

Germ Cell Tumors

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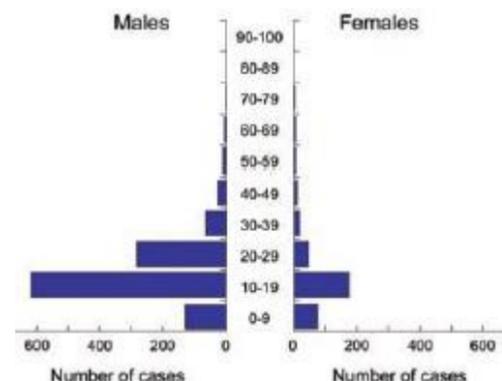
EPIDEMIOLOGY

Geographic INCIDENCE varies considerably:

- most prevalent in **far-east Asia** (2–3% of primary intracranial neoplasms), esp. **Japan** (0.17 cases per 100 000 person-years).
- in West, **0.3–0.6% of primary intracranial tumours** (3–4% of *pediatric* primary intracranial tumours) with incidence of 0.09 cases per 100 000 person-years.

Age and sex distribution

- 80–90% case at **age < 25 years** (peak 10–14 years).
- all histologic variants exhibit predilection for **males!** (esp. teratomas – 89% patients are males).
Boys in childhood or adolescence



ICD-O CODES

- Germinoma 9064/3
- Teratoma 9080/1
- Mature teratoma 9080/0
- Immature teratoma 9080/3
- Teratoma with malignant transformation 9084/3
- Yolk sac tumour 9071/3
- Embryonal carcinoma 9070/3
- Choriocarcinoma 9100/3

ETIOLOGY

- A. Neoplastic offsprings of primordial germ cells that in aberrant fashion ‘home’ to embryonic CNS rather than developing genital ridges.
- B. Elevated circulating GONADOTROPIN levels:
 - predilection for **peripubertal** subjects
 - localization to **diencephalic** centres (regulating gonadal activity)
 - ↑ incidence in **KLINFELTER syndrome** (47 XXY - chromosome X overdosage); patients also predisposed to mediastinal germ cell tumours.

CLASSIFICATION, PATHOLOGY

- morphological and immunophenotypic homologues of extra-neuraxial germ cell tumors.

- 40-65% of pineal region tumors; from residual primordial tissue derived from ectoderm, mesoderm, or endoderm.
see also p. 2626 (germ cell tumors in ovaries) >>
see also p. 2611 (germ cell tumors in testicles) >>
see also Intro (various topics) 2.jpg >>
- found primarily in **midline** (like extragonadal tumors):
 - pineal region (55%)
most prevalent neoplasms of pineal region in children!
 - suprasellar cistern (32%)
 - pineal & suprasellar (7%)
 - 3rd ventricle (3%)
 - basal ganglia/thalamus (3%)
 - spinal canal
- often multifocal.
- congenital **holocranial** examples may be encountered (usually teratomas).
- histologically indistinguishable from those found *extracranially* (incl. mediastinum and gonads).
Often mixed histologic composition! (only GERMINOMA and TERATOMA are likely to be encountered as pure types)
 - pathologist should communicate relative representation of each component present.

A. **GERMINOMA (s. INTRACRANIAL SEMINOMA)**

- B. **NONGERMINOMATOUS germ cell tumors** - derived from **totipotential germ cells** that aberrantly migrated to cranial midline during embryogenesis:
 - 1) **EMBRYONAL CELL CARCINOMA*** (5%).

- 2) **TERATOMA** (18%);
 mature teratoma.
 immature teratoma (s. teratoid)
- 3) **YOLK SAC TUMOR (s. endodermal sinus tumor)*** (7%)
- 4) **CHORIOCARCINOMA*** (5%)
- 5) **MIXED** germ cell tumor (e.g. *TERATOCARCINOMA* - embryonal carcinoma containing elements of immature teratoma).

*highly malignant

GERMINOMA (S. INTRACRANIAL SEMINOMA)

(commonest histology - 60-70% of all germ cell tumors) - intermediate degree of malignancy; arise from **primordial germ cells** - large round cells interspersed with **lymphocytes** (!!!) and septae of fibrous tissue (virtually pathognomonic "**two-cell**" appearance - contrast between smaller, darkly staining lymphocytes and larger, pale staining cytoplasm of neoplastic cells);

mature dark lymphocytes + large pale* germinoma cells

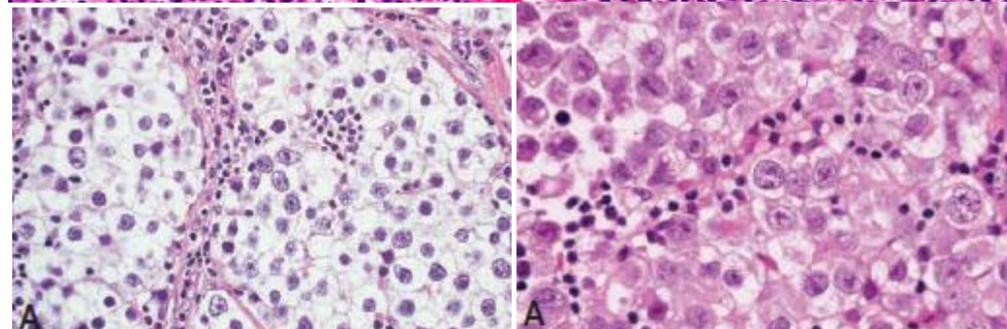
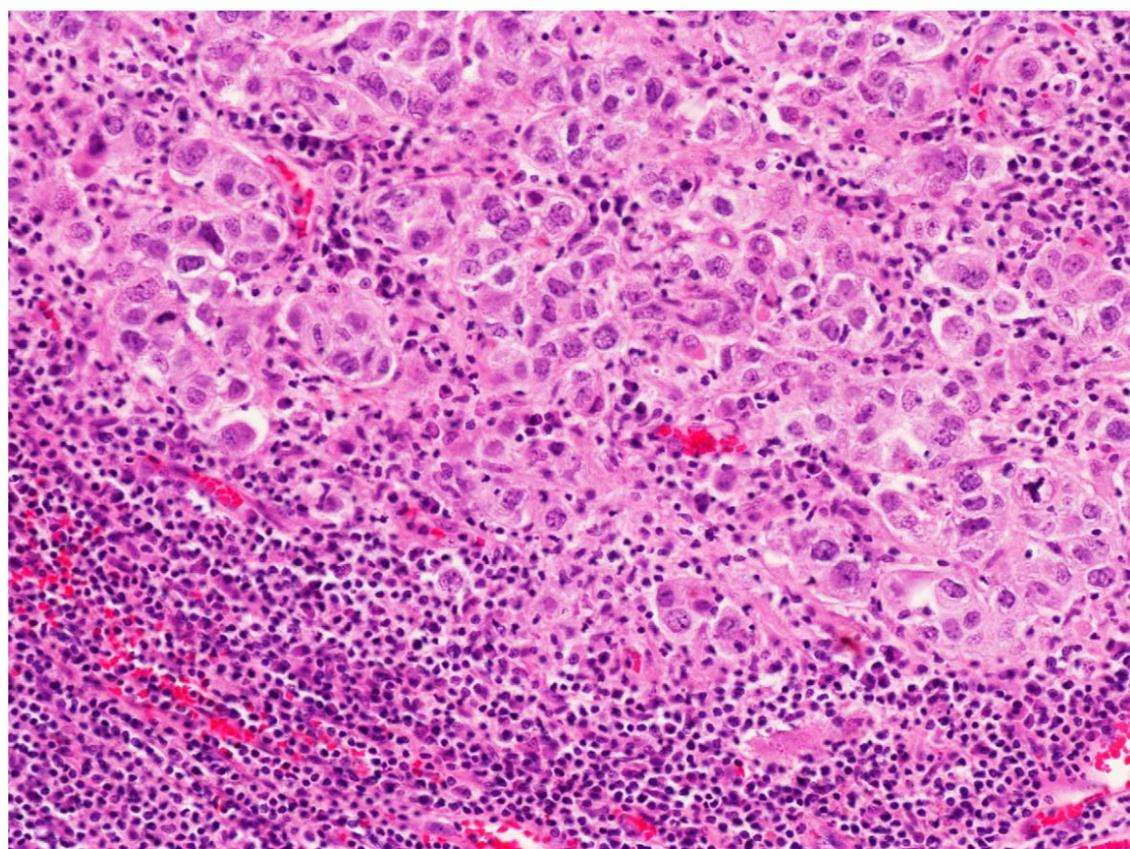
*lipids in cytoplasm

- **large undifferentiated cells** (neoplastic counterparts of primordial germinal elements) with abundant cytoplasm (strikingly clear due to glycogen) in monomorphous sheets / lobules
- conspicuous mitoses but necrosis is uncommon.
- tumor cell cytoplasm is glycogen-rich (PAS-positive).
- characteristic **cellular junctions** (simplified desmosomes) and focal **microvilli** within intercellular lumina (microvilli is histologic characteristic that distinguishes intracranial lesion from its extracranial correlate).
- delicate fibrovascular septa infiltrated by small **T cells**
- may also contain **syncytiotrophoblastic giant cells** with β -HCG positivity (but no virulence of choriocarcinomas) – so called **MIXED GERMINOMA** (vs. **PURE GERMINOMA**)
- most constant **immunohistochemical** attributes - strong cell **membrane** labelling for **c-kit** + **nuclear** reactivity for **OCT4**
- infiltrating germinomas can elicit **atypical gliosis** (may be confused with malignant glioma).
- **noncaseating granulomatous inflammation** (with multinucleated giant cells) can be found in biopsy taken from periphery of some germinomas.
- **occur** in gonads, in midline CNS (pineal or suprasellar region), midline body (mediastinum or sacrococcygeal region).
 - although histologically identical in all sites, germinomas in **testes** are called **SEMINOMAS**, in **ovaries** **DYSGERMINOMAS**, and in **CNS** **GERMINOMAS** (previously called **ATYPICAL TERATOMAS**).
- **macro**: solid (necrosis and haemorrhage suggest presence of more malignant components).

Germinoma of suprasellar region in 7-year-old girl:

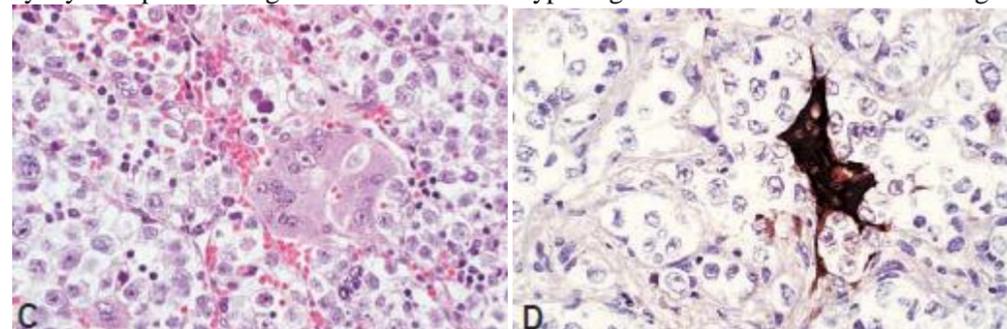


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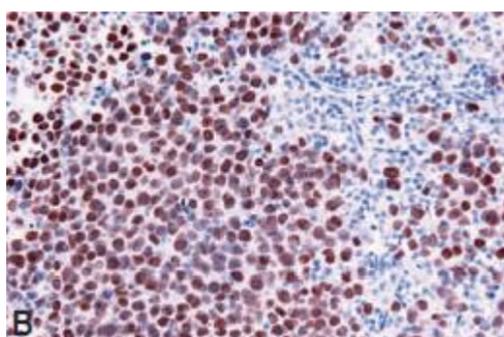
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Syncytiotrophoblastic giant cell in otherwise typical germinoma with immunostaining for β -HCG:



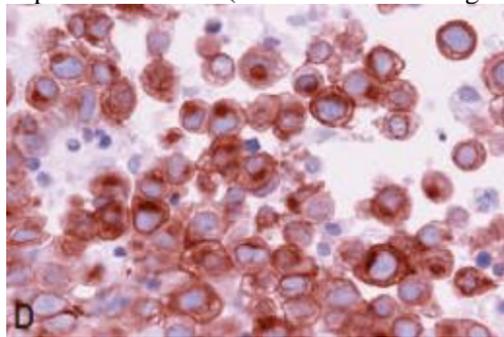
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Nuclear OCT4 immunoreactivity:



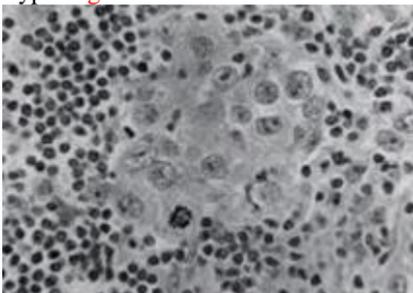
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Expression of c-kit (membranes and Golgi regions):

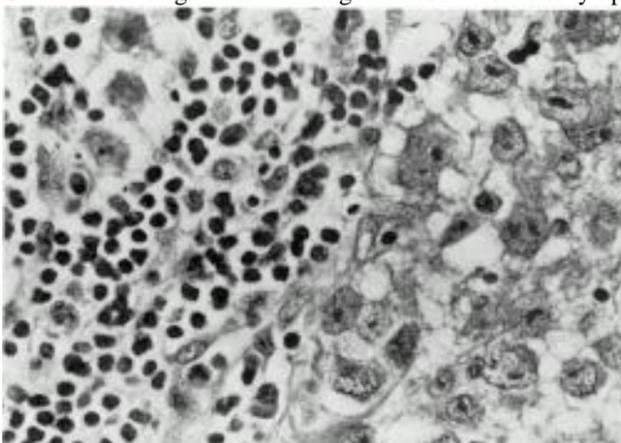


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Typical **germinoma**:



Germinoma - large cells with large nucleoli + focus of lymphocytes:

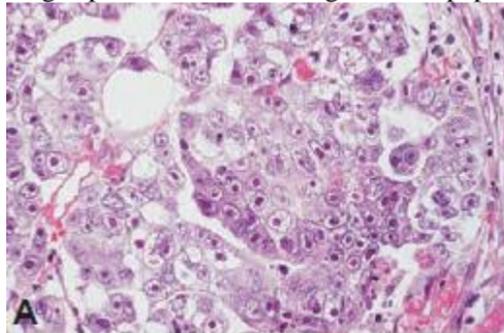


EMBRYONAL CELL CARCINOMA

- least differentiated tumor.

- **large cells** that proliferate in cohesive nests and sheets.
- abundant clear to somewhat violet-hued cytoplasm
- high **mitotic rate** and zones of **coagulative necrosis**
- may exceptionally replicate structure of early embryo, forming "**embryoid bodies**" (germ discs and miniature amniotic cavities).
- dense and diffuse cytoplasmic labelling for **cytokeratins!!!**
- positive **PLAP** and **OCT 4** immunoreactivity.
- absent c-kit expression.

Large epithelial cells forming abortive papillae and glandular structures with macronuclei:



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TERATOMA

- result from maturation along **embryonic** cell lines;

Mature teratoma - exclusively **fully differentiated, 'adult-type' tissue elements** - well encapsulated, noninvasive mixture of tissues (mucous-laden cysts, fat, chondroid nodules or bony spicules; rarely, teeth or well-formed hairs) derived from **all 3 germinal layers**.

vs. DERMOID – only ectoderm & mesoderm; EPIDERMOID – only ectoderm

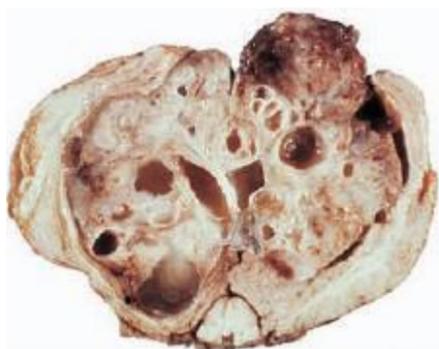
- mitotic activity is low / absent.
- **ectodermal** components are most common (skin, brain, choroid plexus); then **mesodermal** (cartilage, bone, fat and muscle); then **endodermal** (cysts lined by epithelia of respiratory or enteric type).
- advanced organogenesis and somatic organization may result in intracranial **FETUS-IN-FETU** (vs. incorporation of dizygotic twin via neural tube defect)

Immature teratoma (s. teratoid) - contains **incompletely differentiated components** (even in minimal amounts) resembling fetal tissues (small round cells resemble hypercellularity of **MEDULLOBLASTOMA**).

- hypercellular and mitotically active "stroma" (reminiscent of embryonic mesenchyme).
- reports of spontaneous **differentiation into fully mature tissues** over time (but usually in tumours subjected to therapy - "maturation" reflects selective radio- or chemoablation with continued enlargement of residual, differentiated lesions = "**GROWING TERATOMA SYNDROME**").
- **rhabdoid tumor** - atypical teratoid tumor; universal presence of rhabdoid (rod-shaped) cells; characteristic monosomy 22; occurs in infancy and early childhood; clinically aggressive.

Teratoma with malignant transformation - teratomatous neoplasm that contains **malignant component** of conventional somatic type (most often rhabdomyosarcoma or undifferentiated sarcoma)

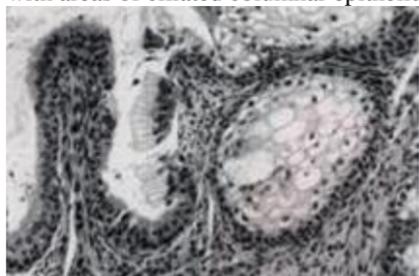
Large **teratoma** of cerebellum in 4 week-old infant, with characteristic cysts and chondroid nodules:



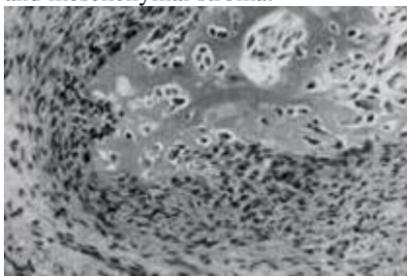
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Mature teratoma (well-differentiated tissue from all 3 germinal layers):

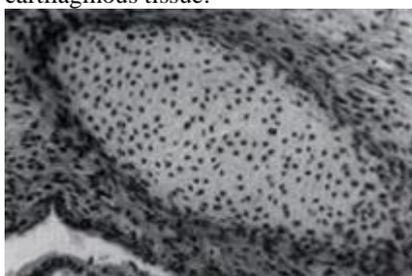
nonkeratinizing squamous epithelium alternating with areas of ciliated columnar epithelium:



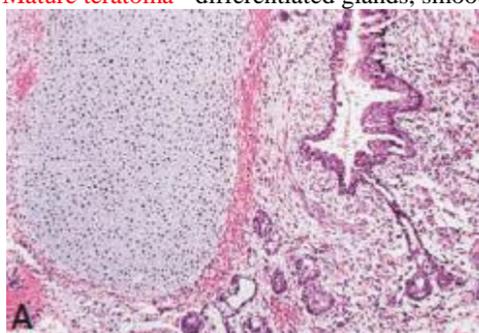
osteoid bone with surrounding periosteal tissue and mesenchymal stroma:



cartilaginous tissue:

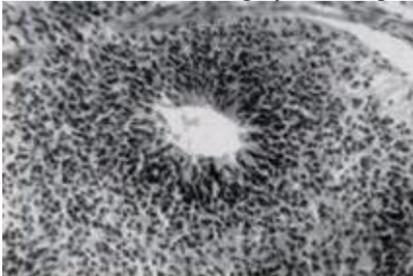


Mature teratoma - differentiated glands, smooth muscle bundles and nodule of moderately hypercellular cartilage:

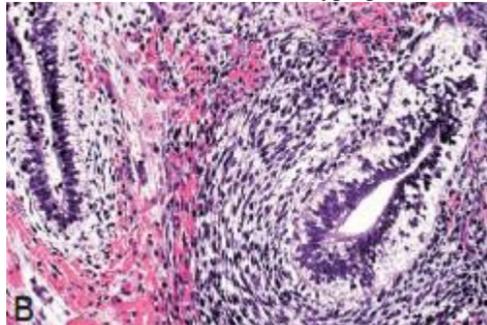


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Immature teratoma - highly cellular primitive elements resembling fetal neural tube structure:

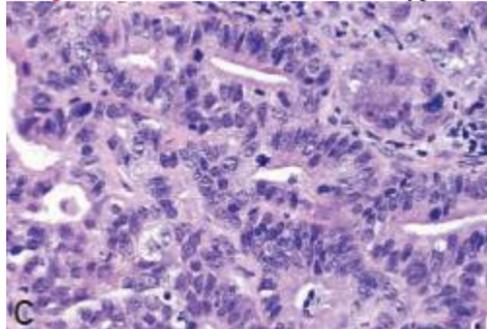


Immature teratoma with fetal-type glands and embryonic mesenchyme-like stroma.



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Malignant transformation into enteric-type adenocarcinoma:

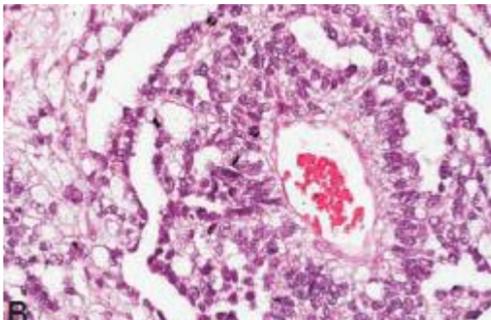
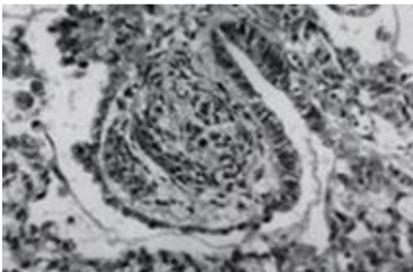


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YOLK SAC TUMOR (s. ENDODERMAL SINUS TUMOR)

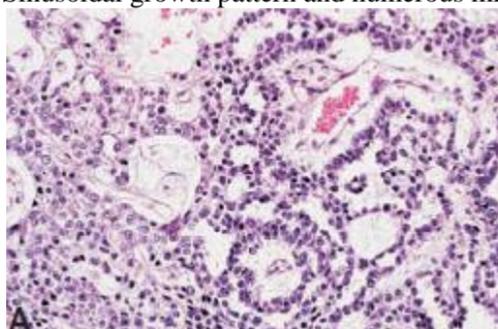
- result from maturation along **extraembryonic** cell lines *towards yolk sac*
- primitive-appearing epithelial cells (representing yolk sac endoderm) in loose, myxoid matrix (resembling extra-embryonic mesoblast)
- contains endodermal sinuses with distinctive papillae (**Schiller-Duval bodies** - pathognomonic glomeruloid structure - tumor cell-lined space with invaginated vascular pedicle covered by single layer of tumor cells).
- diagnostic, though inconstant, feature - **hyaline globules** (brightly eosinophilic, PAS-positive and diastase resistant) *within cytoplasm* or *free* in adjoining stroma.
- **mitotic activity** may be conspicuous, but necrosis is uncommon.
- characteristic immunoreactivity for **AFP** (cytoplasm and hyaline globules).
- macro: gelatinous appearance (accumulation of myxoid material).

Schiller-Duval body:



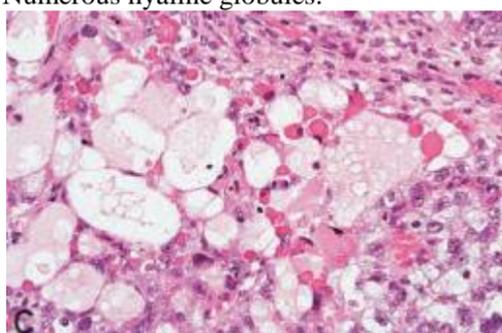
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Sinusoidal growth pattern and numerous mitoses:



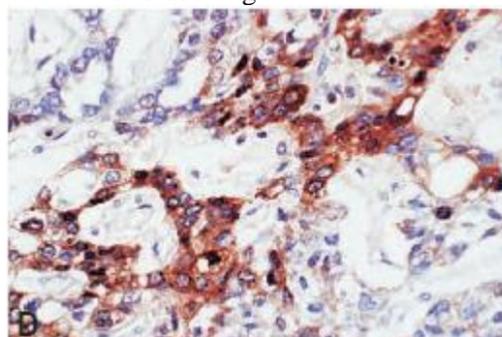
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Numerous hyaline globules:



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AFP immunolabelling:

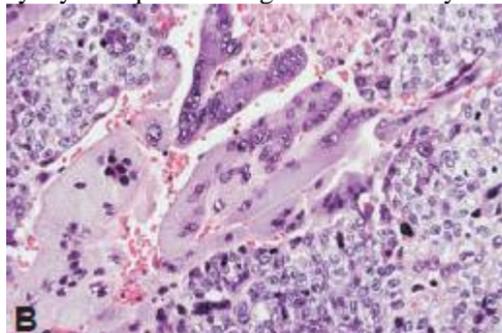


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CHORIOCARCINOMA

- result from maturation along **extraembryonic** cell lines *towards trophoblast*
- large cytotrophoblastic mononucleated cells + giant syncytiotrophoblastic cells.
- ectatic stromal **vascular channels, blood lakes** and extensive **haemorrhagic necrosis** ("menstruation in brain") are rule.
- staining for **β-HCG** and **HPL** are characteristic.

Syncytiotrophoblastic giant cells and cytotrophoblasts:



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CLINICAL FEATURES

See p. Onc28 >>

- more protracted symptomatic interval than other CNS tumors.
- CNS germ cell tumors may also cause **pseudoprecocious* puberty**:
 - *pseudo because hypothalamic-gonadal axis is not mature
 - a) tumor secretion of **hCG** [properties of LH] → testosterone production by neoplastic syncytiotrophoblasts in **boys**.
 - b) tumor expression of **cytochrome P450 aromatase** → conversion of C19 steroids to estrogens → precocious puberty in **girls**.

DIAGNOSIS

MRI

- largely non-specific.

Useful generalizations (except teratomas):

- **solid** masses
- iso- / hyperdense relative to grey matter
- prominent homogenous contrast **enhancement**
- intratumoral **hemorrhage** is particularly characteristic of CHORIOCARCINOMA.

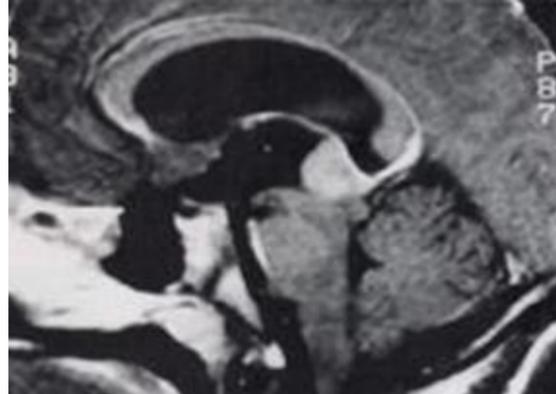
Teratoma

- **TERATOMAS** can contain tissue from all 3 germinal layers → well-circumscribed benign tumor with multicystic markedly heterogenous MRI signals (**fat*** and **calcification** are typical; can demonstrate ring enhancement).

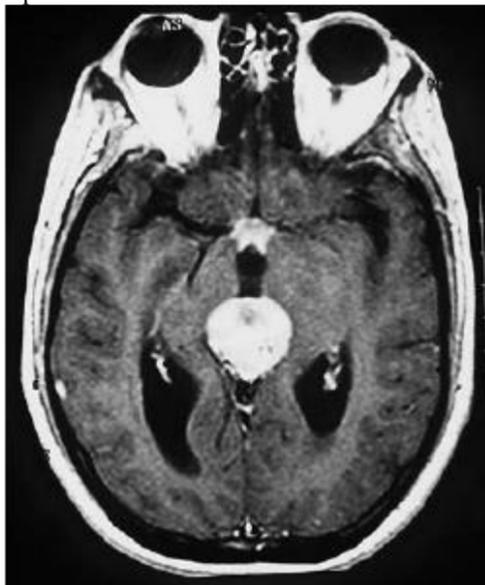
*areas of low attenuation (adipose tissue) help to distinguish it from other pineal region tumors.

- **MRI of spine** - for drop metastasis (perform before and after surgery). see p. Onc3 >>

Contrast T1-MRI (**germinoma**) - homogenous enhancement:

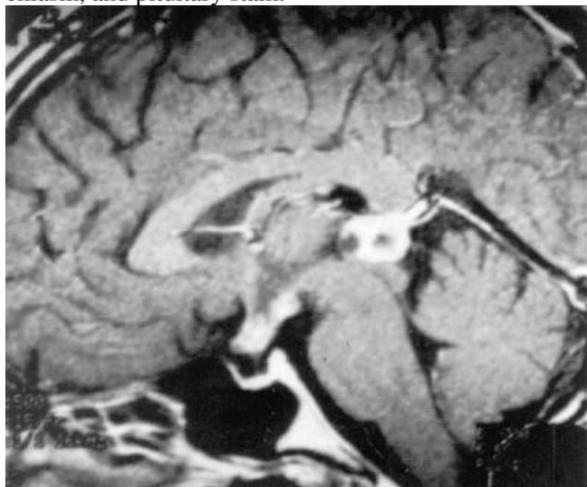


MRI of solid, contrast-enhancing **germinoma** of pineal region, with smaller CSF-borne metastasis in suprachiasmatic cistern:

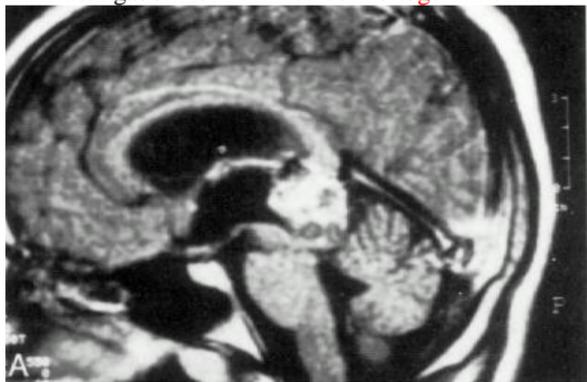


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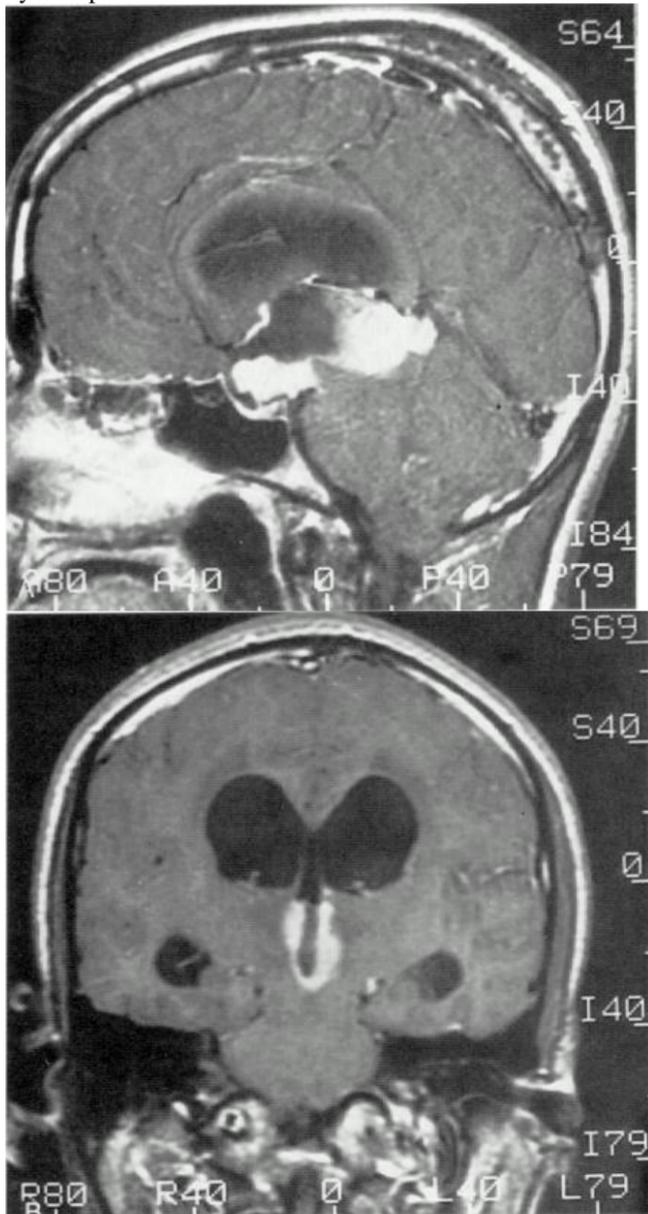
MRI with gadolinium - multicentric **germinoma** involving pineal region, infiltrating mammillary bodies, optic chiasm, and pituitary stalk:



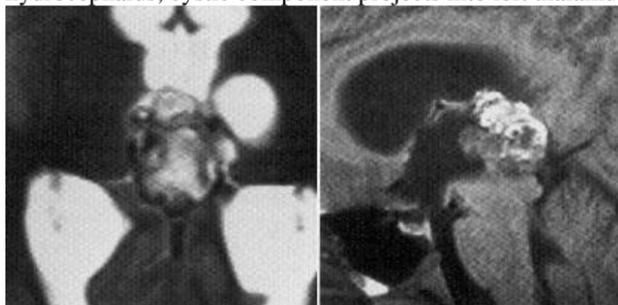
MRI with gadolinium - **mixed dermoid/germinoma**:



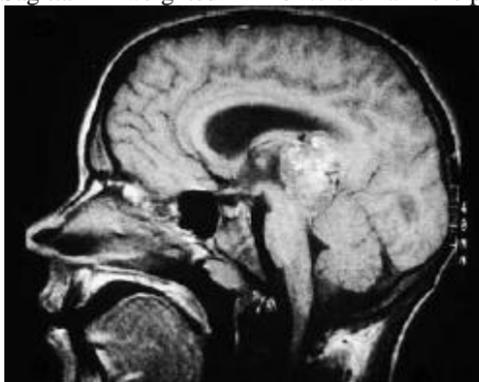
Contrast MRI - pineal and suprasellar **germinoma**, with spread along walls of 3rd ventricle; obstructive hydrocephalus:



Pineal **teratoma** (T2- and T1-MRI) - large, mixed signal intensity tumor infiltrates midbrain and causes hydrocephalus; cystic component projects into left thalamus:



Sagittal T1-weighted MRI of **teratoma** in the pineal region, occupying dorsal aspect of third ventricle:



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SERUM AND CSF TUMOR MARKERS

(extremely important prior to surgical resection - provides reference point for follow-up – response to therapy and recurrence)

Presurgical assessment: **AFP** and **β-HCG** in serum and CSF

- **CSF levels** tend to be more sensitive and should be compared with **serum levels**; see p. 1707a >>
Absence of AFP or β-hCG does not rule out mixed germ cell tumor!
N.B. AFP and β-hCG may also be elevated in other conditions! see p. 1707a >>
- 1) **alpha-fetoprotein (AFP)** indicates presence of **fetal yolk sac elements** – *ENDODERMAL SINUS TUMORS*, *EMBRYONAL CELL CARCINOMAS*, *IMMATURE TERATOMAS* (*MATURE TERATOMAS* do not secrete AFP)
 - 2) **β-hCG** produced by **trophoblastic elements** – *CHORIOCARCINOMAS*, *EMBRYONAL CELL CARCINOMAS*, *MIXED GERMINOMAS* with syncytiotrophoblastic giant cells (*PURE GERMINOMAS* are nonsecretory).

Tumor	AFP	β-hCG
<i>pure germinoma</i>		
<i>mixed germinoma</i> with syncytiotrophoblastic giant cells		+
<i>mature teratomas</i>		
<i>immature teratomas</i>	±	
<i>endodermal sinus tumors</i>	+	
<i>choriocarcinomas</i>		+
<i>embryonal cell carcinomas</i>	+	+

- 3) *GERMINOMAS* also secrete lactic dehydrogenase (LDH) isoenzyme and placental alkaline phosphatase (PLAP) – but useful only on immunohistochemical slides; some use also for follow up in serum!s

BIOPSY

- recommended whenever possible! (except in markedly elevated AFP and β-hCG)

VENTRICULAR ENDOSCOPY

- especially sensitive to disclose minute tumour nodules on or beneath ependyma that are not detectable on MRI

TREATMENT

Therapy is based on tumor pathology;

e.g. markedly elevated AFP and β-hCG (pathognomonic for *GERM CELL TUMORS*) → chemotherapy or radiotherapy without tissue biopsy (initial surgical intervention may become obsolete for *GERMINOMAS*)

GERMINOMAS – radiation.

NONGERMINOMATOUS GERM CELL TUMORS – chemotherapy → restaging → radiation.

SURGERY

See p. Onc28 >>

- some centers give trial dose of radiation to pineal tumor – radiation “melts” germinomas.

RADIOTHERAPY

- depends upon tumor histology:

- a) *mature teratomas* – cured with surgery alone (no adjuvant radiation) → follow with serial MRIs.
- b) **malignant germ cell tumors**: 40 Gy to ventricular system → 15 Gy to tumor bed (in 1.8 Gy daily fractions).

N.B. *GERMINOMAS* are among most radiosensitive tumors (vs. nongerminomatous malignant germ cell tumors) and tend to spread along ventricular walls
5-year survival rates > 75% and 10-year survival rates 69% have been reported with radiation 50 Gy.

NONGERMINOMATOUS MALIGNANT GERM CELL TUMORS (whether localized or disseminated) → chemotherapy → restaging:

localized tumors → 54-60 Gy to tumor → 24 Gy to ventricular field.

disseminated tumors → craniospinal irradiation (54-60 Gy to tumor, 45 Gy to ventricular system, 35 Gy to spinal cord, 45 Gy to any localized spinal cord lesions).

- **prophylactic spinal irradiation** is controversial (current trend is to administer spinal irradiation 35 Gy *only for documented seeding*); rate of drop metastases is highest for *ENDODERMAL SINUS TUMORS*.
- **radiosurgery** has no role (*GERMINOMAS* have excellent long-term response to fractionated radiation, and it is unlikely that radiosurgery can improve on these results).

CHEMOTHERAPY

- means of minimizing amount of radiation for children.

Germ cell tumors are sensitive

Although systemic germ cell tumors are very chemosensitive, CNS germ cell tumors are less responsive!

- *NONGERMINOMATOUS germ cell tumors* benefit most - chemotherapy prior to radiation!
EINHORN regimen = cisplatin + vinblastine + bleomycin
Most common regimen: cisplatin (or carboplatin) + etoposide
- *GERMINOMAS* are so radiosensitive that chemotherapy is not required (platinum-based chemotherapy first-line treatment only in very young children in order to avoid radiation).
- delayed surgery after radiation therapy and chemotherapy is indicated for residual tumors whose germ cell markers have normalized (residual tumor is likely to be benign germ cell elements that are resistant to radiotherapy and chemotherapy).

PROGNOSIS

Prognosis – mostly depends on histology:

MATURE TERATOMAS (potentially curable) > *GERMINOMAS* (excellent prognosis; > 90% 5-yr survival; 85% 10-year survival following craniospinal irradiation alone) > *NONGERMINOMATOUS GERM CELL TUMORS* (patients rarely survive beyond 2 years)

- **local recurrence** and **CSF-borne dissemination** are usual patterns of disease progression.
Metastases within CNS and vertebral column are most common causes of death!
ICH is most common cause of death in CHORIOCARCINOMA!

Can recur locally / distally as late as 5 yrs after diagnosis! – regular follow-up:

- 1) **MRI**
- 2) **tumor marker*** follow-up: q 1-2 months for 1 year → q 3 months for 1 year → less frequently.

*even if markers were not abnormal at diagnosis

BIBLIOGRAPHY for ch. “Neuro-Oncology” → follow this [LINK >>](#)