass arising from falx (arrows); note "dural tail" that extends along falx (white arrows):
**Parasagittal meningioma (contrast T1-MRI)** - enormous tumor arising from falx.

**Clival/foramen magnum meningioma (contrast T1-MRI)** - marked compression of medulla.

**Subfrontal meningioma** (A - noncontrast CT; B - contrast CT; C - lateral projection of common carotid arteriogram) - large isodense circumscribed mass in anterior cranial fossa; foci of calcification centrally; enhances homogeneously; edema in white matter of both frontal lobes and posterior displacement and splaying of frontal horns of lateral ventricles. On arteriogram mass is delineated by tumor blush and there is posterior displacement of anterior cerebral arteries (arrowhead), mirroring mass effect seen on CT; ophthalmic artery is enlarged as its ethmoidal branches supply tumor (arrow).

**A. T2-MRI** - grey-matter isointense mass deeply indents left cerebral convexity; broad dural base, surrounding displaced cerebral sulci and small pial vessel between tumor and brain surface (arrowhead) are all features of extra-axial lesion.

**B. Contrast T1-MRI** - tumor enhances and there is ‘dural tail’ (arrow).

**C. Perfusion-weighted MRI** - increased blood volume of tumor compared to normal cortex and white matter.

**Tentorial meningioma**

**A. T2-MRI** - isointense tumor; central low-signal-intensity structures (arrow) are hypertrophied meningeal vessels supplying meningioma.

**B. Contrast T1-MRI** - homogeneously enhancing dural-based neoplasm; note thickened dura adjacent to meningioma; enhancing dural tail (arrow).
A. Contrast T1-MRI - large, dural-based, homogeneously enhancing meningioma; right transverse sinus also enhances, suggesting that flow may be altered within dural sinus (arrow).

B. Lateral view of left external carotid arteriogram - hypertrophy of posterior branch of middle artery (arrow); note starburst pattern of increased vascularity related to arterial supply to meningioma.

Parasagittal meningioma (contrast T1-MRI) - en plaque meningioma extending along right parietal convexity; obliterating invasion of sagittal sinus (lack of flow void).

Juxtasellar meningioma has encased suprachiasmatic carotid artery.

Temporal meningioma (contrast MRI) - large, slowly growing tumor affecting “silent area” of brain.

Contrast CT - meningioma in patient who presented with only mild cognitive deficits.

Suprasellar meningioma (contrast T1-MRI) lobulated, enhancing suprasellar mass arises from region of tuberculum sellae and extends down into pituitary fossa displacing pituitary stalk posteriorly; dural ‘tails’ (arrowheads) extend over planum sphenoidale and clivus.

DIFFERENTIAL DIAGNOSIS (of meningioma-like tumors)
1. Dural metastasis
2. Dural lymphoma
3. Dural histiocytoma

TREATMENT
• small asymptomatic tumors are best left for observation (esp. for elderly patients) - repeat MR in 3-6 months - to establish growth pattern (growth only few mm excludes major mimickers – metastasis, lymphomas).
• growth > 2 mm / year – indication for surgery (unless patient is old and tumor unlikely will reach the size to become symptomatic).

SURGERY
See p. Op340 >>

RADIOThERAPY
- clinical benefit in many case series.
  Meningiomas are not very radiosensitive! – not relevant for SRS
  a) ADJUVANT therapy - for incompletely resected* / high grade** / recurrent tumors.
     *subtotal resection – wait 1.5-3 mos, then SRS
     **after gross total resection of atypical meningiomas, EBT appears not to affect progression-free survival and overall survival – observation rather than EBT may be indicated! vs. After subtotal resection of atypical meningiomas, EBT or SRS improves tumor control and delays progression, but this effect may be diminished in tumors with spontaneous necrosis.
  b) PRIMARY treatment - for optic nerve meningiomas, some unreactable tumors.

Stereotactic radiosurgery (15-16 Gy) - excellent local tumor control used mainly for:
1) small (<5 cm) residual or recurrent lesions when surgery is significantly risky.
2) meningiomas involving skull base or cavernous sinus

• primary SRS gives 86-97% long-term local control for benign small- and medium-size meningiomas (<3.5 cm); meningiomas (durability of this response is beyond 10 years) - equivalent to a Simpson grade I resection.
• radiation-induced edema is the main cause of post-treatment morbidity (esp. with 16 Gy – up to brain herniation).

Meningioma of cavernous sinus:
  a) tumor is small enough and sufficiently far from optic pathways – radiosurgery
  b) lesion is too big or too close to optic pathways – combined approach (resection of portion of lesion out of cavernous sinus + radiosurgery) or conventional radiotherapy

Meningioma involving optic pathways (sellar, parasellar meningiomas) - concern for radiation-induced optic neuropathy.

CHEMOTHERAPY
- disappointing!
  • reserved for malignant cases after failure of surgery and radiotherapy.
  • drugs that had no effect in studies - TENEOZOLOMIDE, HYDROXYUREA, MIFEPRISTONE (RU-486), INTERFERON-α, RINOTEICAN.

SUNITINIB (Sutent®) - small-molecule tyrosine kinase inhibitor
  • targets vascular endothelial growth-factor receptors (VEGFR) and platelet-derived growth-factor receptors, both of which are highly expressed in meningiomas.
  • might be the first effective medical treatment for recurrent atypical/malignant meningioma,
  • 60% rate of grade 3/4 toxicity!!!!

PROGNOSIS
Meningiomas can be cured surgically!
  • 5-year survival 73-94%
  • average survival – 9 years.

RECURRENT (by 5 years)*: *average interval for recurrence is 5 years.
• presumably removed tumors - 10% (20% at 20 years), when dural attachment is cauterized but not removed – 15%; when definite portion of tumor remains - 39%.
• routine follow-up MRI is best means of detecting recurrence.
• recurrent meningiomas ordinarily represent focal benign neoplasms - can again be treated by surgical resection.
• major clinical factor in recurrence is extent of resection; less powerful predictors of recurrence: young age and male gender.

Significant predictors of poor outcome:
  1) mitotic index > 8/50 HPF
  2) malignant (WHO II/III) tumor grade
  benign meningiomas have recurrence rates 7-25%, atypical meningiomas 29-32%, anaplastic meningiomas 50%.
  3) progesterone receptor score of 0 (i.e. absence of progesterone receptors)
  N.B. significant subset of histologically and clinically benign meningiomas also lacks progesterone receptor expression.
  • brain invasion and bone invasion are independent predictors of tumor recurrence!

BIBLIOGRAPHY for ch. “Neuro-Oncology” >> follow this LINK >>

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Please visit website at www.NeurosurgeryResident.net