Tumors of Hematopoietic System

Last updated: April 12, 2020

About lymphomas in general → see p. 1587 >>

PRIMARY CNS LYMPHOMA (PCNSL)

(old names - ***Primary Reticulum Cell Sarcoma, Microglioma***)

- extranodal malignant non-Hodgkins lymphomas arising in CNS + absence of lymphoma outside nervous system at time of diagnosis (i.e. differential from secondary CNS involvement in systemic lymphomas).

EPIDEMIOLOGY

ICD-O code 9590/3

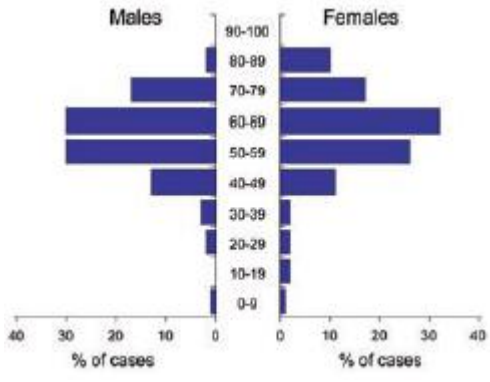
INCIDENCE

- **AIDS epidemic** → markedly increased INCIDENCE world-wide: 0.8–1.5% → 6.6%
  - prior to introduction of HAART, incidence in AIDS patients was about 3600-fold higher than in general population (2–12% patients developing primary CNS lymphomas, mainly during late-stage AIDS)
- CNS involvement occurs in 22% of **post-transplant** lymphomas (55% are confined to CNS).
- in **immunocompetent** patients, incidence has increased in some but not all series and populations; current incidence in immunocompetent patients ≈ 51 per 10,000,000.
- currently, account for 1-2% of primary CNS tumors.

AGE AND SEX

- male: female = 3:2 (but among HIV-infected 95% are males).
- affects all ages (peak 6-7 decade)
- age at manifestation among immunocompromised patients:
  inherited immunodeficiency patients - 10 years
  transplant recipients - 37 years
  AIDS - 39 years (90% males).

Age and sex distribution in immunocompetent patients:



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

ETIOLOGY

- no unique molecular marker has been identified to discriminate PCNSL from its systemic counterpart (i.e. systemic lymphoma metastatic to CNS).
- commonly associated with ***immunodeficiency states*** (AIDS patients, transplant recipients, congenital immunodeficiencies);
  - overwhelmingly common risk factor for HIV-related PCNSL is intravenous drug abuse!

- all PCNSLs in AIDS patients express *Epstein-Barr virus*-related genome (HIV reduces host immunity to EBV infection → chronic stimulation of lymphocyte clones by EBV may be sufficient to produce lymphoma); EBV genome is present in tumour cells in > 95% patients, vs. in 0–20% of immunocompetent patients

  c-myc *gene translocations occur in EBV-associated lymphomas that occur outside CNS but not in PCNSL*
- involvement of other viruses has been largely ruled out (incl. HHV-6, HHV-8, polyomaviruses SV40 and BKV).
  - 56 % patients* have *human herpes virus 8* in their tumors (direct causal relationship has not yet been established).

    *both immunocompetent and immunocompromised

HISTOGENESIS HYPOTHESES

A. B-cells transformed at site elsewhere in body and then develop adhesion molecules specific for cerebral endothelia.
B. Lymphoma cells systematically eradicated by intact immune system but may escape immune system within CNS. Astrocyte-derived B cell activating factor of tumour necrosis factor family (BAFF) may support survival of malignant BAFF-receptor expressing B cells.
C. Polyclonal intracerebral inflammatory lesion may expand clonally within brain and progress to monoclonal neoplastic state.

PATHOLOGY

PCNSL - rare form of extranodal non-Hodgkin lymphoma:

95-98% - high-grade *diffuse large B-cell lymphoma* (DLBCL), frequently of immunoblastic type; show immunohistochemical expression of pan-B markers (CD19, CD20 and CD79a).
2% - T cells
remainder - poorly characterized low-grade lymphomas, Burkitt lymphomas.

- originates in brain, leptomeninges, spinal cord, or eyes.
  - *tumor likely arises in extraneural environment with subsequent localization to CNS, possibly by virtue of specific neurotropism.*
  - *how lymphoma can develop within CNS, which lacks lymph nodes and lymphatics, remains unanswered; however, lymphocytes do normally traffic in and out of CNS.*
- diffuse growth pattern but typically *remains confined to CNS* (rarely spreads outside nervous system) - can be classified as stage 2 disease.

  PCNSL is non-Hodgkin lymphoma arising in and confined to CNS! –
  PCNSL is primary CNS tumor without evidence of systemic lymphoma!

  N.B. *if lymphoma is also found outside of CNS* → diagnosis is *non-Hodgkin lymphoma metastatic to CNS*.
- **multiple** in 25% cases (50% in AIDS) - easily mistaken for metastases.
- relatively well defined compared with gliomas but are not as discrete as metastases.
- neither *necrosis* nor *hemorrhage* is dominant feature (necrosis is frequent in AIDS patients!).

LOCATION

- 60% in **supratentorial space**, 13% in posterior fossa, 1% in spinal cord.
- 25–50% are **multiple** (60–85% in AIDS and posttransplant subjects).
- brownish masses involving ***periventricular white matter, basal ganglia, corpus callosum***!!!
  - tumor may spread *through white matter tracts*, such as corpus callosum, or *through CSF pathways* (diffuse periependymal or intraventricular CT/MRI enhancement).
- ***OCULAR involvement*** (uvea or vitreous humor) occurs in 20% cases at time of diagnosis (may antedate intracranial lesions).
- localized ***intradural spinal masses*** may develop.

  vs. *METASTATIC NON-HODGKIN'S LYMPHOMA* - tends to be ***spinal epidural*** or ***meningeal*** (epidural or leptomeningeal)!; *HODGKIN'S DISEASE* rarely involves either brain or meninges!
- secondary **meningeal spread** is seen in 30–40% (primary leptomeningeal lymphoma may account for up to 8% of these tumors); at autopsy, 50-100% patients have ***leptomeningeal lesions***.
- primary **dural / epidural** malignant lymphomas are very rare (i.e. dural-based lymphoma – most likely metastatic systemic lymphoma)
- **distant metastases** is present in 6–10%
- NEUROLYMPHOMATOSIS (rare) - lymphoma restricted to peripheral nerve
- ***complete systemic staging*** is recommended (8% patients have occult lymphoma)

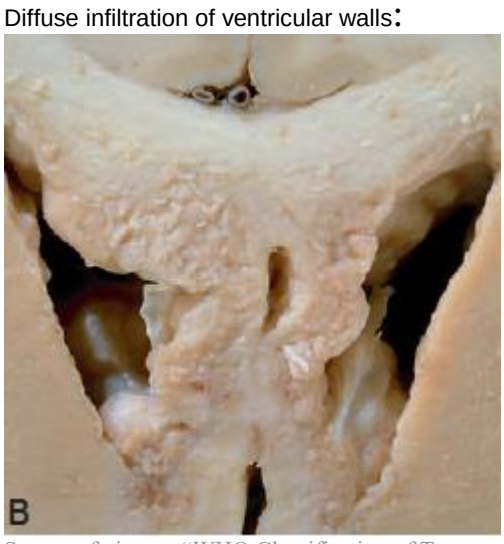
  N.B. secondary CNS lymphomas occur preferentially in meninges (but parenchymal lesions may also occur)

MACROSCOPY

- single or multiple masses in cerebral hemispheres.
- deep-seated and adjacent to ventricular system (superficial tumors may also be encountered)
- form well demarcated, firm, centrally necrotic, focally hemorrhagic, grey-tan, yellow to virtually indistinguishable from adjacent neuropil with poor demarcation (resemble gliomas)

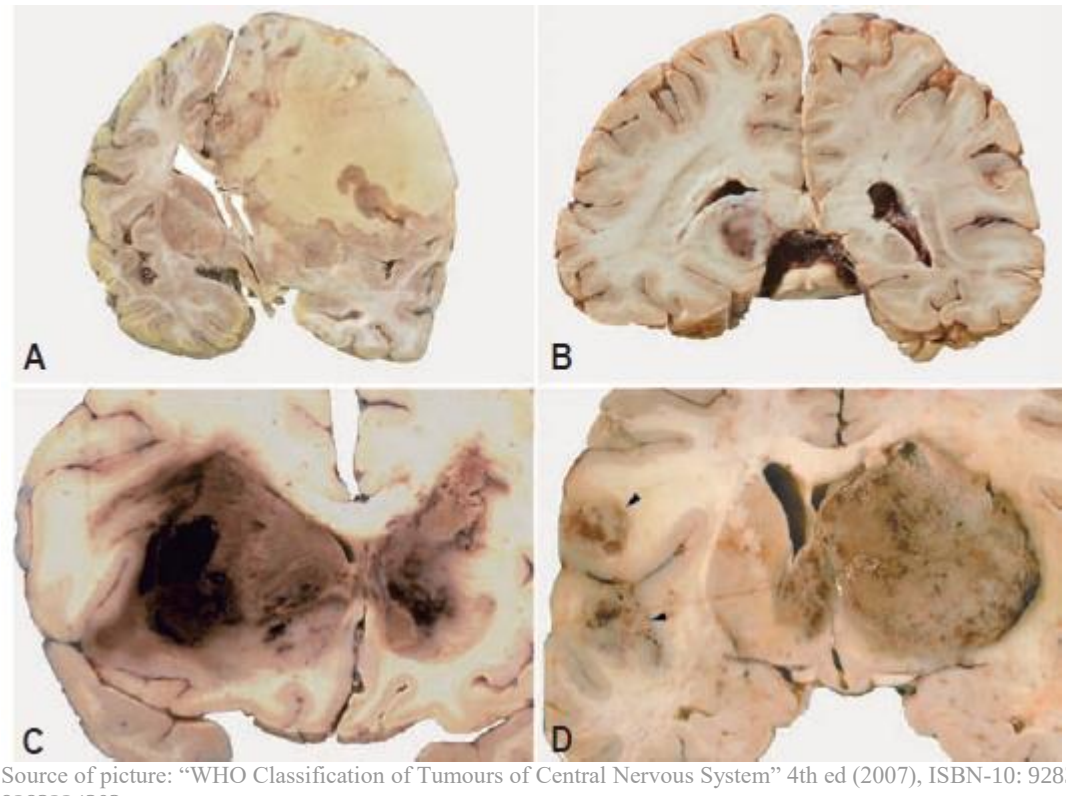
  LYMPHOMATOSIS CEREBRI - diffusely infiltrating forms

Diffuse infiltration of ventricular walls:



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

A. Large, necrotizing B-cell lymphoma in HIV-1-infected seven month old infant.
B. B-cell lymphoma involving medial temporo-occipital lobe.
C,D. Primary malignant CNS lymphomas of basal ganglia with extension into contralateral hemisphere. **D** Note the additional foci in left insular region (*arrows*).



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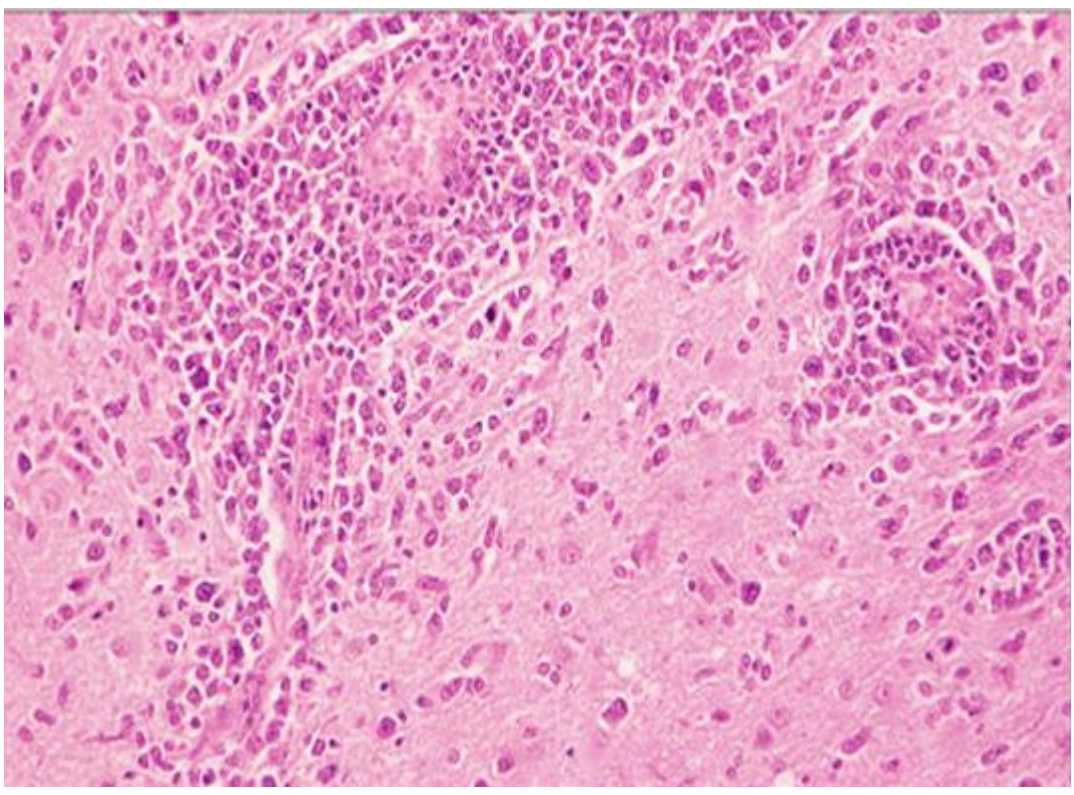
HISTOLOGY

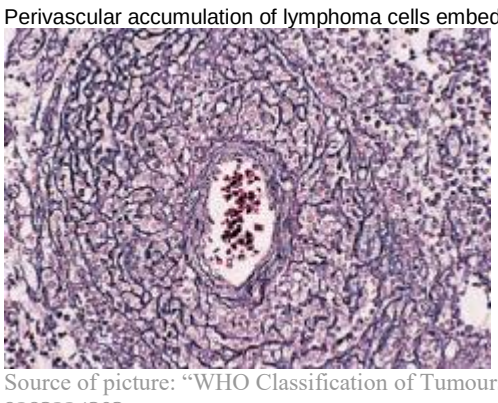
- diffusely infiltrative, densely cellular.
- ***predilection for blood vessels*** (lymphoid collars around small cerebral vessels is typical - ***angiocentric growth pattern***) – differentiate form viral infections!!!
- *reticulin stains* demonstrate that tumor cells are separated from one another by silver-staining material ("hooping" pattern - characteristic of PCNSL).
- *reactive T-cell infiltrates* can be present in varying degrees (not in AIDS patients).
  if patient is treated by corticosteroids, reactive T cells may be all that is apparent on biopsy specimen, making accurate diagnosis difficult.

PROLIFERATION

- proliferative activity is high with Ki-67/MIB-1 labelling indices even > 90%
- ***apoptotic cells*** are detected in majority (77%) of tumours; ↑↑↑ upon corticosteroid treatment.

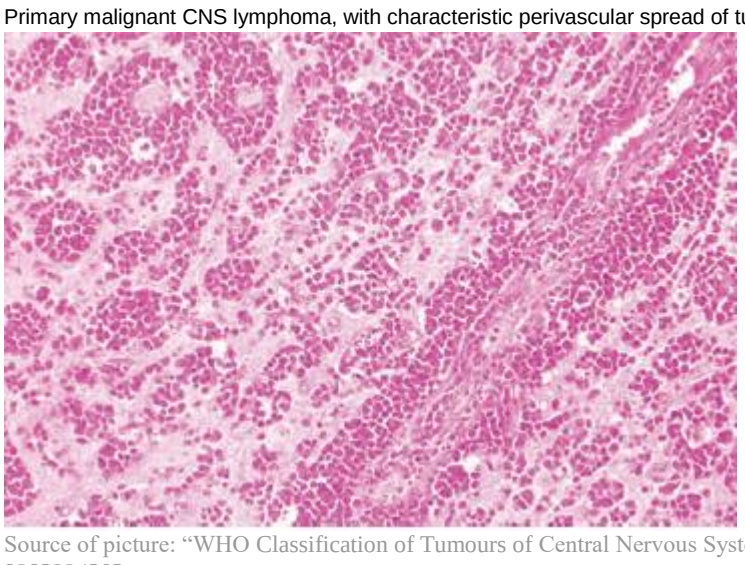


Perivascular accumulation of lymphoma cells embedded in concentric network of reticulin fibers:



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

Primary malignant CNS lymphoma, with characteristic perivascular spread of tumour cells:



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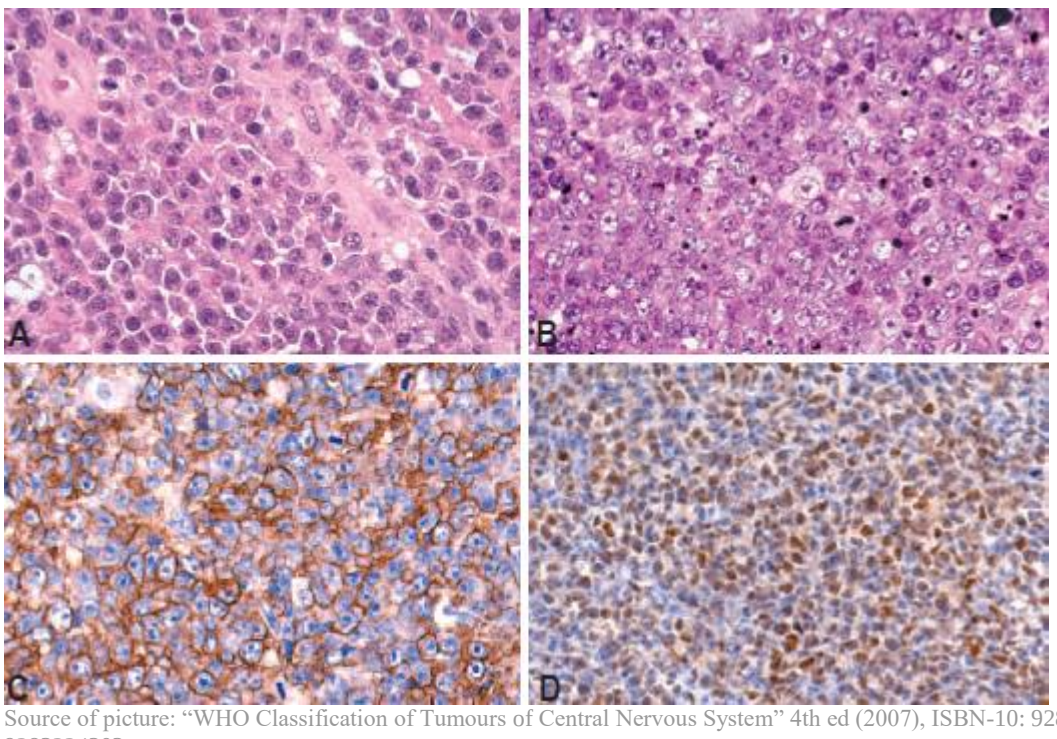
Histological features of primary malignant lymphomas.
A Malignant, diffuse large B-cell lymphoma.
B Highly anaplastic malignant lymphoma with numerous mitotic figures and extensive apoptosis.
C Tumour cells express pan-B-cell marker CD20.
D Expression of BCL6 protein by tumour cells



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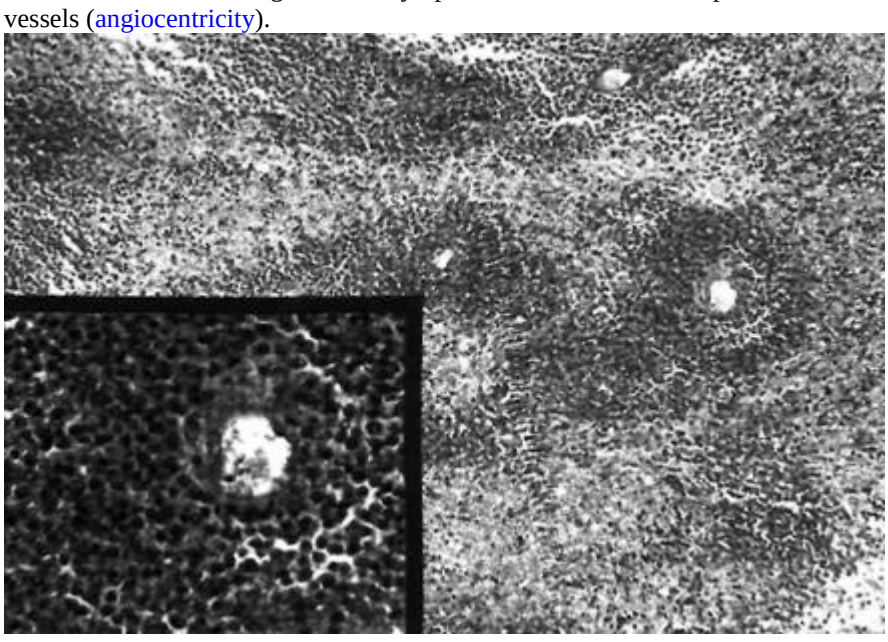
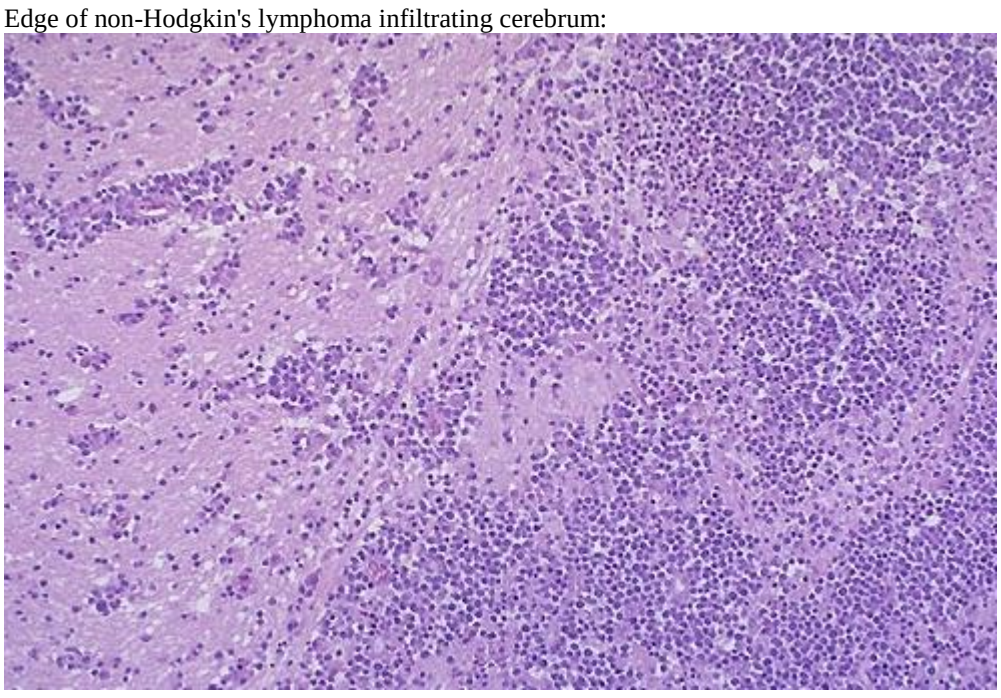
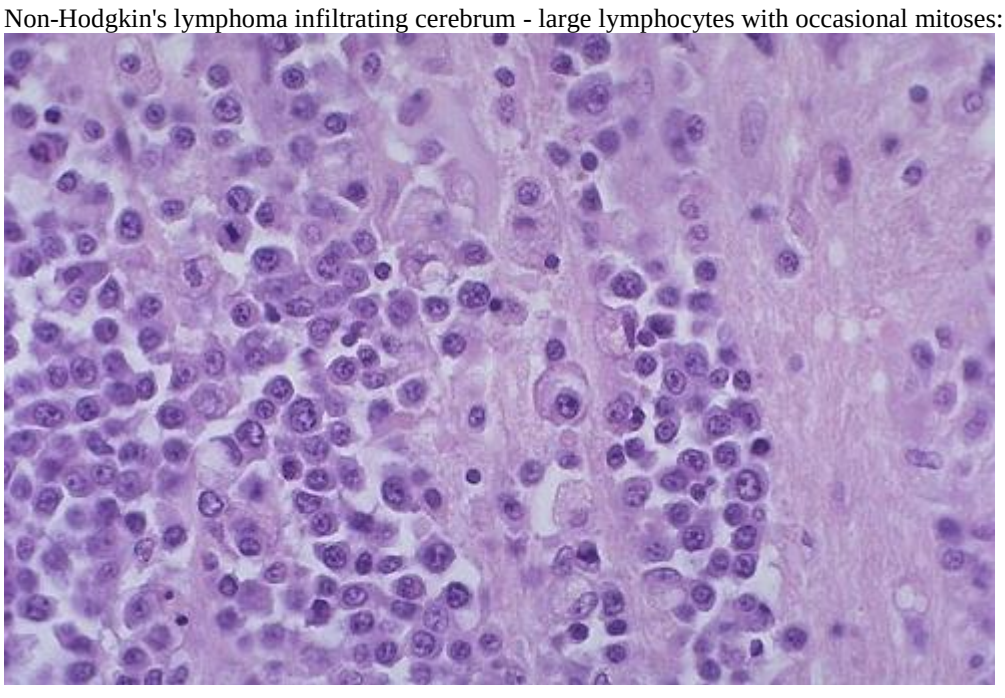
Clusters of tumor cells have infiltrated tissue, with special predilection for perivascular locations; scattered reactive gliosis in between tumor clusters.
Inset: tumor cells with high nuclear cytoplasmic ratio without cell processes; characteristically infiltrate walls of blood vessels (angiocentricity).



Edge of non-Hodgkin's lymphoma infiltrating cerebrum:



Non-Hodgkin's lymphoma infiltrating cerebrum - large lymphocytes with occasional mitoses:



CLINICAL FEATURES

- progressive symptoms:

1. Intracranial mass lesion (as any other malignant brain tumor):
   - because *frontal lobe* is most frequently involved region, ***neurocognitive changes*** (dementing process with lethargy) are common presenting symptoms (20–30%)
     - ANGIOTROPIC LYMPHOMA manifests as rapidly progressing dementia with multifocal neurological deficits
     - AIDS patients are likely to present with **encephalopathy** (correlates with multifocal, diffuse MRI enhancement) – up to progressive dementia or stupor with no focal signs.
   - ***focal neurological deficits*** (50–80%)
   - *seizures* are less common (5-20%) (most PCNSLs involve deep brain structures rather than seizure-prone cerebral cortex).

2. Ocular involvement (uveitis or vitreous lymphoma) ***blurred vision*** or ***asymptomatic***.
   - lymphoma can originate within eye → eventually develop cerebral lymphoma (after several years of latency).
   - disease outside of globe but within orbit is not feature of ocular lymphoma, but rather metastasis from systemic lymphoma.

3. Focal deposits on cranial / spinal nerve roots → ***neuropathies***, ***radiculopathies***.

- 50% of transplantation-associated primary CNS lymphomas appear within 1 year after transplantation

DIAGNOSIS

Until diagnosis confirmation, corticosteroids should be withheld (unless patient is in immediate danger of herniation - rare situation) - steroids may alter or even eliminate ability to establish diagnosis pathologically! (biopsy following steroid administration often yields normal, necrotic, or nondiagnostic tissue).

Steroid-induced resolution of intracranial mass does not establish diagnosis of PCNSL, because nonneoplastic contrast-enhancing processes (e.g. MS, sarcoidosis) can also resolve!

CBC

HIV testing

Toxoplasma gondii serology

Chest X-ray, chest & abdominal CT (staging procedures - to rule out metastatic disease)

Ophthalmologic examination - for all patients.

- *cellular infiltrates in vitreous* on slit-lamp examination → vitrectomy (may establish diagnosis – no need for brain biopsy).

IMAGING

- brain & spinal cords:

N.B. steroid-treated lesions may disappear within hours! (send CSF before starting steroids)

CT – isodense or hyperdense (due to ***hypercellularity***); enhance homogeneously.

T1-MRI – isointense on noncontrast MRI.

- smoothly rounded homogeneous dense enhancement (ring enhancement is rarely seen, but is common in AIDS due to central necrosis – strongly mimics *Toxoplasma encephalitis*!!!).

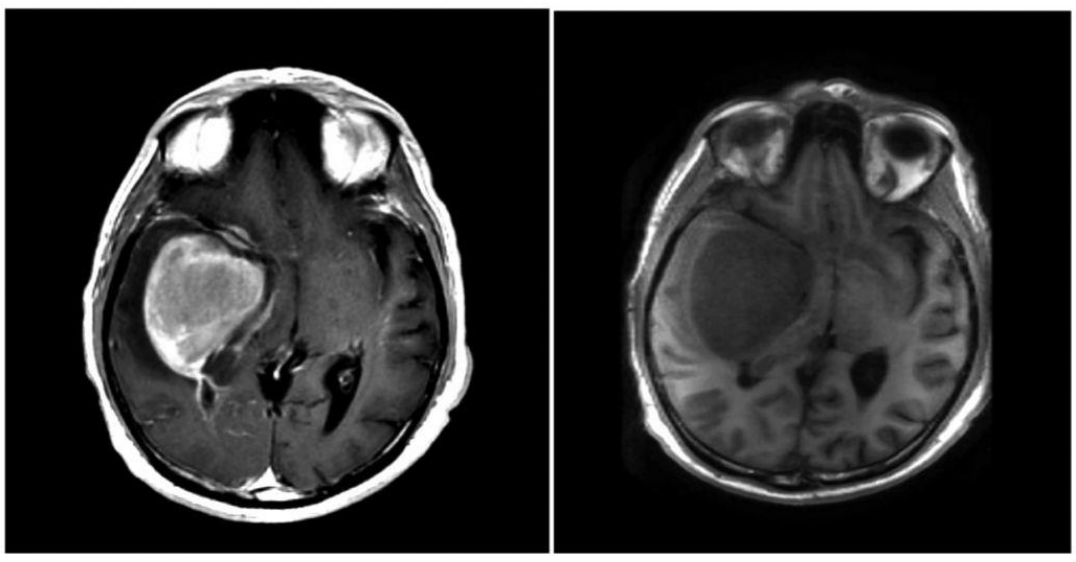
  Prominent contrast enhancement ("ligh bulb") is characteristic of PCNSL!
  Diffusion restriction – rather unique among tumors (other tumors do not restrict)
- diffuse bilateral symmetrical subependymal or intraventricular enhancement indicates characteristic spread mode (may mimic butterfly glioma).
- less edema than in malignant gliomas and metastases.

SPECT / PET – for AIDS patients (ring-enhancing mass lesions) to help distinguish between hypometabolic toxoplasmosis and hypermetabolic PCNSL.

For *AIDS patients*, most difficult problem – differentiate between PCNSL and Toxoplasma – frequently coexist!

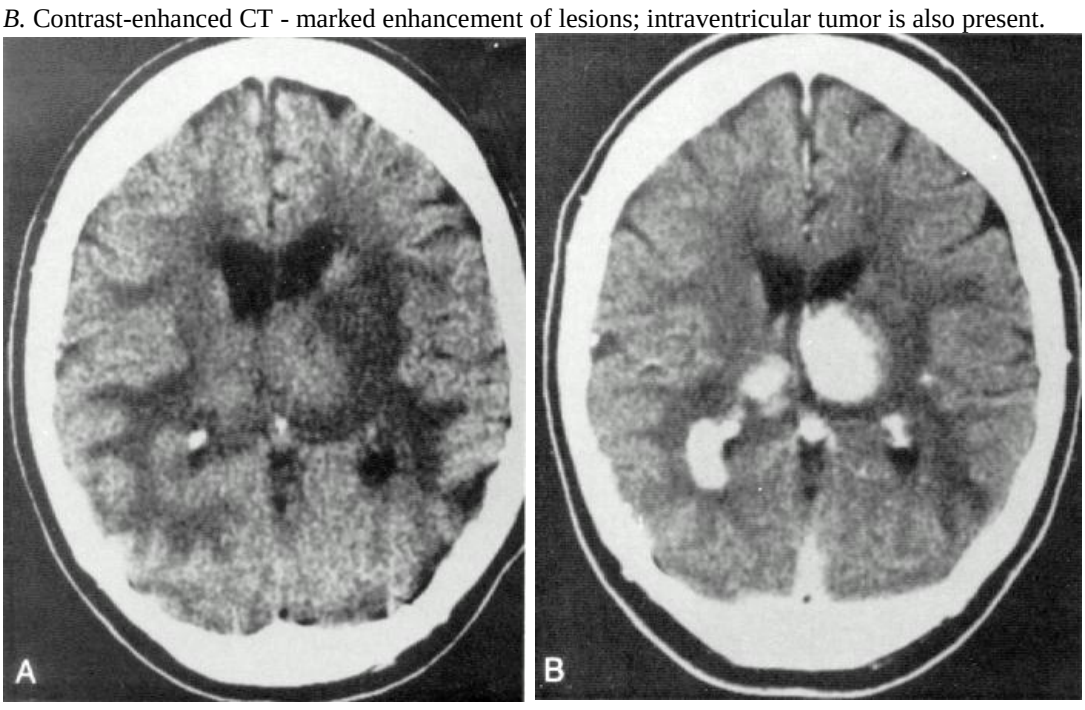
– positive *Toxoplasma serology*, presence of *multiple lesions* favors toxoplasmosis

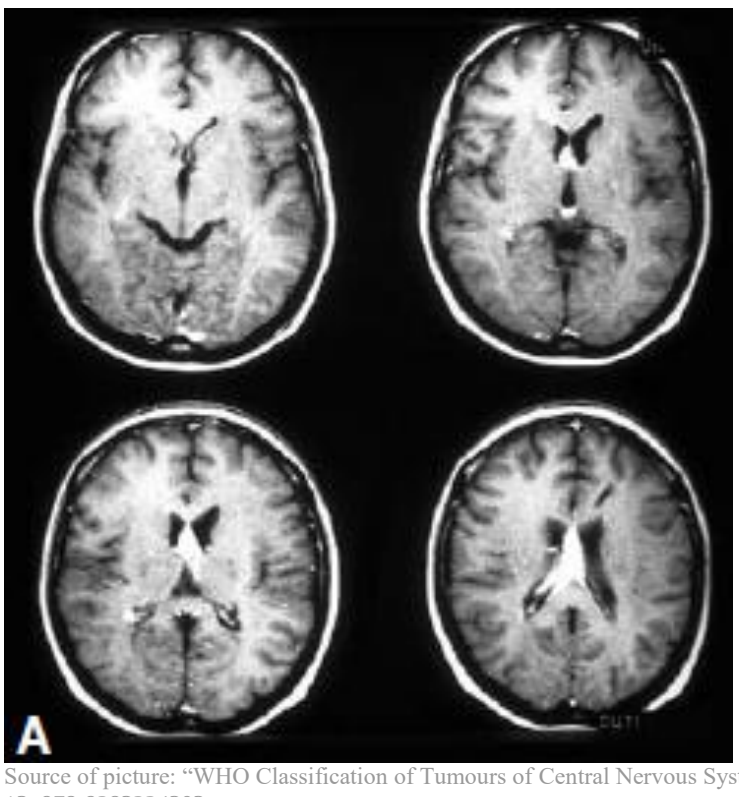
T1 MRI wo/w



Source of picture: Yun et al. 2016

Thalamic PCNSL:
A. Noncontrast CT - isodense bilateral thalamic lesions with white matter edema.
B. Contrast-enhanced CT - marked enhancement of lesions; intraventricular tumor is also present.





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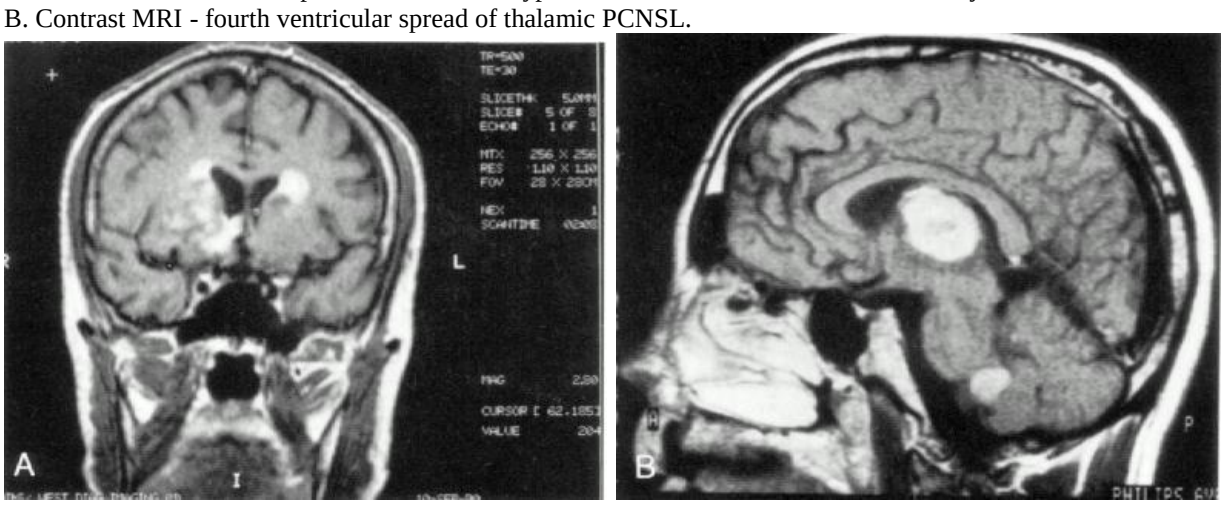
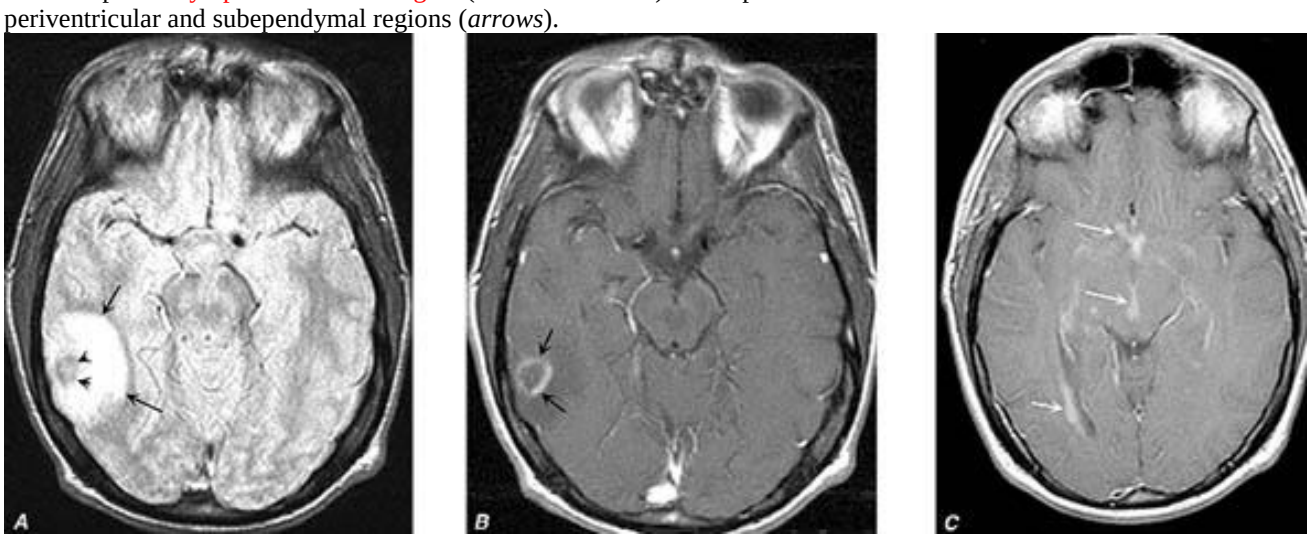
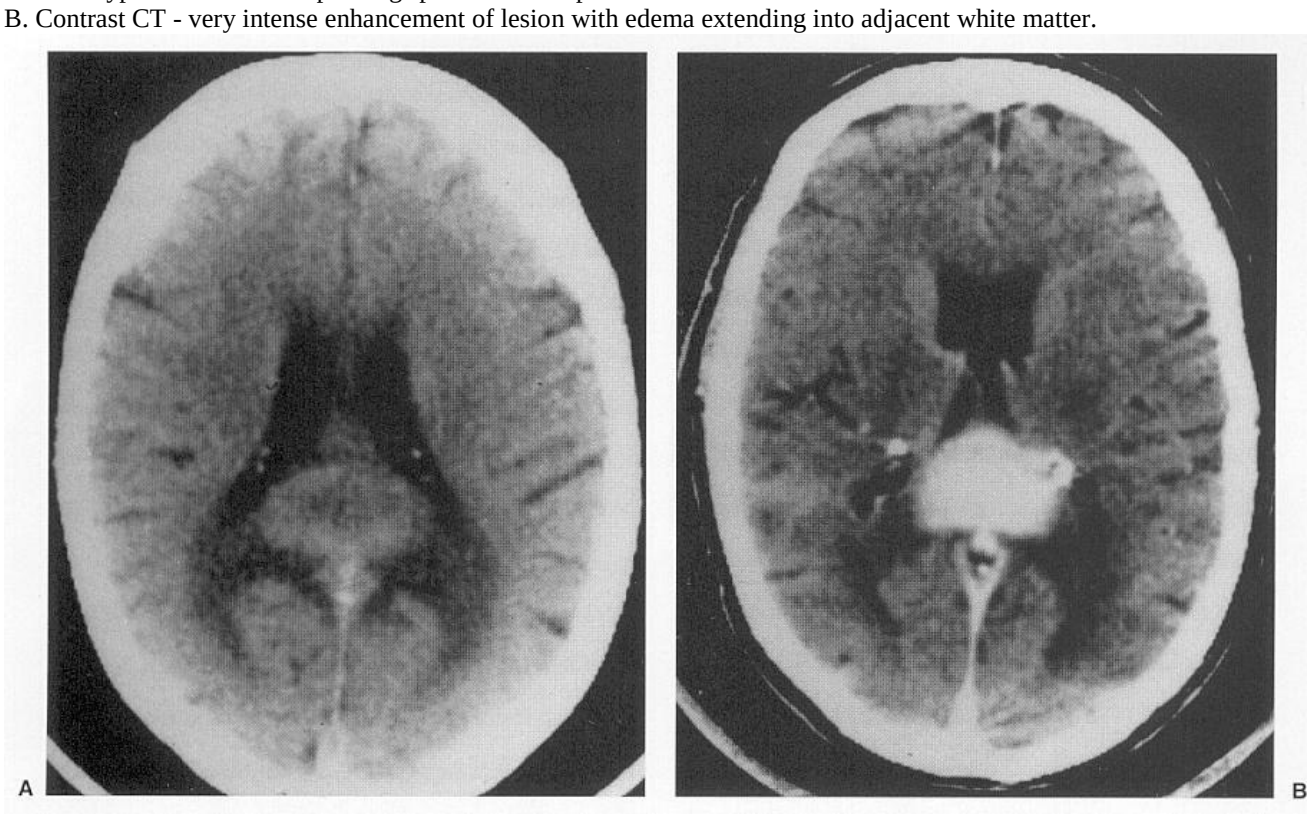
Ependymal spread:
A. Contrast MRI - bilateral periventricular and hypothalamic lesions that enhance markedly.
B. Contrast MRI - fourth ventricular spread of thalamic PCNSL.



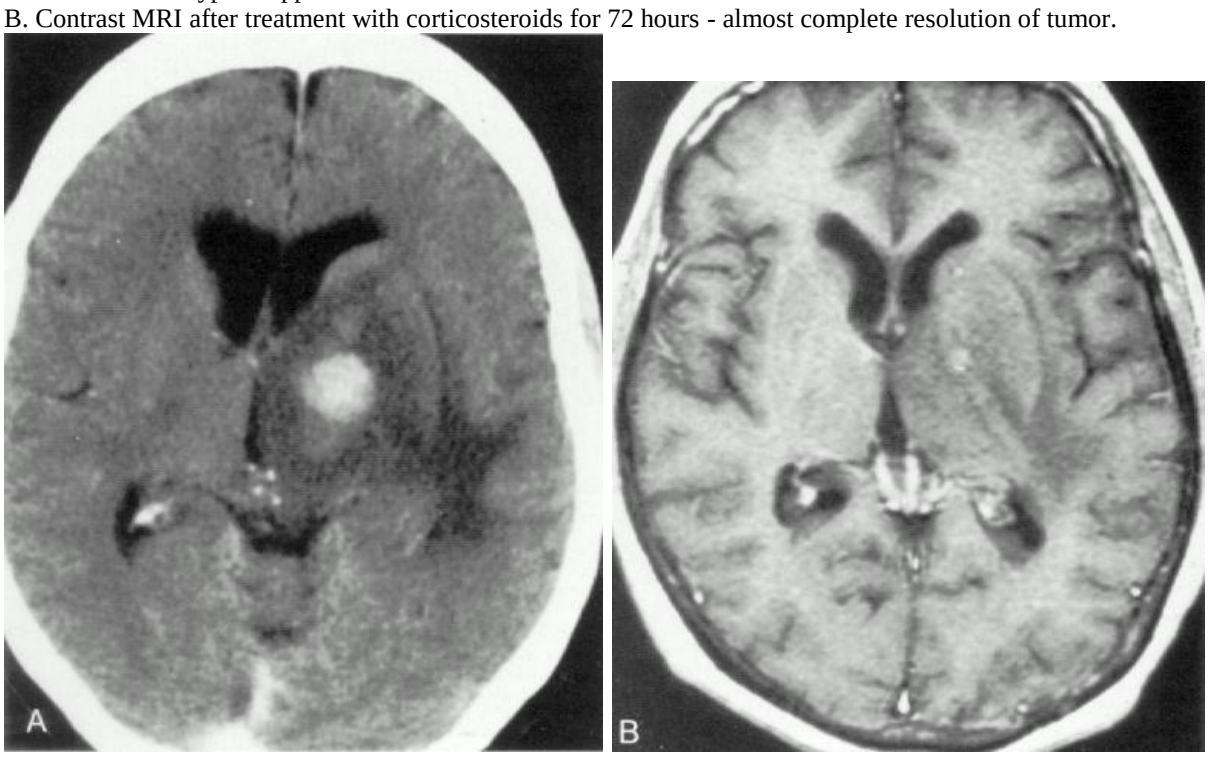
A. Proton density-MRI - low signal intensity nodule (*small arrows*) surrounded by ring of high signal intensity edema (*larger arrows*).
B. Contrast T1-MRI - ring enhancement surrounded by nonenhanced rim of edema.
C. Other patient lymphomatous meningitis (contrast T1-MRI) - multiple areas of abnormal enhancement in periventricular and subependymal regions (*arrows*).



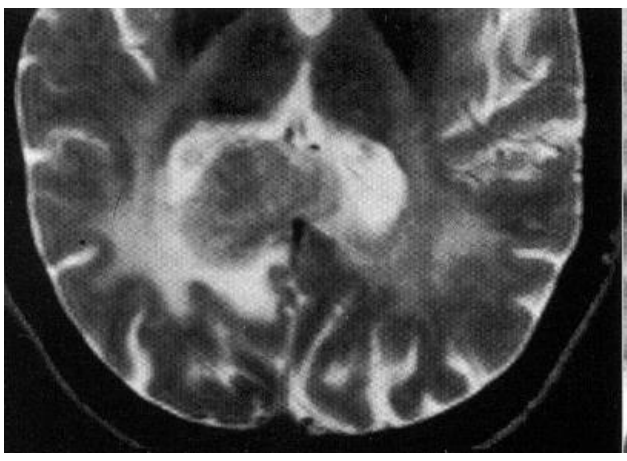
A. CT - hyperdense lesion expanding splenium of corpus callosum.
B. Contrast CT - very intense enhancement of lesion with edema extending into adjacent white matter.



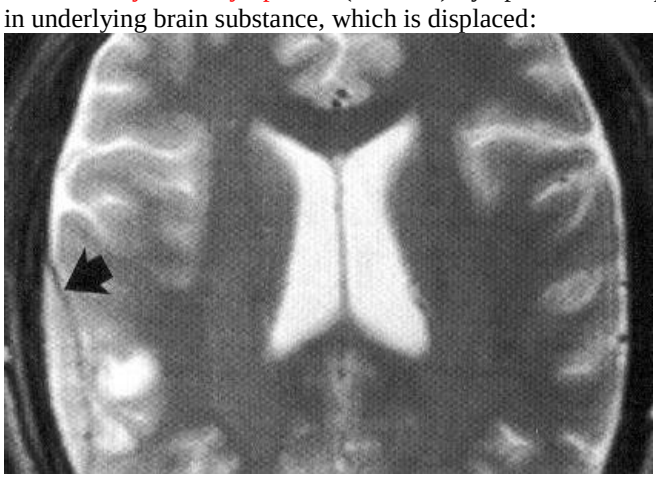
Resolution with corticosteroid treatment:
A. Contrast CT - typical appearance of PCNSL.
B. Contrast MRI after treatment with corticosteroids for 72 hours - almost complete resolution of tumor.



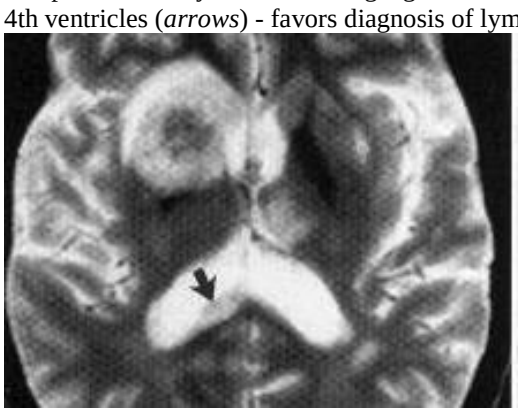
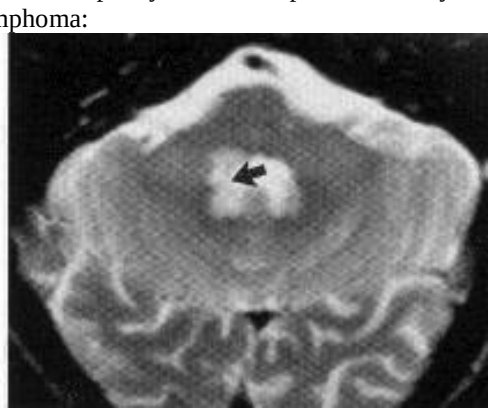
PCNSL involving corpus callosum (A - T2-MRI; B - T1-MRI); rim enhancement is seen:



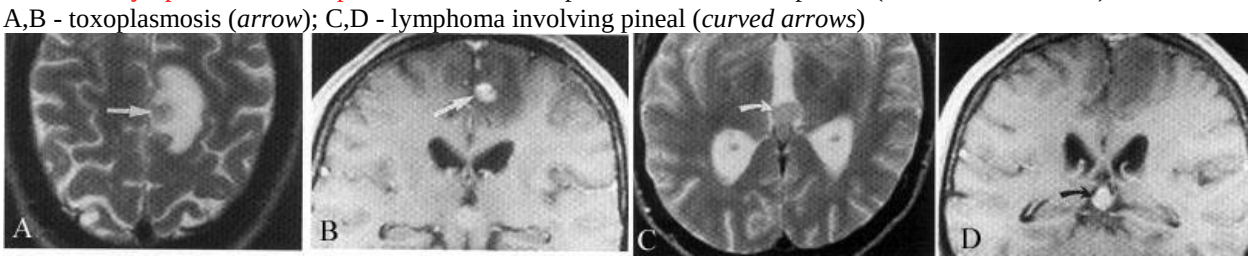

Metastatic systemic lymphoma (T2-MRI): lymphomatous deposit is based on, and is lifting, dura (arrow); edema in underlying brain substance, which is displaced:



Multifocal PCNSL (T2-MRI): multiple masses, most of which show mixed T2 signal intensity; like multiple toxoplasmosis they involve basal ganglia, however, subependymal tumor spread is clearly seen around lateral and 4th ventricles (*arrows*) - favors diagnosis of lymphoma:

Coexistent lymphoma and toxoplasmosis confirmed postmortem in AIDS patient (A,C – T2, B,D – T1):
A,B - toxoplasmosis (*arrow*); C,D - lymphoma involving pineal (*curved arrows*)



CSF CYTOLOGY

- pleocytosis / normal cell counts (with reactive and malignant lymphocytes in leptomeningeal disease), normal glucose (↓ in leptomeningeal disease), protein↑.
- **cytology** is diagnostic in 5–30%* of PCNSL (70–95% of metastatic malignant lymphomas)

*flow cytometry

N.B. unequivocally *positive CSF cytology* eliminates need for brain biopsy! (but cytology is usually low-yield for definite diagnosis)

N.B. if there is pressure to start steroids, do LP and *send CSF before starting steroids*!

- for HIV-infected or other immunocompromised patients check for syphilis, cryptococcal antigen.

STEREOTACTIC BRAIN BIOPSY

- most appropriate method for diagnosis!

- surgery is restricted to stereotactic biopsy to establish histological diagnosis!!!
- even partial resection is associated with worse survival
- corticosteroids should be withheld before biopsy (unless herniation is imminent) - dramatic response to corticosteroids is usually temporary, but can occasionally be long-term

N.B. no patient should be treated for PCNSL without definitive cytologic proof of diagnosis:
a) vitrectomy
b) positive CSF cytology
c) brain biopsy

TREATMENT

- reasonably good response! (*most radiosensitive & chemosensitive CNS tumor*!)

- before beginning treatment, systemic disease (that would alter planned chemotherapy) must be ruled out!
- lower intensity of immunosuppression, if feasible, in transplant recipients who develop PCNSL.
- *AIDS patient with positive toxoplasmosis serology* → **trial with anti-toxoplasmosis antibiotics**:
  a) improvement of lesions within 2 weeks → presumptive evidence for toxoplasmosis.
  b) absence of response → stereotactic biopsy.

SURGERY

HISTORICAL ERA

- surgery has no therapeutic role* (disease is multifocal, diffusely infiltrative in deep location)! - surgical resection prolongs survival to only ≈ 3.3-5 months

Surgery has only diagnostic role (biopsy)! i.e. surgery with a cytoreductive goal has traditionally been abandoned

if craniotomy is undertaken because diagnosis of PCNSL is not considered preoperatively, intraoperative frozen section establishes diagnosis of PCNSL → operation is terminated

*results from studies concluding resection offered no benefit and potentially worsened outcomes (relatively small sample sizes and were conducted prior to the modern neurosurgical era)

- although up to 2/3 of the patients present with a single lesion on imaging, *microscopic disease is often present beyond the radiographically visible lesion* (histopathology – diffuse*, angiocentric growth pattern, with cuffs of tumor cells around cerebral vasculature).

*mirrors gliomas

- surgery for cytoreduction is not standard for PCNSL, though it is occasionally performed for *symptomatic relief of severe mass effect* or *if the lesion mimics other pathology on imaging* studies (vs. management of other intra-axial tumors including brain metastasis and diffusely infiltrative gliomas - surgery contributes to oncologic control and is associated with a survival advantage).

MODERN ERA

(after introduction of high-dose methotrexate and modern neurosurgical techniques)

Resection vs. biopsy

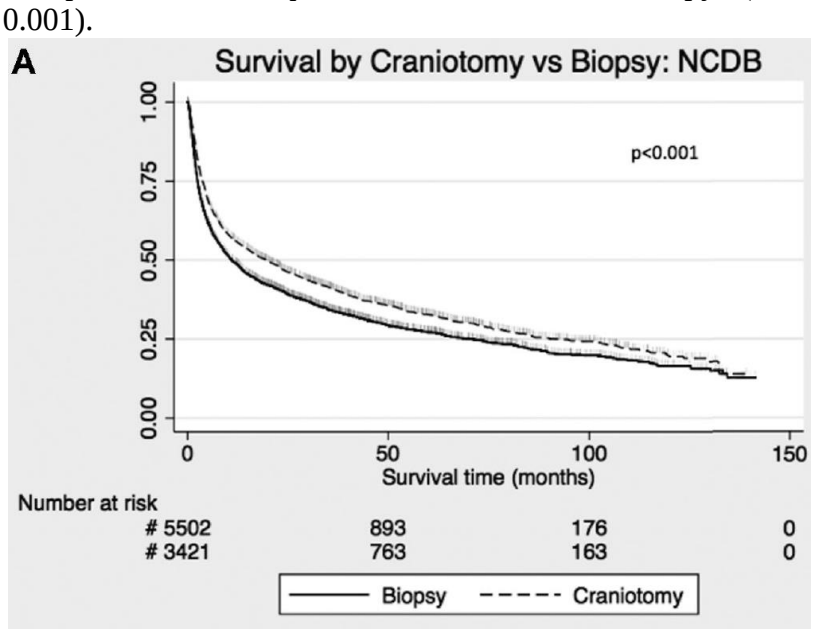
Ali I Rae et al. Craniotomy and Survival for Primary Central Nervous System Lymphoma. Neurosurgery 84:935–944, 2019, nyy096, https://doi.org/10.1093/neuros/nyy096

Cytoreductive craniotomy is associated with survival benefit over biopsy (independent of chemotherapy, radiotherapy, and baseline prognostic factors) particularly for those patients in favorable prognostic categories.

N.B. data is retrospective - has selection biases inherent in choosing resective candidates in undiagnosed lesions - naturally favor those with single, more superficial lesions in patients with more favorable survival characteristics. The data does not support the practice of chasing diffuse lymphoma lesions.

- > 9000 patients from National Cancer Database-Participant User File (NCDB, n = 8936), Surveillance, Epidemiology, and End Results Program (SEER, n = 4636), and an institutional series (IS, n = 132) – some databases overlap!
- craniotomy is associated with increased survival over biopsy in 3 retrospective datasets:

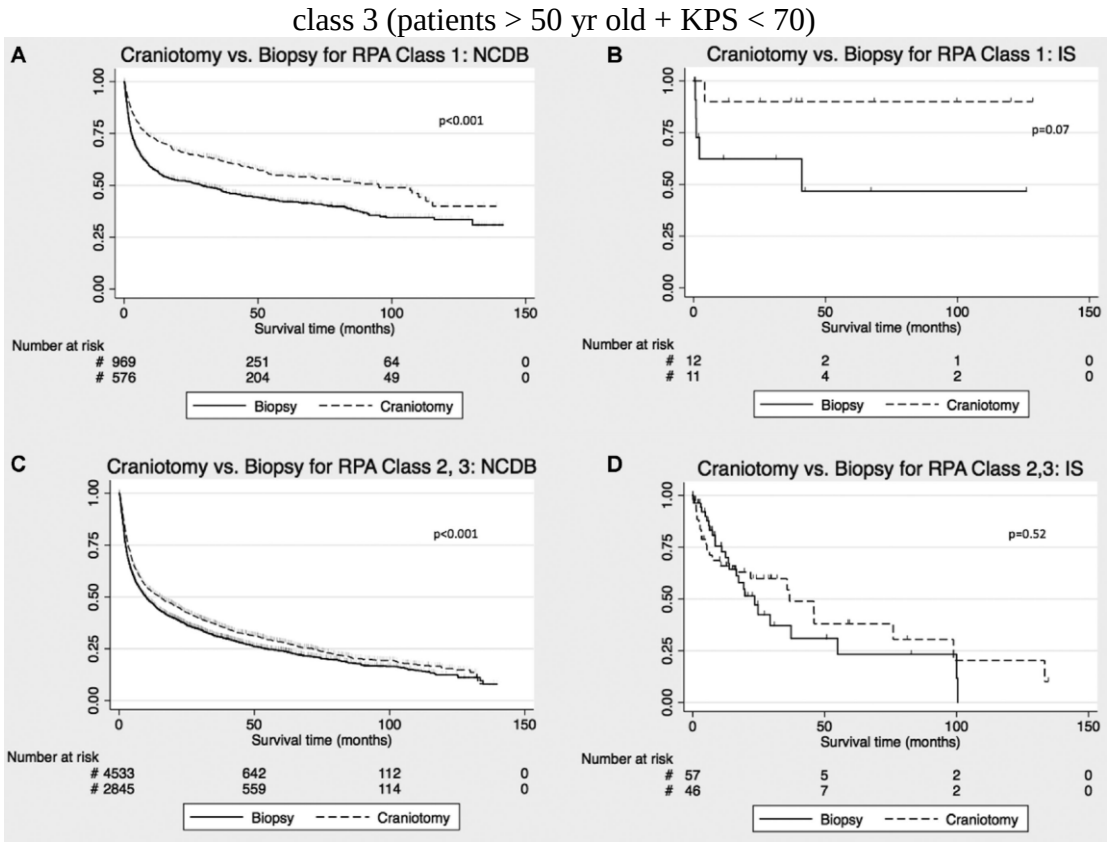
a) **NCDB**: craniotomy was associated with increased median survival over biopsy (19.5 vs 11.0 mo), independent of subsequent radiation and chemotherapy* (hazard ratio [HR] 0.80, P < 0.001).



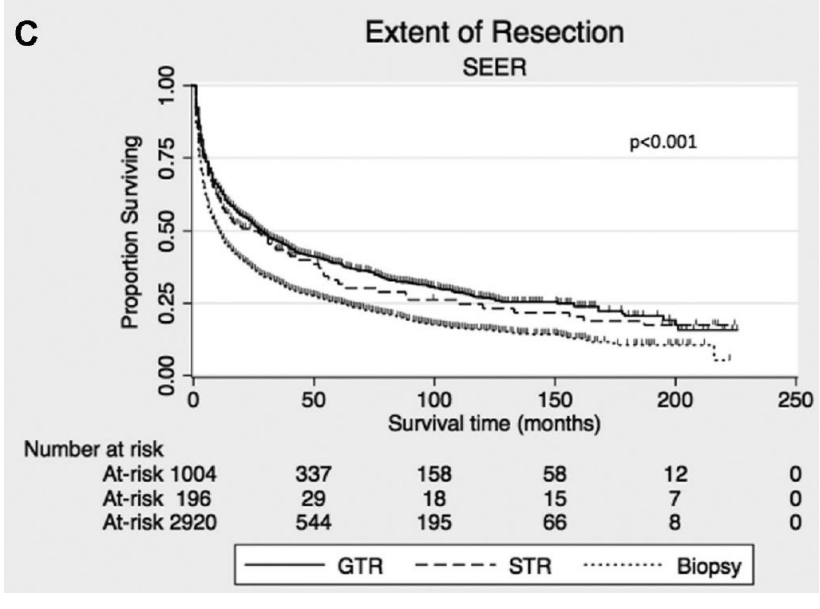
*in multivariable analysis, **craniotomy** (HR 0.80, 95% CI [0.75, 0.84], P .001), **age** (HR 1.03 for each 1-yr increase, 95% CI [1.03, < 1.03], P .001), lower **Charlson-Deyo score** (HR 1.18, 95% < CI [1.14, 1.25], P .001), **chemotherapy** (HR 0.40, < 95% CI [0.37, 0.42], P .001) and **radiation therapy** (HR 0.90, 95% CI [0.84, 0.95], P .001) were independently predictive of survival.

RPA* classes: survival benefit associated with craniotomy was 3-fold greater within class 1 group (95.1 vs 29.1 mo, HR 0.66, P < 0.001), but was smaller for RPA 2-3 (14.9 vs 10.0 mo, HR 0.86, P < 0.001).

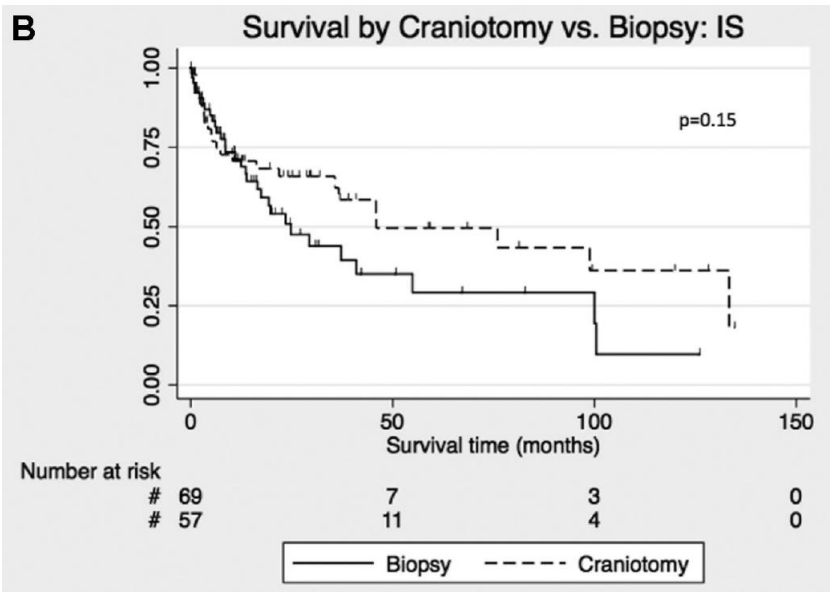
*Memorial Sloan Kettering recursive partitioning analysis (RPA) classes:
class 1 (patients < 50 yr old)
class 2 (patients ≥ 50 yr old with KPS ≥ 70)
class 3 (patients > 50 yr old + KPS < 70)



b) **SEER**: gross total resection was associated with increased median survival over biopsy (29 vs 10 mo, HR 0.68, P < 0.001), trend toward longer survival with more extensive resection.



c) **IS**: similar trend with survival for craniotomy vs biopsy (HR 0.68, P = 0.15).



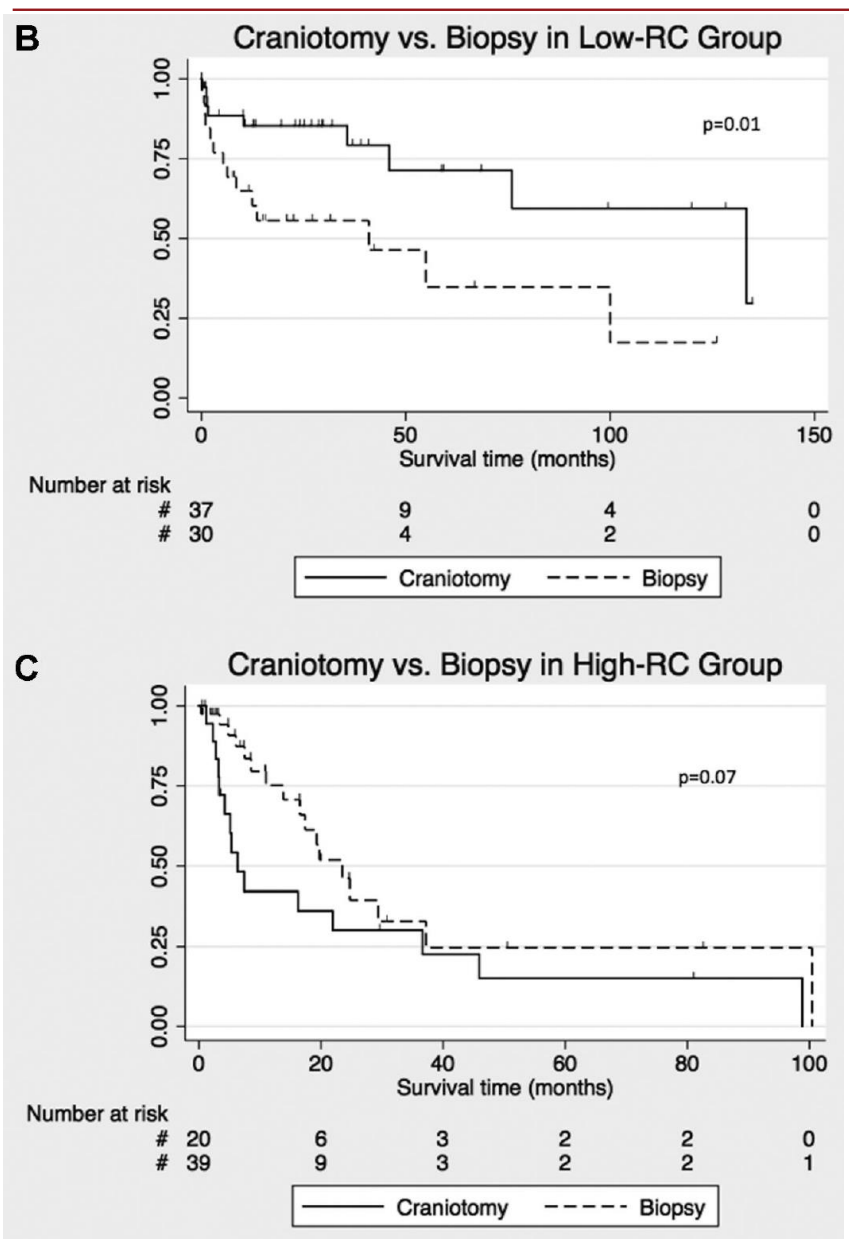
Surgical risk category (RC) considering lesion location* and number, age, and frailty was developed - craniotomy was associated with increased survival vs biopsy for patients with low RC (133.4 vs 41.0 mo, HR 0.33, P = 0.01), but not high RC in the IS (actually, trend toward shorter survival in high-RC patients who underwent craniotomy vs biopsy (HR 1.90, 95% CI [0.93, 3.88], P = 0.08)

*lesions involving brainstem, basal ganglia, corpus callosum, or periventricular areas were classified as deep. Deep vs superficial lesion location was not predictive of survival in univariable or multivariable analysis.

TABLE 3. Clinical Risk Category Scale for Calculating Surgical Risk in Patients With PCNSL

Risk factor	Point score
Difficulty with activities of daily living	1
History of diabetes mellitus	1
Lung or respiratory disease	1
Congestive heart failure	1
History of myocardial infarction	1
Other cardiac disease	1
Arterial hypertension	1
Clouding, delirium, or cognitive impairment	1
History of Transient Ischemic Attack (TIA)	1
History of stroke	1
Peripheral vascular disease	1
Age > 55 yr	1
Multiple CNS lesions	1
Deep lesion involving brainstem, basal ganglia, corpus callosum, or periventricular area	1

Total score of 4 or more indicates high surgical risk.



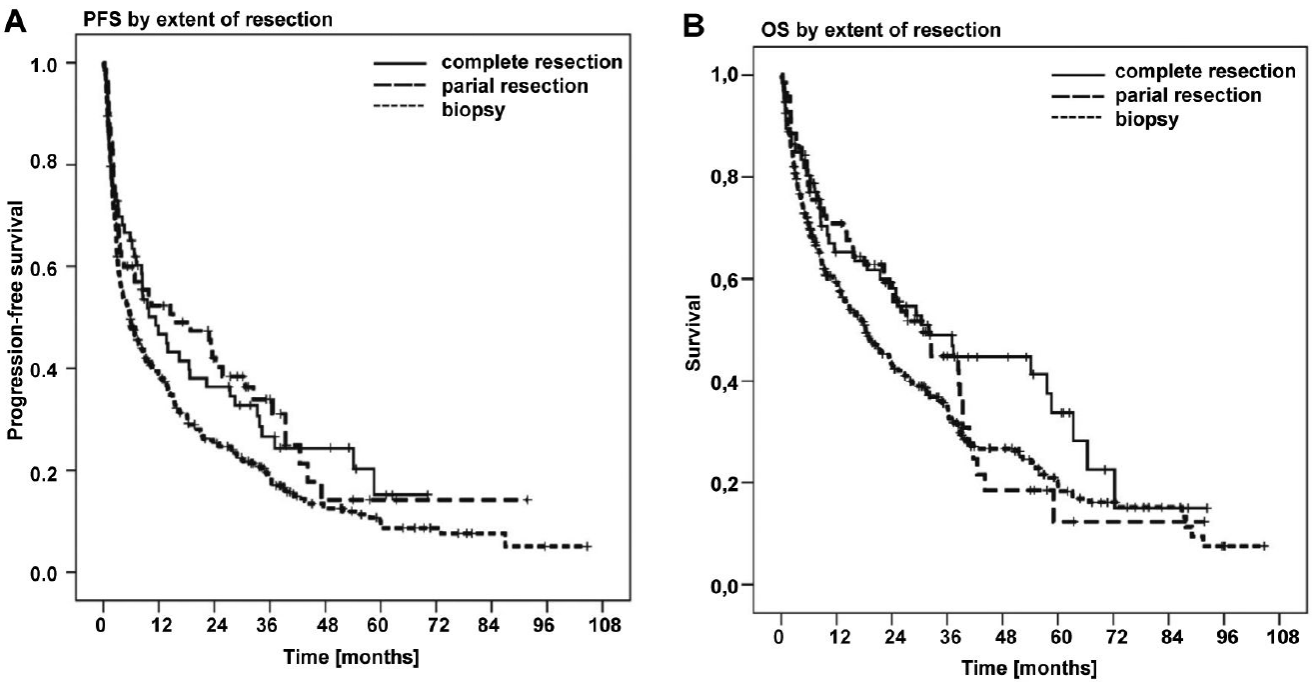
- combining craniotomy and chemotherapy was associated with an ***additive increase in survival*** (median survival was 25.1 mo with chemotherapy and biopsy, vs. 37.4 mo with chemotherapy and craniotomy).

Resection vs. biopsy

Weller M et al. Surgery for primary CNS lymphoma? Challenging a paradigm. Neuro Oncol. 2012; 14:1481–1484.

- overall and progression free survival was statistically superior if patient underwent total or subtotal resection (vs. just biopsy):

  PFS significantly increased in patients with gross or subtotal resection vs. biopsy (p=0.005), no difference seen in gross total vs. subtotal resection (p=0.023).
  OS improved for both gross total resection alone and gross or subtotal resection vs. biopsy (p=0.024), no difference in OS seen between gross and subtotal resection (p=0.297):



European Association for Neuro-Oncology guidelines for immunocompetent patients: surgery is recommended for large, compressive lesions.

Hoang-Xuan K et al. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. Lancet Oncol. 2015; 16:e322–332.

CHEMOTHERAPY

High-dose ***systemic*** METHOTREXATE - most successful treatment strategy!

- patients must be *hydrated adequately* + SODIUM BICARBONATE 3 g q4h during 24 hours prior to and during methotrexate therapy (avoid fruit juices that might acidify urine).
- avoid salicylates, NSAIDs, and sulfonamides.
- for *LEPTOMENINGEAL LYMPHOMA*, ***intrathecal*** drug is needed.

Avoid corticosteroids during chemotherapy!

Avoid METHOTREXATE following radiotherapy – ↑risk of treatment-related encephalopathy

Alternatives – CYTARABINE, (intrathecal) THIOTEPA, PROCARBAZINE.

- *standard regimens* (such as CHOP - CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, PREDNISONE) are ineffective (difficulty of BBB penetration).
- unique feature of PCNSL (compared to other brain tumors) is **exquisite sensitivity to cytotoxic effect of corticosteroids**

N.B. steroid-induced remission is short-lived and is not definitive treatment!

RADIOTHERAPY

- **whole-brain radiation therapy (WBRT)** - best second-line* treatment (radiotherapy alone is insufficient to provide durable remission or cure):

a) delivered after 12-16 wk of chemotherapy (adjuvant WBRT).
b) only after METHOTREXATE failure! (i.e. WBRT is deferred if patient has complete response to chemotherapy)

- 40-45 Gy in 20-25 daily treatments.
- additional boosts do not improve local control.
- *OCULAR LYMPHOMA* → primary treatment is 36 Gy to both eyes (ocular lymphoma is predominately binocular process).

*WBRT is mainstay of treatment in ***immunocompromised patients***; chemotherapy is reserved for patients with relapsed disease after WBRT

PROGNOSIS

- poor (despite highly responsive nature of PCNSL to initial treatment); modern prognosis – 15-30% 5-year survival on multiagent chemotherapy (radiotherapy for recurrences).

PCNSL has worse outcomes compared to other systemic or extranodal lymphomas

Median survival 3-4 yrs:

WBRT alone - 18 months (4 months in AIDS patients).
Chemotherapy alone - 48 months.
WBRT + chemotherapy - 44 months (18 months in AIDS patients).

5-year survival only 3-4% (similar to *GLIOBLASTOMA MULTIFORME*) – due to brain recurrence after initial response.

- in largest polychemotherapy trial with Bonn protocol (including methotrexate) achieved median overall survival of 50 months, with best treatment results in patients < 61 years (5-year survival: 75%)

SPECIFIC FORMS

INTRAVASCULAR MALIGNANT LYMPHOMATOSIS (S. NEOPLASTIC ANGIOENDOTHELIOSIS, ANGIOTROPIC LYMPHOMA)

- cerebral vessels plugged with neoplastic B lymphocytes (originally were thought to be of endothelial origin) - tumor cells have particular surface features that promote binding to endothelium → usual sites of lymphoma involvement (lymph nodes and bone marrow) are spared, whereas skin, CNS, and occasionally peripheral nerves are preferentially involved.

- series of TIA / stroke-like events → progressive dementia.
- fever and weight loss.
- ESR may be elevated; anemia & thrombocytopenia may be present.
- 50% patients have cutaneous involvement.
- CT / MRI - multiple cerebral in infarctions; with time, parenchymal brain lymphoma develops.
- bone marrow is usually normal.

NEUROLYMPHOMATOSIS

- involves both CNS and PNS.

- axonal and/or demyelinating neuropathy.

HISTIOCYTIC TUMOURS

- heterogeneous group of tumours / tumour-like masses composed of histiocytes
- commonly associated with histologically identical extracranial lesions.

There is no indication that **microglia** give rise to any one of histiocytic disorders!

CLASSIFICATION

1. **Dendritic cell related disorders** (Langerhans cell histiocytosis is most common)
2. **Macrophage-related disorders** of varied biological behaviour (such as hemophagocytic lymphohistiocytosis and Rosai-Dorfman disease)
3. **Malignant histiocytic disorders** (such as monocytic leukemia and histiocytic sarcoma).

ETIOLOGY

- ***abnormal immune response**** is felt to play potentially important etiologic role.
  *likely genetic (except *infection-associated hemophagocytic lymphohistiocytosis* – associated with EBV)
- in most patients, there is either mild or no underlying defect in immunologic integrity and clinical course is benign.

1. LANGERHANS CELL HISTIOCYTOSIS (LCH)

- LCH was previously referred to as histiocytosis X (embracing eosinophilic granuloma, Hand-Schüller- Christian disease, Abt-Letterer-Siwe disease and Hashimoto-Pritzker disease).
- primary gene responsible for familial hemophagocytic lymphohistiocytosis is perforin 1 (PRF1) gene on chromosome 10q22.

INCIDENCE

- LCH typically occurs in **children** (mean, 12 years), ***without sex preference***
- in children < 15 years, LCH incidence is 0.5 / 100 000 children / year (vs. non-LCH is rarer - 1:1 000 000 / year).

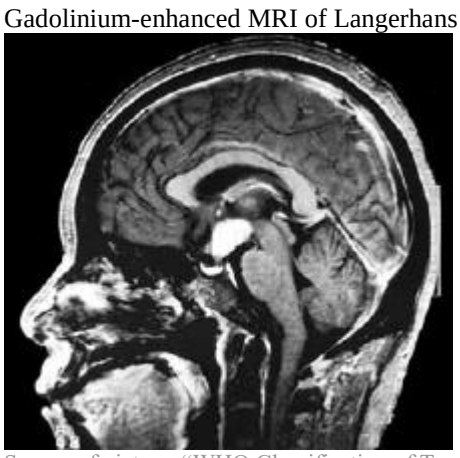
CLINICAL FEATURES

- most common - diabetes insipidus (25%)
- hypothalamic dysfunction (obesity, hypogonadism, growth retardation)
- signs of raised ICP
- CN palsies
- seizures
- visual disturbances (visual field defect, optic atrophy)
- ataxia
- progressive tetra- and paraparesis

MRI

1) lesions of bone - craniofacial and skull base (56%) with or without soft-tissue extension
2) intracranial, extra-axial changes - hypothalamic-pituitary region (50%), meninges (29%) or choroid plexus (6%)
3) intracranial, intra-axial changes (white matter and gray matter), cerebral atrophy

Gadolinium-enhanced MRI of Langerhans cell histiocytosis in hypothalamic region (Hand-Schüller-Christian disease).



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

PATHOLOGY

LOCALIZATION

- currently LCH is classified on basis of extent as ***unifocal***, ***multifocal*** (usually polyostotic) and ***disseminated disease***.
- most common form (2/3 of cases) - eosinophilic granuloma - solitary bone (osteolytic) lesion of skull or spine.
- Hand-Schüller- Christian disease - multifocal bone lesions with hypothalamic involvement.
- Abt-Letterer- Siwe disease - involves skin, lymph nodes, viscera (rarely CNS).
- in brain principal involvement is hypothalamus and posterior pituitary (historical names - hypothalamic granuloma, Gagel's granuloma and Ayala disease); also infundibulum, optic chiasm, choroid plexus and cerebral hemispheres.
  a) most cases - ***extensions*** from osseous foci
  b) ***primary***

MACROSCOPY

- yellow or white lesions.
- vary from discrete dural-based nodules to granular parenchymal infiltrates.
- CNS lesions may be well-delineated or ill-defined.

HISTOPATHOLOGY

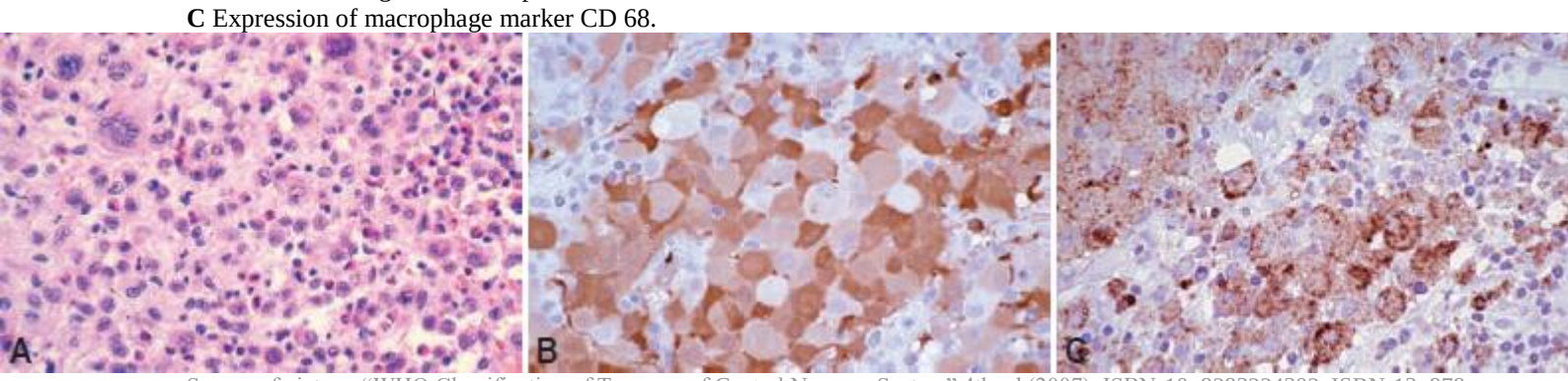
Infiltrates are composed:

1) immature, partially activated dendritic **Langerhans cells**

- ultrastructural hallmark - **Birbeck granules** (34-nm wide *rod-shaped* or *tennis-racket shaped* intracytoplasmic pentalaminar structures with cross-striation and zipper-like central core, possibly originating from cell membrane and/or Golgi apparatus)
- consistently express S-100 protein, vimentin and certain histiocyte markers; **CD68** (protein highly expressed by cells in the monocyte lineage: microglia, histiocytes) – differentiates histiocytosis from lymphoma.
- ***nuclei*** of Langerhans cells are slightly eccentric, ovoid, reniform or convoluted with linear grooves and inconspicuous nucleoli.
- ***cytoplasm*** of Langerhans cells is large (15–25 μm in diameter) and pale to eosinophilic.
- ***proliferation***: Ki-67/MIB-1 indices range 4-16%
- Touton giant cells may occur.
- abundant deposition of collagen.

2) **macrophages**
3) **lymphocytes, plasma cells**
4) variable fraction of **eosinophils** - may form into aggregates and undergo necrosis to produce granulomas or abscesses.

A Mixed infiltrate composed of histiocytes, lymphocytes, eosinophils and multinucleated cells.
B Immunolabelling with S-100 protein.
C Expression of macrophage marker CD 68.



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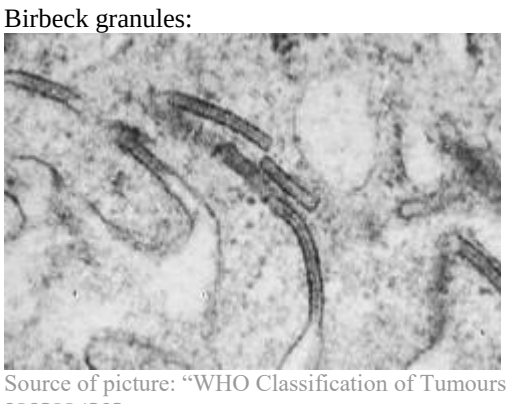
Birbeck granules:



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PROGNOSIS

- no prognostic significance of histopathologic features.
- survival rates - at 5, 15, and 20 years - 88%, 88%, and 77%
- event-free survival rate - 30% at 15 years
- **unifocal disease** - may spontaneously recover or requires minimal treatment, e.g. surgical resection
- **multisystemic disease with organ dysfunction** may resist systemic chemotherapy (mortality rate reaches 20%)
- late sequelae - skeletal defects (42%), diabetes insipidus (25%), growth failure (20%), hearing loss (16%), and other CNS dysfunction (14%).

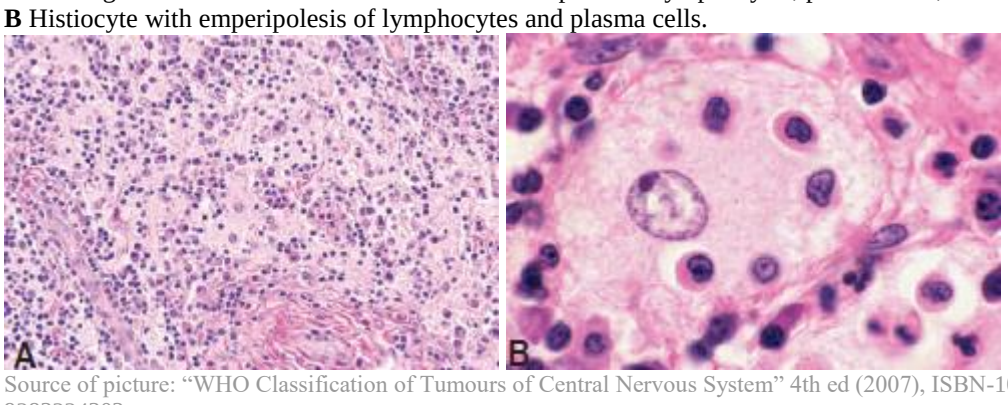
2. NON-LANGERHANS CELL HISTIOCYTOSES

- arise from **bone marrow derived mononuclear phagocytes (macrophages)** at various stages of development and activation.
- absence of Langerhans cells

ROSAI-DORFMAN DISEASE

- most common in children and young adults
- disease of lymph nodes
- intracranial disease (usually seen in adults) - dural-based solitary or multiple masses; parenchymal or intrasellar lesions
- intracranial extension from orbital mass or from nasal and paranasal cavities.
- clinically - intracranial space–occupying mass.
  - 'classical' **cervical lymphadenopathy** + **fever** + **weight loss** (triad is absent in 70%)
  - 52% have no associated systemic disease
- radiology - mimics meningioma.
- carries favourable prognosis after ***complete resection*** or after ***corticosteroid*** treatment.
- histopathology - sheets or nodules of histiocytes; **EMPERIPOLESIS** - well-preserved lymphocytes and plasma cells within cytoplasm of histiocytes.

A Heterogeneous dural-based cellular infiltrate composed of lymphocytes, plasma cells, and large pale histiocytic cells
B Histiocyte with emperipolesis of lymphocytes and plasma cells.



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ERDHEIM-CHESTER DISEASE

- manifests in adults (mean, 55 years).
- may involve brain (preferentially cerebellum), spinal cord, cerebellopontine angle, choroid plexus, pituitary, meninges and orbit
  Diabetes insipidus and progressive cerebellar dysfunction are common!
- MRI - **retention of gadolinium enhancement for several days**

- histopathology - lipid-laden histiocytes (CD1a-, CD68+, S-100 protein -), Touton-like multinucleated giant cells, scant amount of lymphocytic infiltrates, minimal number of eosinophils and fibrosis.

HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

- **autosomal recessive** systemic disease of **early infancy** (mean, 3 months)
- CNS involvement is seen in almost all patients (may be isolated) - diffusely involves ***leptomeninges*** and, multifocally, ***brain***.
- MRI - **focal** hyperintense lesions in white and grey matter, **diffuse** T2 signal in white matter, delayed myelination and parenchymal atrophy
- clinically - prolonged fever, hepatosplenomegaly and cytopenias; neuro - irritability, bulging fontanelle, neck stiffness, seizures, cranial nerve palsies, ataxia and hemiplegia
- labs - ↑triglyceride and ferritin, low fibrinogen.
- characteristic impaired function of natural killer cells and cytotoxic T-cells
- lethal without allogeneic stem cell transplantation.
- histopathology - meningeal and cerebral non-malignant diffuse **infiltrations** of lymphocytes and macrophages with haemophagocytosis, multifocal cerebral **necroses**.

JUVENILE XANTHOGRANULOMA (JXG) AND XANTHOMA DISSEMINATUM

- juvenile xanthogranuloma - young children with solitary cutaneous nodule; may arise in brain or meninges (have been reported)
- xanthoma disseminatum - multicentric intracerebral cases in young adults + extracranial involvement of skin, eyes, oral and respiratory mucosa.

Juvenile xanthogranuloma composed of histiocytes, multinucleated Touton cells and lymphocytes.

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

MALIGNANT HISTIOCYTIC DISORDERS

- extremely rare
- histiocytic sarcoma - may primarily involve brain and meninges.
- intracranial follicular dendritic cell (FDC) sarcoma.

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