Tumors of Hematopoietic System

PRIMARY CNS LYMPHOMA (PCNSL)

(official names - Primary Reticular Cell Sarcoma, Microglioma)
- extracranial malignant non-Hodgkin lymphomas arising in CNS + absence of lymphoma outside nervous system at time of diagnosis (i.e. differential from secondary CNS involvement in systemic lymphomas).

ICD-O code 9590/3

EPIDEMIOLOGY

INCEDECE

• AIDS epidemic = markedly increased incidence worldwide: 0.8–1.5% = 6.6% prior to introduction of HAART, incidence in AIDS patients was about 3000-fold higher than in general population (2–12% of 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;

• 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).

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!
**HISTOGENESIS HYPOTHESES**

A. B-cells transformed at site elsewhere in body and then develop adhesion molecules specific for cerebral endothelium.

B. Lymphoma cells systematically eradicated by 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), frequency of immunoblastic type; show immunohistochemical expression of pan-B markers (CD19, CD20 and CD79a).

- 2% T cells

- low-grade lymphomas, Burkitt lymphomas.

- originates in brain, leptomeninges, spinal cord, or eyes.
- tonsillar or extranodal environment with subsequent localization to CNS, possibly by virtue of specific neoproteins
- low-grade lymphomas may develop within CNS; e.g. thalamus, basal ganglia, and posterior cerebral region
- diffuse growth pattern but typically remains confined to CNS (rarely spreads outside nervous system) - can be classified as stage II disease.

**LOCATION**

- 60% supratentorial space: 13% in posterior fossa, 1% in spinal cord.
- 25–50% are multiple (60–85% in AIDS and posttransplant subjects).
- brownish masses involving pia-arachnoid white matter, basal ganglia, corpus callosum.
- tumor may spread through white matter tracts, such as corpus callosum, or through CSF pathways (diffuse peripendymal or intraventricular CT/MRI enhancement).

- ocular involvement (uveitis or vitrous humor) occurs in 20% cases at time of diagnosis (may antedate intracranial lesions).
- localized intradural spinal masses may develop.

**MACROSCOPIC**

- 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 normal with poor demarcation (resemble gliomas).

**LYMPHOMATOSIS CEREBRI** - diffusely infiltrating forms

- diffuse infiltration of ventricular walls:

**Note the**


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

**Histology**
- diffusely infiltrative, densely cellular.
- predilection for blood vessels (lymphoid collars around small cerebral vessels is typical - \textit{angiocentric growth pattern}) - differentiate from 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.
Clusters of tumor cells have infiltrated tissue, with special predilection for perivascular locations; scattered reactive gliosis in between tumor clusters. 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%)
   - ANGIOCENTRIC 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!

**CBHIV 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).

**DIAGNOSTIC 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 homogenous 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**


**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.

**REFERENCES**

Yun et al. 2016
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 (large 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).

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)

N.B. unequivocally positive CSF cytology eliminates need for brain biopsy! (but cytology is usually low-yield for definitive diagnosis)
N.B. if there is pressure to start steroids, do LP and send CSF before starting steroids!

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

TREATMENT
- reasonably good response! (most radiosensitive & chemo-sensitive 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 ≈ 3.5 months
- although up to 2/3 of the patients present with a single lesion on imaging, microscopie disease is often present beyond the radiographically visible lesion (histopathology – diffuse*, angiocentric growth pattern, with cuffs of tumor cells around cerebral vasculature).

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 worse outcomes (relatively small sample sizes and were conducted prior to the modern neurosurgical era)

*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**


Cytoreductive craniotomy is associated with survival benefit over biopsy (independent of chemotherapy, radiation therapy, 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 favors 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).
  
  b) SEER: gross total resection was associated with increased median survival over biopsy (29 vs 10 mo, HR 0.66, 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).

**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)
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>
<thead>
<tr>
<th>Risk factor</th>
<th>Point score</th>
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<tbody>
<tr>
<td>Difficulty with activities of daily living</td>
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<tr>
<td>History of diabetes mellitus</td>
<td>1</td>
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<tr>
<td>Lung or respiratory disease</td>
<td>1</td>
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<tr>
<td>Congestive heart failure</td>
<td>1</td>
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<tr>
<td>History of myocardial infarction</td>
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<tr>
<td>Other cardiac disease</td>
<td>1</td>
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<tr>
<td>Arterial hypertension</td>
<td>1</td>
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<tr>
<td>Clouding, delirium, or cognitive impairment</td>
<td>1</td>
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<tr>
<td>History of transient ischemic attack (TIA)</td>
<td>1</td>
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<tr>
<td>History of stroke</td>
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<tr>
<td>Peripheral vascular disease</td>
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<tr>
<td>Age &gt; 55 yr</td>
<td>1</td>
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<tr>
<td>Multiple CNS lesions</td>
<td>1</td>
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<tr>
<td>Deep lesion involving brainstem, basal ganglia, corpus callosum, or periventricular area</td>
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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


- 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.

**CHEMOTHERAPY**

High-dose systemic chemotherapy - most successful treatment strategy!
- patients must be hydrated adequately + sodium bicarbonate 3 g qid during 24 hours prior to and during methotrexate therapy (avoid fruit juices that might acidify urine).
- avoid salicylates, NSAIDs, and sulfonamides.
- for patients who fail initial treatment, a second line of treatment is needed.

- Avoid corticosteroids during chemotherapy!
- Avoid methotrexate following radiotherapy
- Risk of treatment-related encephalopathy

**RADIONUCLIDE THERAPY**

Whole-brain radiation therapy (WBRT) - best second-line treatment (radiotherapy alone is insufficient to provide durable remission or cure):
- delivered after 12-16 wk of chemotherapy (adjunct WBRT).
- 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)

**SPECIFIC FORMS**

**Intravascular Malignant Lymphomatosis** vs. *Neoplastic Angioendotheliomatosis*
- cerebral vessels plugged with neoplastic B lymphocytes (originally 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 (8%)
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).

**PATHOLOGY**
- 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 (osteoelastic) 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 hypothalaminus 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

* = likely genetic (except infection-associated hemophagocytic lymphohistiocytosis – associated with EBV)
neurotactin. 
- Birbeck granules (34-nm wide red-shaped or tennis-racket shaped intracytoplasmic lamelliform 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 histoicytic markers.
- C68 (protein highly expressed by cells in the monocyte lineage: microglia, histiocyes) – differentiates histiocytosis from lymphoma.
- Nuclei of Langerhans cells are slightly eccentric, ovoid, reniform or convoluted with linear grooves and inconvencious nuclei.
- Cytoplasm of Langerhans cells is large (15–25 μm in diameter) and pale eosinophilic.
- Proliferaation: Ki-67/MB-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 Immunohistochemistry with S-100 protein.

C Expression of macrophage marker CD 68.

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.
- Classic cervical lymphadenopathy + fever + weight loss (tried is absent in 70%)
- 52% have no associated systemic disease.
- Radiology - mimics meningioma.
- Carrel Favourable Prognosis after complete resection or after corticosteroid treatment.
- Histopathology - sheets or nodules of histiocytes.

ERDHEIM-CHESTER DISEASE
- Manifests in adults (mean, 55 years).
- May involve brain (preferentially cerebellum), spinal cord, cerebellopontine angle, choroid plexus, pinitary, meninges and orbit.
- Diabetes insipidus and progressive cerebellar dysfunction are common.
- MBII - retardation of gonadal enhancement for several days.

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.

JUVENILE XANTHOGANULOMA (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.

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 >>