Vascular Tumors

Last updated: April 12, 2020

HEMANGIOBLASTOMA

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

- classified by WHO as meningeal tumors of uncertain origin.

primitive endothelial cells around 4th ventricle?

- 1-2.5% of all intracranial neoplasms, but:
  1) 8-12% of **posterior fossa** tumors! (most common *primary adult intraaxial 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 ÷ 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 angiomatosis (*von Hippel's disease*) - usually in peripheral retina (vision is unaffected; exudation in region of angiomata may lead to retinal detachment); histologically identical to capillary haemangioblastoma
   H: photocoagulation / cryocoagulation.
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 [**pheochromocytoma**], 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 29 years.
- birth incidence - 1 in 30,000-45,000.
- genetics: **VHL gene** - tumor-suppressor gene on 3p25-26 (encodes protein pVHL that inhibits "elongation" step during RNA synthesis).
- constitutive overexpression of VEGF
- perform ***screening of all family members***:
  1) analysis for germline mutations of VHL gene
  2) *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).

TYPES

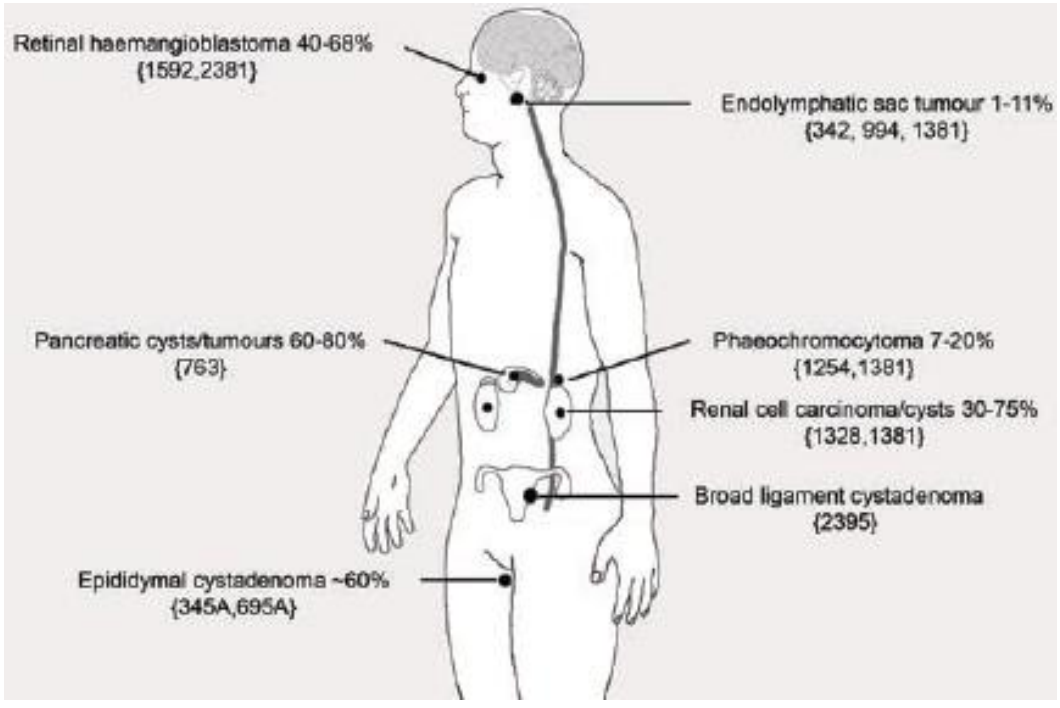
Correlation between different VHL phenotypes and VHL mutations:

VHL Type	Phenotype	Examples of mutations
Type 1	Predominantly without phaeochromocytoma	*VHL* 75 del Phe *VHL* Arg 161 Stop
Type 2	Predominantly with phaeochromocytoma but not with renal cell carcinoma	*VHL* Arg 161 Pro *VHL* Tyr 98 His
Type 2B	Predominantly with phaeochromocytoma and renal cell carcinoma	*VHL* Arg 167 Trp *VHL* Arg 167 Gln
Type 2C	Predominantly with only phaeochromocytoma	*VHL* Leu 188 Val

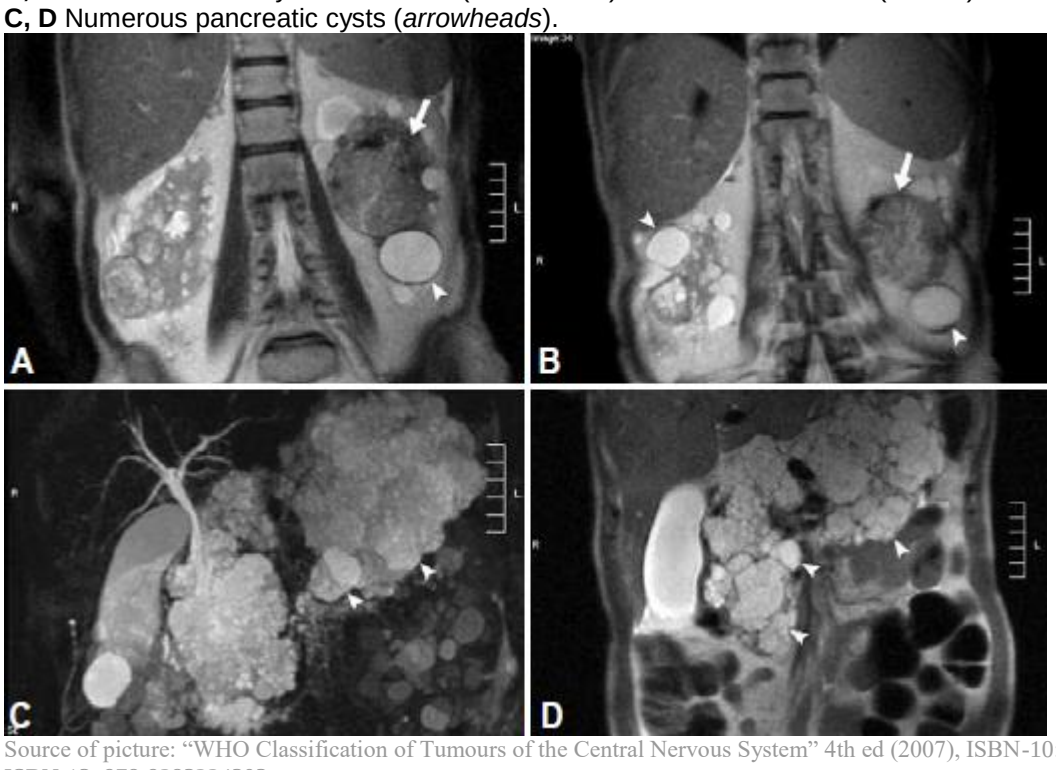
DIAGNOSIS

A. Two CNS hemangioblastomas
B. At least two items present of the following:
   a) family history
   b) single CNS hemangioblastoma
   c) single visceral tumor associated with VHL disease

- germline VHL mutations can virtually always be identified.
- NIH surveillance: MRI of brain and C-spine.



A, B Numerous renal cystic structures (*arrowheads*) and solid renal mass (*arrows*).
C, D Numerous pancreatic cysts (*arrowheads*).



Source of picture: "WHO Classification of Tumours of the Central Nervous System" 4th ed (2007), ISBN-10: 9283224302, ISBN-13: 978-9283224303 >>

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

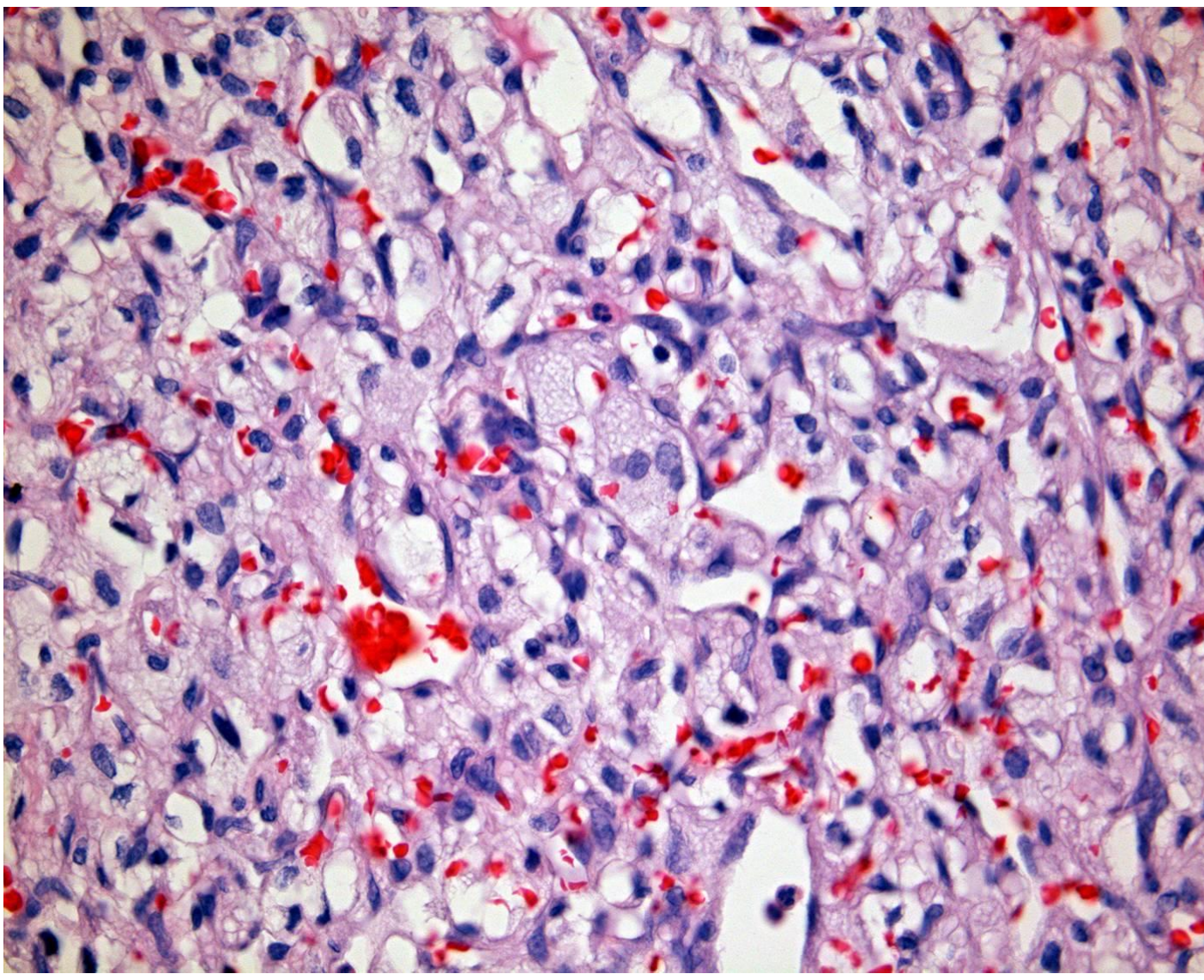
- cherry-red in color (highly-vascular - *may simulate AVM* macroscopically!!!).
- 50% in ***cerebellum***, 50% in ***spinal cord***.
- ≈ 30% are **solid**.
- ≈ 70% are as **mural nodule** and **cyst** that contains yellow proteinaceous fluid; cyst wall is glial nonneoplastic reaction to secreted fluid; mural nodule is touching pial surface of cerebellum.
- ***starts 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.

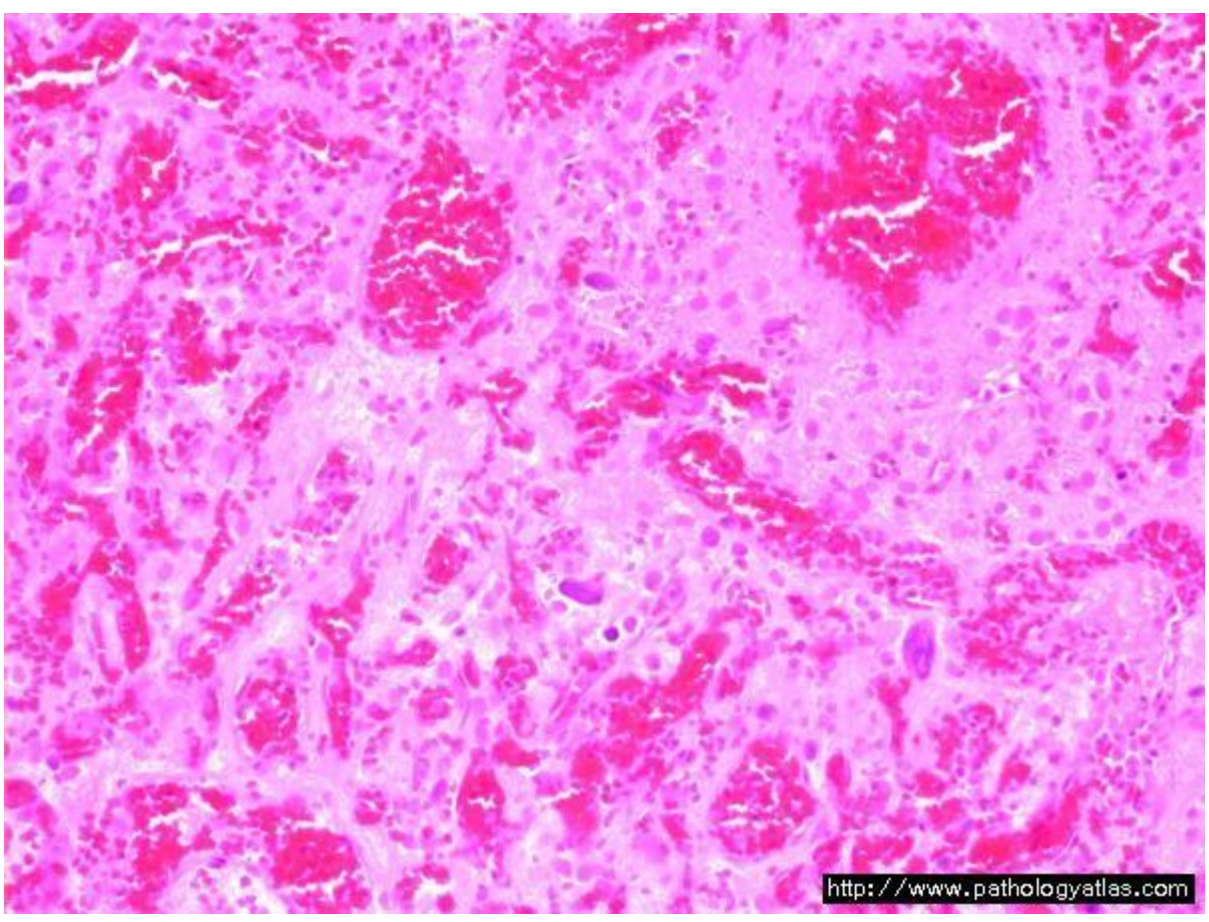
HISTOLOGY

- primitive vascular channels with 3 types of cells:

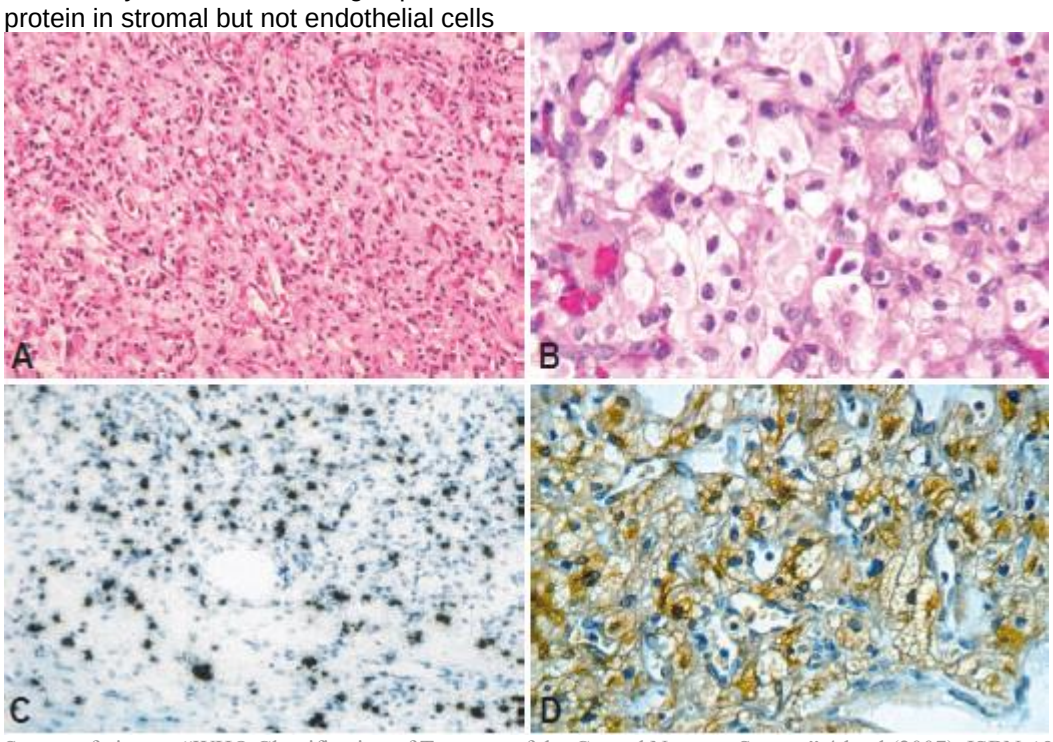
1) nonneoplastic relatively normal-appearing vascular ***endothelial cells*** that line capillary spaces.
2) nonneoplastic small, perivascular ***pericytes*** with dark compact nuclei and sparse cytoplasm.
3) neoplastic ***stromal cells*** with multiple vacuoles and granular eosinophilic cytoplasm (glycogen) rich in lipids*; some nuclear pleomorphism; represent abnormally differentiating mesenchymal cells of angiogenic lineage, with some morphological features of endothelium, pericytes, and smooth-muscle cells.
   *"bubbly cytoplasm" - can be mistaken for *XANTHOCHROMIC ASTROCYTOMAS*
   Lindau hypothesis (1931) - derived from embryonal cell types with divergent differentiation potentials.
4) ***brachyury protein*** - present in majority of hemangioblastomas (helps to differentiate from clear cell renal cell carcinoma metastases in von Hippel-Lindau syndrome).
   specificity 100%, sensitivity 91%, high positive (100%) and negative (89%) predictive values and high diagnostic accuracy (95%) in the differential diagnosis between HBL and CCRCC metastatic to the CNS or meningioma.

Vascular tumor with vacuolated stromal cells

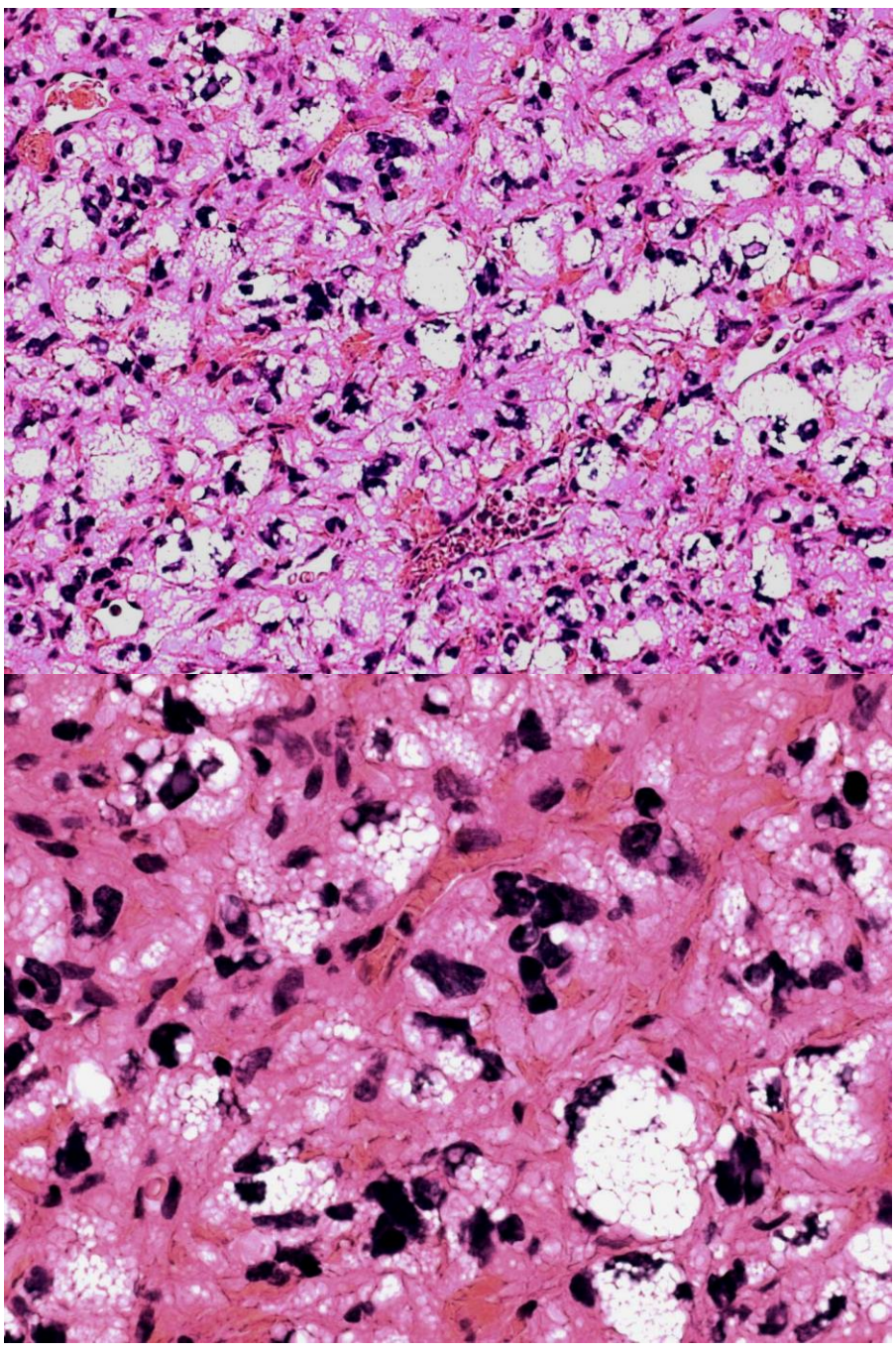




A Cellular variant showing many stromal cells. **B** Cellular variant showing densely packed tumour cells. **C** *In situ* hybridization showing expression of VEGF mRNA in stromal cells. **D** Immunostaining for VHL protein in stromal but not endothelial cells



Source of picture: "WHO Classification of Tumours of the Central Nervous System" 4th ed (2007), ISBN-10: 9283224302, ISBN-13: 978-9283224303 >>



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

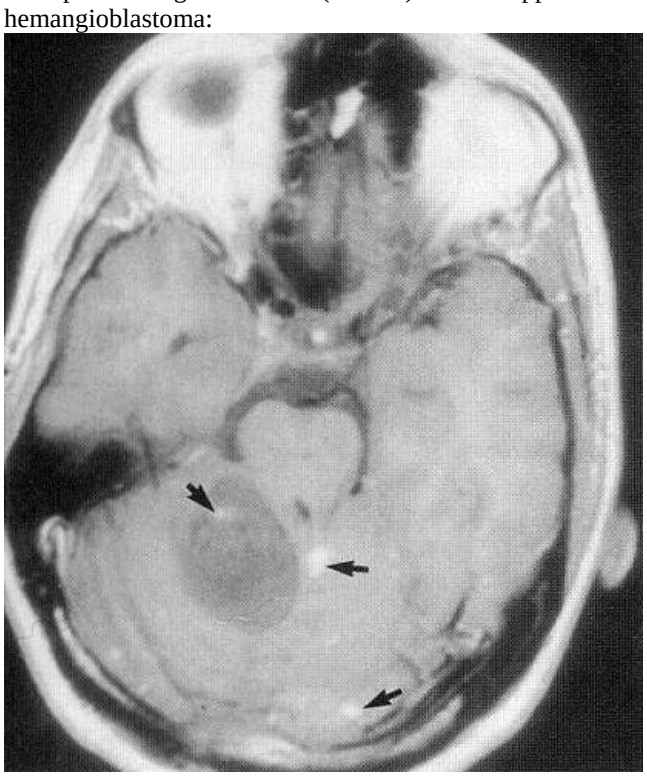
Enhances more than ependymoma or astrocytoma!

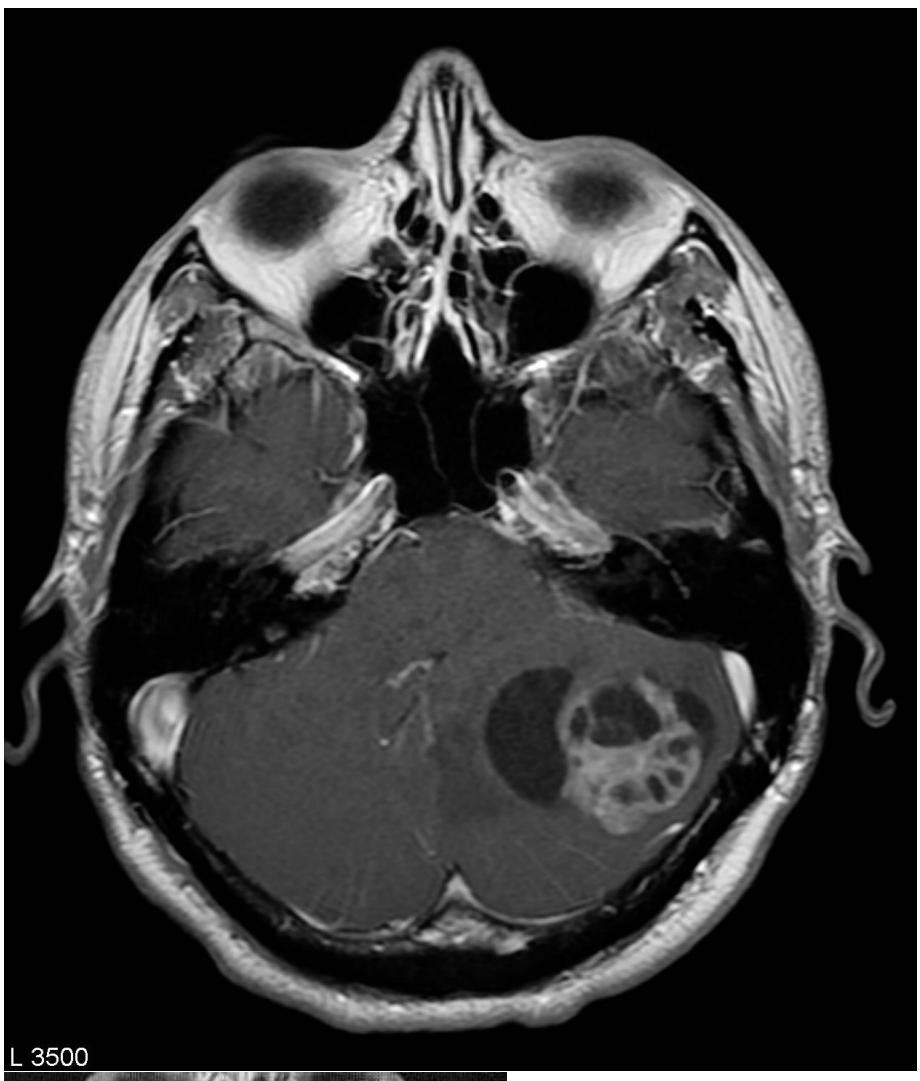
- <u>complete neural axis imaging</u>:
  CT / **MRI**:
  a) clearly delineated *intensely enhancing* **mass**
  b) **cyst** with *nonenhancing wall** + *intensely enhancing* mural tumor **nodule**.
  *no need to resect vs. cystic metastases (have enhancing wall)
  N.B. hemangioblastomas ***with enhanced 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.

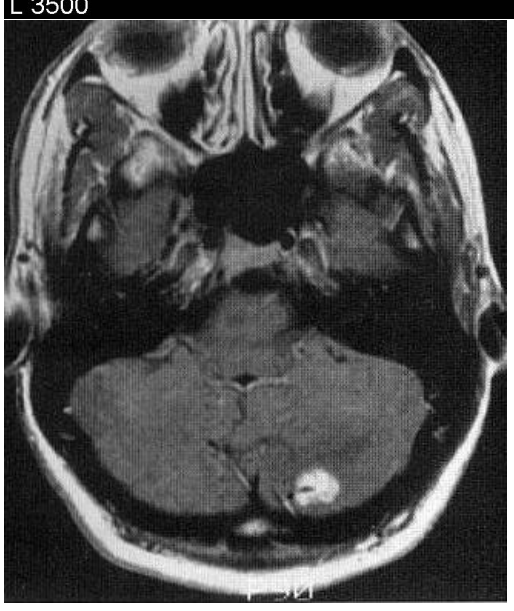
  Angiography (usually done before surgery) - highly vascular tumor blush, enlarged feeding arteries and draining veins.

- <u>detect VHL disease complex</u>:
  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

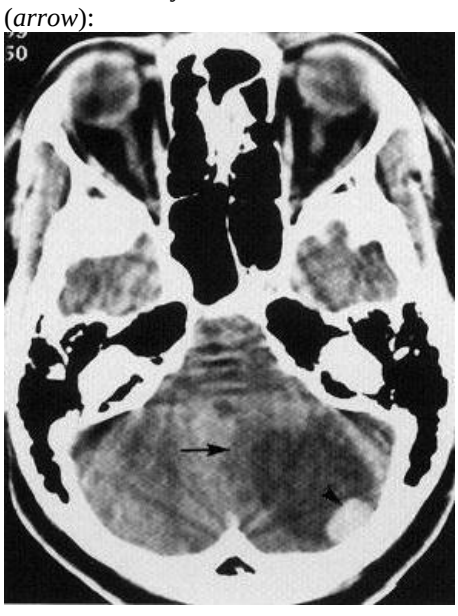
Multiple hemangioblastomas (*arrows*) in von Hippel-Lindau disease (T1-MRI); large cyst associated with right cerebellar hemangioblastoma:



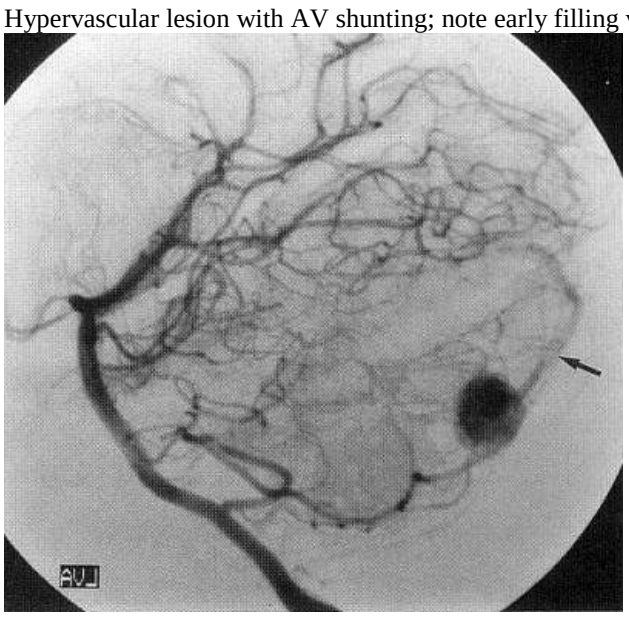




Contrast CT - cystic mass in left cerebellar hemisphere with enhancing mural nodule (*arrowhead*) and surrounding edema (*arrow*):



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**.

brain - see p. Op340 >>
spinal cord - see p. Op260 >>

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!
  *surgical 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).
- grossly - 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 >>