Vascular Tumors

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HEMANGIOBLASTOMA

- rare benign vascular neoplasm that arises almost exclusively in CNS.

• classified by WHO as meningeval tumors of uncertain origin.

• 1-2.5% of all intracranial neoplasms, but:
  1) 8-12% of posterior fossa tumors (most common primary adult intracranial posterior fossa tumor).

Cerebellar hemangioblastomas = LINDAU TUMORS (Lindau first described them in 1926)

2) 3-7% of spinal cord tumors. see p. Onc50

3) extremely rare in supratentorial compartment, optic nerve, brainstem, peripheral nerves.

• male-to-female ratio = 2:1.

• usual age at diagnosis - third or fifth decades (rarely affect children).

VON HIPPEL-LINDAU (VHL) DISEASE

20.25% hemangioblastomas are part of von Hippel-Lindau (VHL) disease - autosomal dominant deletion of VHL (tumor suppressor gene on 3p) with 90% penetrance and delayed expression:

1) retinal angiomas (von Hippel's disease) - usually in peripheral retina (vision is unaffected; exudation in region of angioma may lead to retinal detachment); histologically identical to capillary haemangioblastoma

2) CNS hemangioblastomas - (Lindau's syndrome); occur in 84% patients by age of 60 yrs; some may produce erythropoietin-like substances → asymptomatic polycythemia; tumors tend (94%) to occur as multiple (vs. in sporadic cases - solitary); occur in cerebellum, brainstem, spinal cord, and nerve roots (vs. in sporadic cases - cerebellum); supratentorial and PNS lesions are rare.

3) various visceral tumors - kidneys [renal cell carcinoma, cysts, angiomas], adrenal glands [pheochromocytomas], pancreas [cysts], epididymis [papillary cystadenomas, cysts], liver [angiomas, cysts], endolymphatic sac tumors. Renal carcinoma (also very vascular) is most common cause of death!

• classified as phakomatosis, although it does not include any cutaneous manifestations!

• often presents at younger age - mean age 20 years.

• birth incidence - 1 in 30,000-45,000.


• constitutive overexpression of VEGF

• perform screening of all family members:
  1) retinal examination including children during first 2 years of life; retinal angioma is indication for MRI

Positive family members → early lifetime screening by MRI (start at age > 10 years).

VHL PHENOTYPES

- correlation between different VHL phenotypes and VHL mutations:

- germline VHL mutations can virtually always be identified.

- NIH surveillance; MRI of brain and C-spine.
**VASCULAR TUMORS**

Osc24 (2)


**PROGNOSIS**
- Patients ultimately develop multiple CNS hemangioblastomas.
- CNS hemangioblastoma and renal cell carcinoma are major causes of death.
- Average life expectancy is 40–50 years.

**TREATMENT**
- Medications for advanced renal cell carcinoma (do not work for hemangioblastoma):
  - **PAZOPANIB** (Votrient) – FDGFR tyrosine kinase inhibitor
  - **SUNITINIB** (Sutent) – PDGFR and VEGFR tyrosine kinase inhibitor

**PATHOLOGY**
- Primitive vascular channels with 3 types of cells:
  1. Nonneoplastic relatively normal-appearing vascular endothelial cells that line capillary spaces.
  2. Nonneoplastic small, perivascular pericytes with dark compact nuclei and sparse cytoplasm.
  3. Neoplastic (stromal cells) with multiple vacuoles and granular eosinophilic cytoplasm (glycogen) rich in lipid, some nuclear pleomorphism, represent abnormally differentiating mesenchymal cells of angiogenic lineage, with some morphological features of endothelium, pericytes, and smooth-muscle cells.

**HISTOLOGY**
- Cherry-red in color (highly-vascular - may simulate AVM macroscopically?!)
- 50% in cerebellum, 50% in spinal cord.
- 70% are mural nodule and cyst that contains yellow proteinaceous fluid; cyst wall is glial nonneoplastic reaction to secreted fluid; mural nodule is touching pial surface of cerebellum.
- Begins at pial surface - grows inside parenchyma attached to pia mater (gets rich vascular supply from pial vessels), but no dural attachment.
- Not invasive (but border does not contain any particular membrane or capsule).
- No calcification.
- Extramedullary and extradural hemangioblastomas have been described.
- Subarachnoid dissemination is extremely rare, tumor enlarges extremely slowly.
- Capable of blood island formation with potential extramedullary hematopoiesis.

**Lindau hypothesis (1931)** - derived from embryonal cell types with divergent differentiation potentials.

**4th ed.** - vascular tumor with vacuolated stromal cells.
A Cellular variant showing many stromal cells. B Cellular variant showing densely packed tumour cells. C In situ hybridization showing expression of VEGF mRNA in stromal cells. D Immunostaining for VHL protein in stromal but not endothelial cells.

**CLINICAL FEATURES**

Long history (≈ 1 yr) of minor neurological symptoms → sudden exacerbation.

- Cerebellar lesions → cerebellar dysfunction, ICP↑ (due to hydrocephalus).
- Spinal cord lesions → pain, progressive spinal cord compression.

**DIAGNOSIS**

Enhances more than ependymoma or astrocytoma!

- Complete neural axis imaging:
  - CT / MRI:
    a) clearly delineated **intensely enhancing mass**
    b) cyst with **nonenhancing wall** + **intensely enhancing mural tumor nodule**

  *Note:* no need to resect vs. cystic metastases (have enhancing wall)

  N.B. hemangioblastomas with **enhanced cyst wall** exist - rare and frequently misdiagnosed preoperatively:
  - Favorable tumor control could be achieved only when gross total resection of both the tumor nodule and cyst wall be performed?
  - Close follow-up is necessary due to high recurrence rate.

- Angiography (usually done before surgery) - highly vascular tumor blush, enlarged feeding arteries and draining veins.

- Detect VHL disease complex:
  1) **ophthalmologic evaluation:** aneurysmal dilation of peripheral retinal vessels (earliest characteristic feature) → tortuous vessels marked by afferent arteriole and venule leading to raised retinal lesion.
  2) **abdominal CT / ultrasound**

Multiple hemangioblastomas (arrows) in von Hippel-Lindau disease (T1-MRI); large cyst associated with right cerebellar hemangioblastoma.
**VASCULAR TUMORS**

**Contrast CT - cystic mass in left cerebellar hemisphere with enhancing mural nodule (arrowhead) and surrounding edema (arrow):**

**Hypervascular lesion with AV shunting; note early filling vein (arrow) indicative of hemangioblastoma:**

**TREATMENT**

**Asymptomatic lesions** may be safely observed with MRI to rule out tumor enlargement (tumor tends to progress in steps).

**Symptomatic lesions** → surgical removal.

N.B. all patients must be screened for PHEOCHROMOCYTOMAS preop (may cause perioperative hypertensive crisis induced by anesthetic or analgesic agents)

**Other options** - endovascular embolization of solid component (tumor vascularity↓), **stereotactic radiosurgery** (does not work well long term – recurrences↓), chemotherapy (BEVACIZUMAB).

Indications for radiotherapy (at least 50 Gy):

- a) unresectable
- b) incompletely excised
- c) recurrence

**PROGNOSIS**

- local recurrences < 25% (esp. in VHL disease*, younger age, multiple hemangioblastomas).
- Morbidity and local tumor recurrence rates are low!

*Nonsurgical treatment may not be curative in VHL.
SOLITARY FIBROUS TUMOR
(HEMANGIOPERICYTOMA)

Solitary Fibrous Tumor is preferred term over Hemangiopericytoma
- Rare dural tumor from perivascular pericytes (high percentage in torcular region); also occurs elsewhere in body.
  * Homozygous deletions of CDKN2/p16 gene are common.
  * Most all SFTs harbor an NAB2-STAT6 fusion gene, which is considered specific to this tumor type.
  * STAT6 immunohistochemistry is a reliable surrogate for detection of the fusion gene.
  * Some classifying it as subtype of meningioma (but do not have mutations of NF2 gene).
  * Usually - smooth, lobulated, well-encapsulated, very vascular.
  * Histology (similar to angioblastic meningioma and hemangioblastoma) - elongated pericytes with processes which wrap around thin-walled vascular channels of single layer of endothelial cells (i.e. cells lie external to vascular endothelium); cells are arranged in whorls or pinwheels, with rich investment of reticulin.
  * Locally aggressive, may metastasize (far more aggressive than ordinary meningiomas).
  * Imaging - lobulated (vs. meningioma - spherical) dural based mass, no calcification, no hyperostosis, multiple areas of flow void (reflect high vascularity).
  * Treatment - surgery → radiotherapy and/or chemotherapy.

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