

Primary CNS Lymphoma (PCNSL)

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

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EPIDEMIOLOGY

INCIDENCE:

2.7% of all primary brain tumors.
6-20% of all HIV-infected patients.
in immunocompetent patients ≈ 51 per 10,000,000

- incidence is increasing! (even among immunologically normal people)
- males : females = 2 : 1 (but among HIV-infected 95% are males).
- median age – 55 yrs (35 years if HIV-infected).

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).

c-myc gene translocations occur in EBV-associated lymphomas that occur outside CNS but not in PCNSL
- 56 % patients* have **human herpes virus 8** in their tumors (direct causal relationship has not yet been established).

*both immunocompetent and immunocompromised

PATHOLOGY

PCNSL - rare form of **extranodal non-Hodgkin lymphoma**:
90% - high-grade **diffuse large B-cell lymphoma** (DLBCL), frequently of immunoblastic type.
10% - poorly characterized low-grade lymphomas, Burkitt lymphomas, T-cell 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.
- 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

- 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).
- at autopsy, 50-100% patients have **leptomeningeal lesions**.
- **ocular involvement** (uvea or vitreous humor) occurs in 20% cases at time of diagnosis.
- 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!

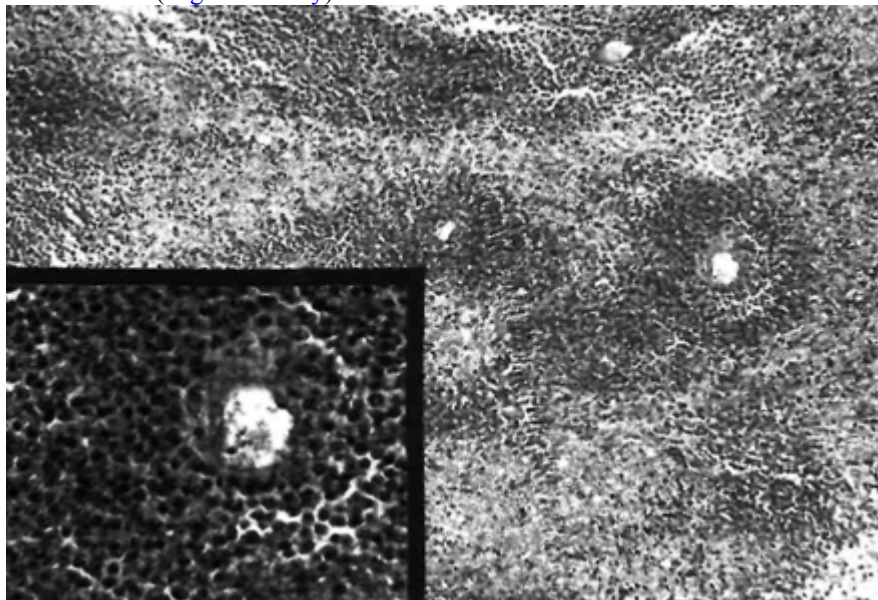
HISTOLOGY

- diffusely infiltrative, densely cellular.
- **predilection for blood vessels** (lymphoid clustering around small cerebral vessels is typical - **vasocentric growth pattern**).
- **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).

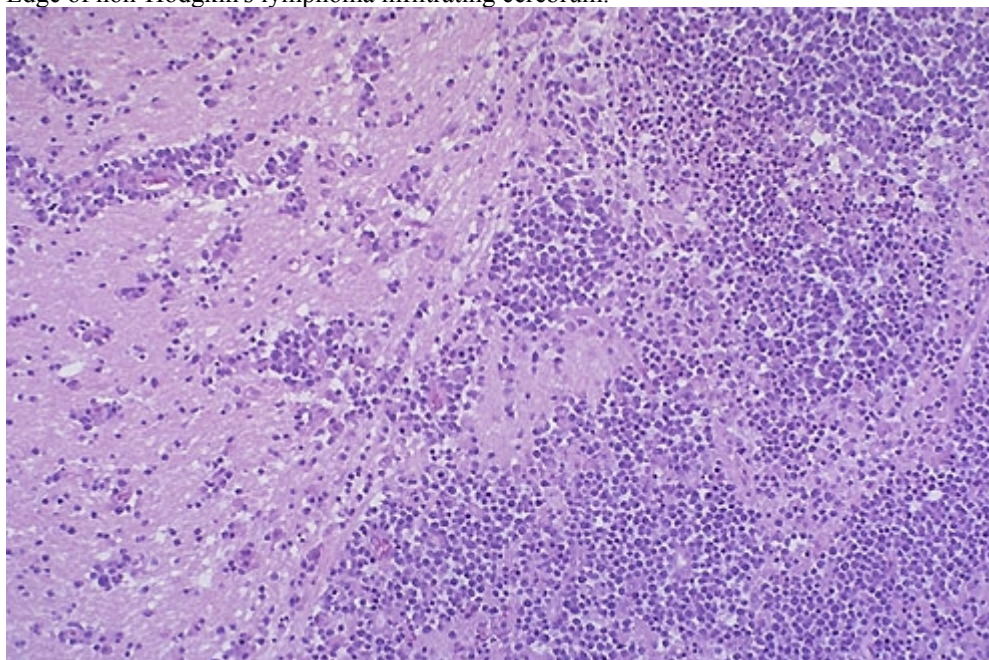
if patient is treated by corticosteroids, reactive T cells may be all that is apparent on biopsy specimen, making accurate diagnosis difficult.

Clusters of tumor cells have infiltrated tissue, with special **predilection for perivascular locations**; scattered **reactive gliosis** in between tumor clusters.

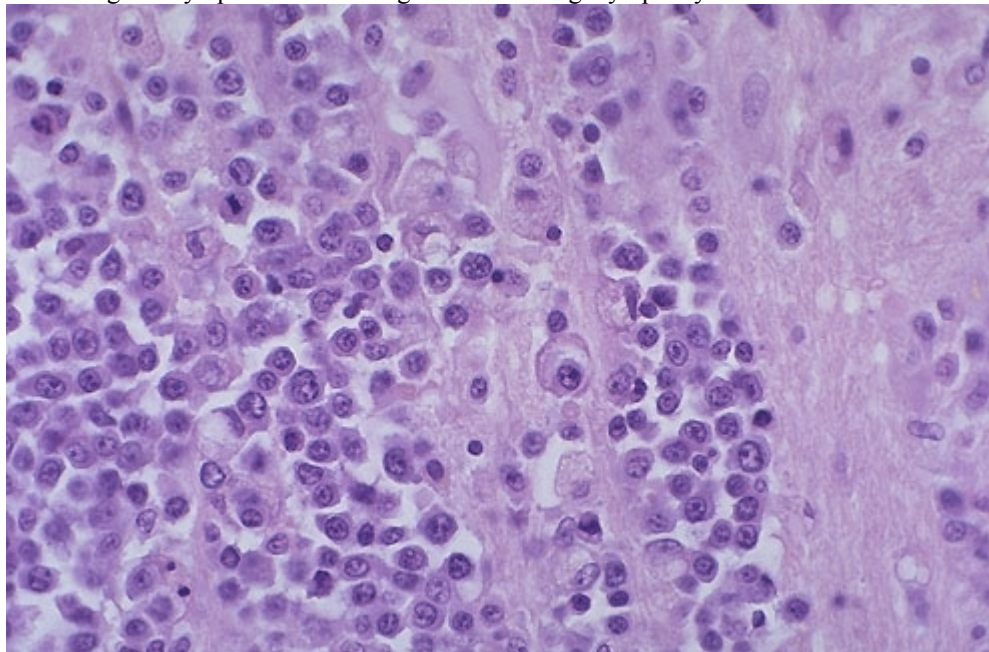
Inset: tumor cells with high nuclear cytoplasmic ratio without cell processes; characteristically infiltrate walls of blood vessels (**angiocentricity**).



Edge of non-Hodgkin's lymphoma infiltrating cerebrum:



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



CLINICAL FEATURES

- **progressive symptoms:**

- Intracranial mass lesion**
 - because *frontal lobe* is most frequently involved region, **neurocognitive changes** (dementing process with lethargy) are common presenting symptoms.
 - seizures** are less common (most PCNSLs involve deep brain structures rather than seizure-prone cerebral cortex).
 - Ocular involvement:** **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.
 - Focal deposits on cranial / spinal nerve roots** → **neuropathies, radiculopathies**.
- AIDS patients are likely to present with **encephalopathy** (correlates with multifocal, diffuse MRI enhancement) – up to progressive dementia or stupor with no focal signs.

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).

Lumbar puncture - reactive and malignant lymphocytes (in leptomeningeal disease), normal glucose (↓ in leptomeningeal disease), protein↑.

- unequivocally **positive CSF cytology** eliminates need for brain biopsy!
- for HIV-infected or other immunocompromised patients check for syphilis, cryptococcal antigen.

IMAGING

- brain & spinal cords:

CT – isodense or hyperdense (due to *dense cellularity*); 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 is characteristic of PCNSL!**
- diffuse periependymal or intraventricular enhancement indicates characteristic spread mode.

SPECT / PET – for AIDS patients to help distinguish between hypometabolic toxoplasmosis and hypermetabolic PCNSL.

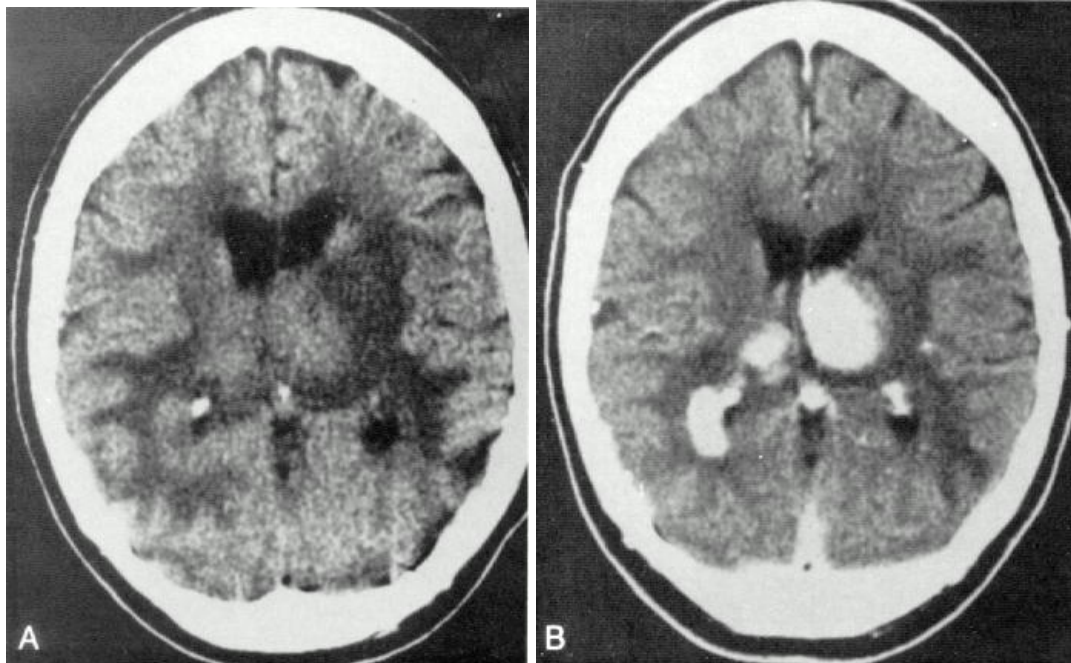
For *AIDS patients*, most difficult problem – differentiate between **PCNSL** and **Toxoplasma** – frequently coexist!

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

Thalamic PCNSL:

A. Noncontrast CT - isodense bilateral thalamic lesions with white matter edema.

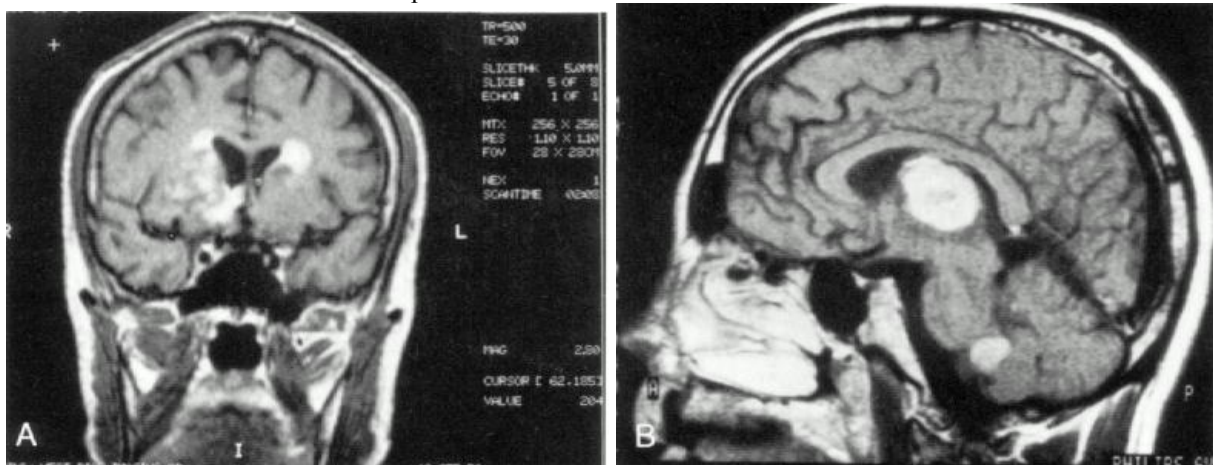
B. Contrast-enhanced CT - marked enhancement of lesions; intraventricular tumor is also present.



Ependymal spread:

A. Contrast MRI - bilateral periventricular and hypothalamic lesions that enhance markedly.

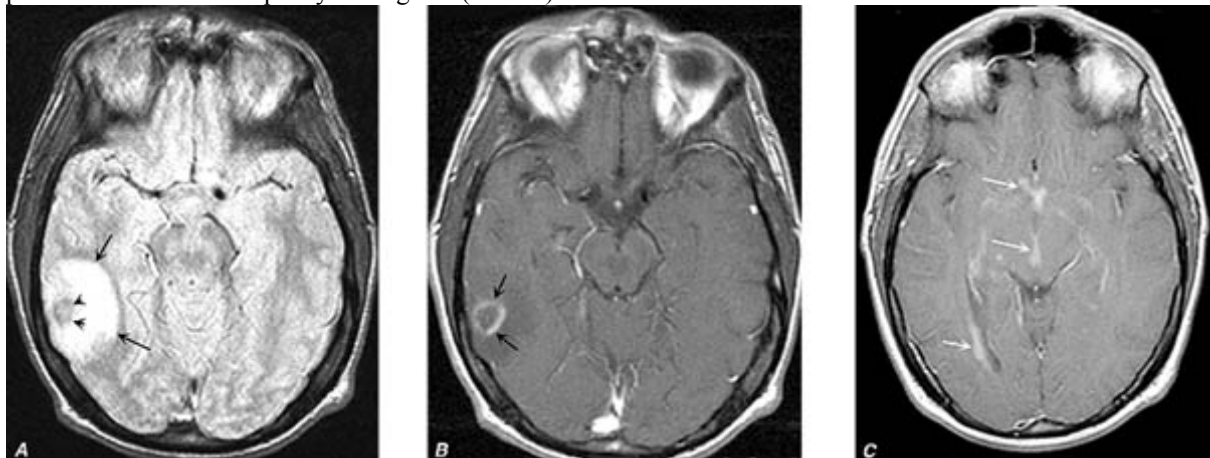
B. Contrast MRI - fourth ventricular spread of thalamic PCNSL.



A. Proton density-MRI - low signal intensity nodule (*small arrows*) surrounded by ring of high signal intensity edema (*larger arrows*).

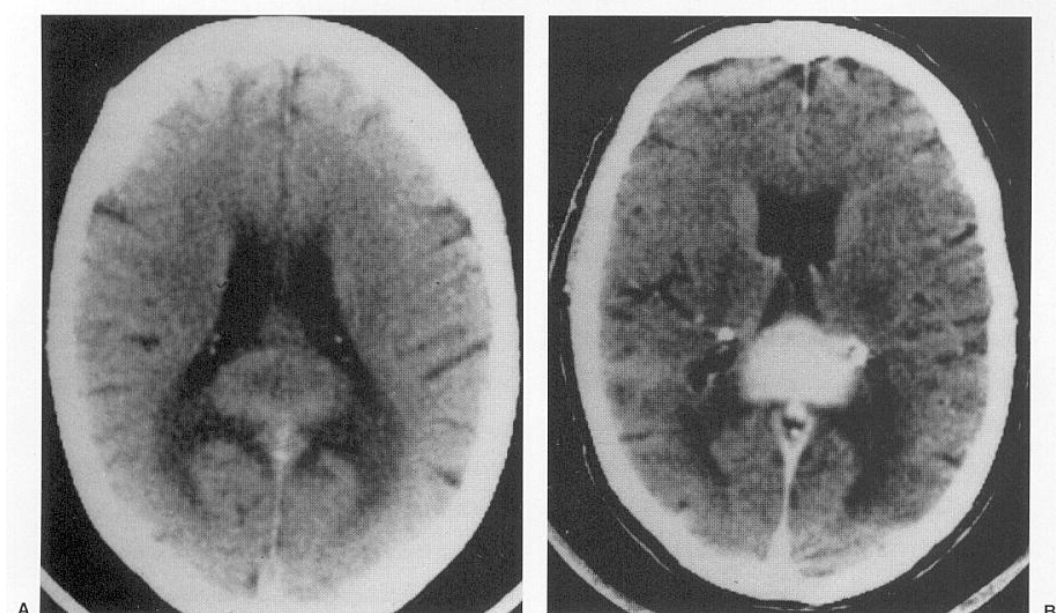
B. Contrast T1-MRI - ring enhancement surrounded by nonenhanced rim of edema.

C. Other patient **lymphomatous meningitis** (contrast T1-MRI) - multiple areas of abnormal enhancement in periventricular and subependymal regions (*arrows*).

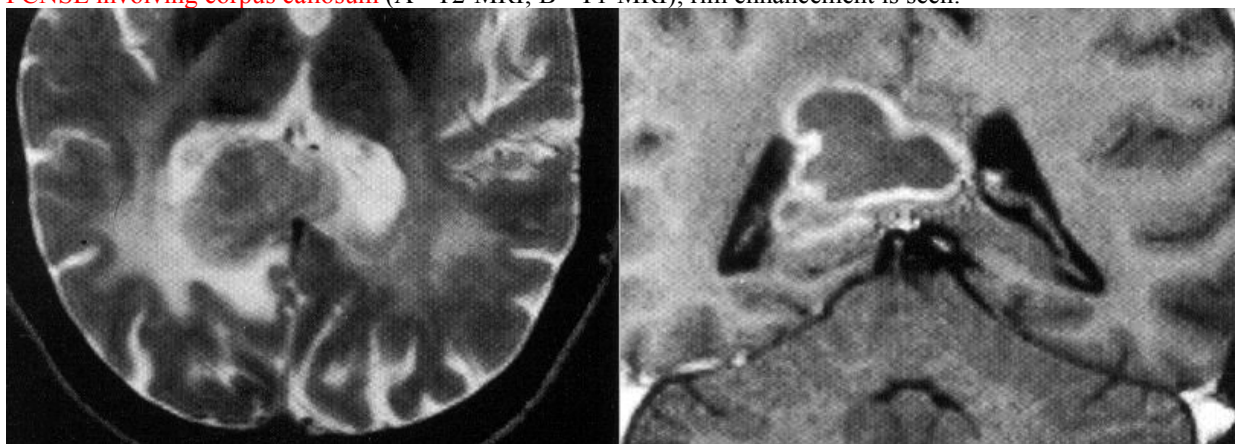


A. CT - hyperdense lesion expanding splenium of corpus callosum.

B. Contrast CT - very intense enhancement of lesion with edema extending into adjacent white matter.



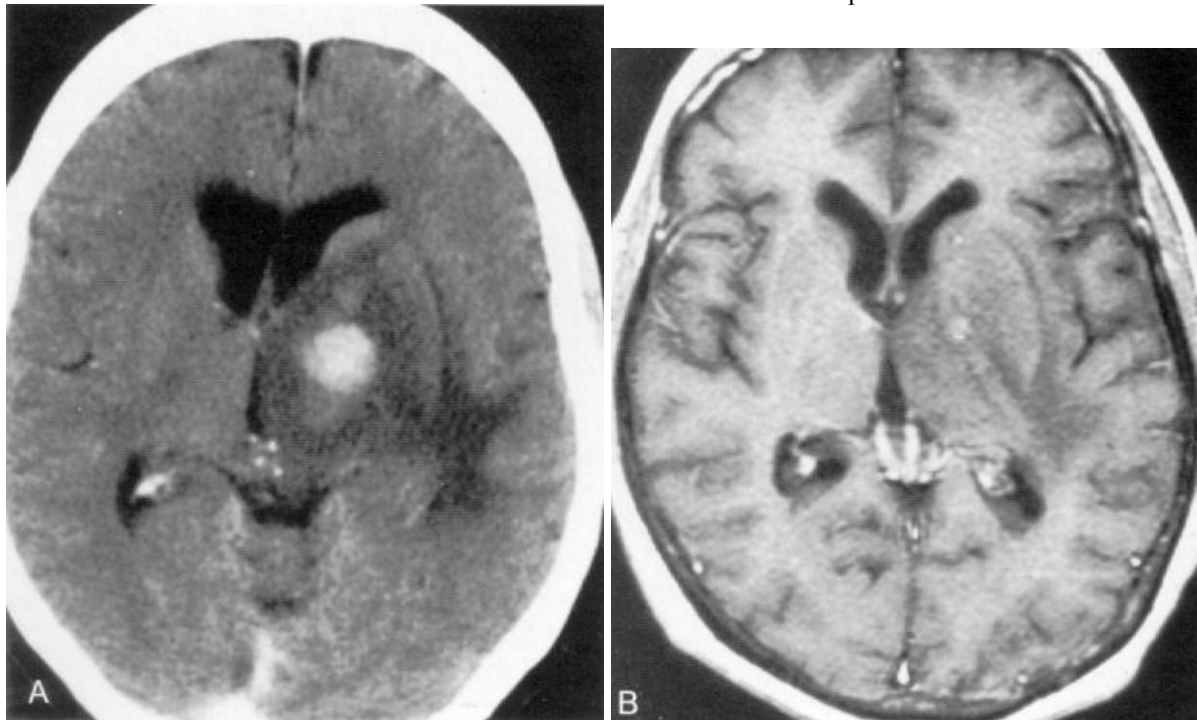
PCNSL involving corpus callosum (A - T2-MRI; B - T1-MRI); rim enhancement is seen:



Resolution with corticosteroid treatment:

A. Contrast CT - typical appearance of PCNSL.

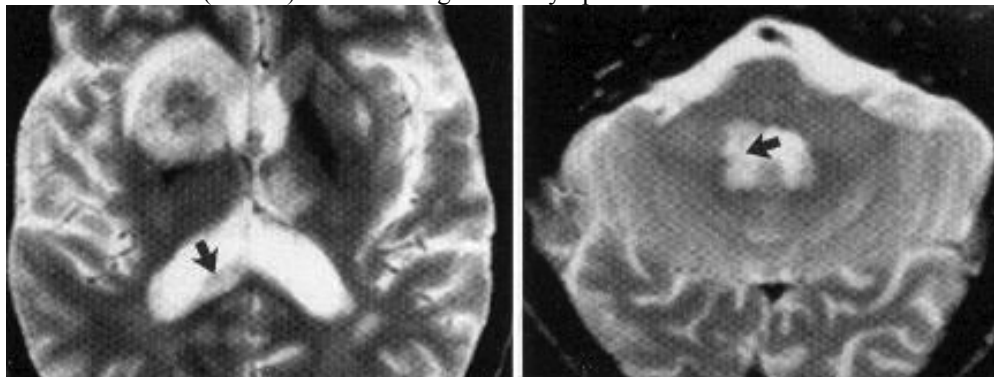
B. Contrast MRI after treatment with corticosteroids for 72 hours - almost complete resolution of tumor.



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

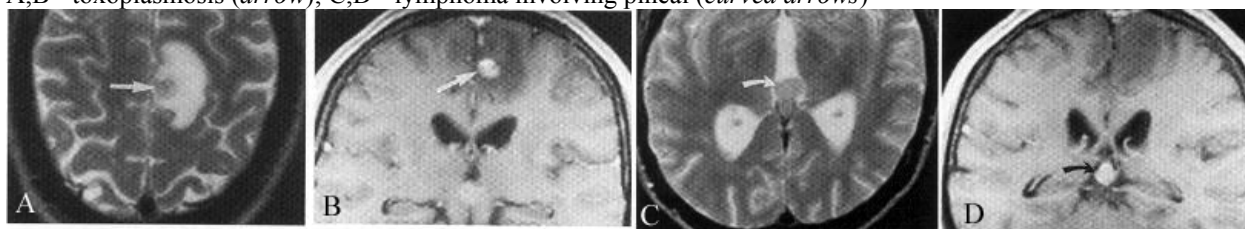


Multifocal PCNSL (T2-MRI): multiple masses, most of which show mixed T2 signal intensity; like multiple toxoplasmosis they involve basal ganglia, however, subependymal tumour spread is clearly seen around lateral and 4th ventricles (arrows) - favours diagnosis of lymphoma:



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)



STEREOTACTIC BRAIN BIOPSY

- most appropriate method for diagnosis!

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!*)

- **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)!

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

- 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 antitoxoplasmosis antibiotics:**
 - a) improvement of lesions within 2 weeks → presumptive evidence for toxoplasmosis.
 - b) absence of response → stereotactic biopsy.

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**:
 - 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)

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.

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 / strokelike 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 infarctions; with time, parenchymal brain lymphoma develops.
- bone marrow is usually normal.

NEUROLYMPHOMATOSIS

- involves both CNS and PNS.
- axonal and/or demyelinating neuropathy.

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