Clinical Application of Pathology

BRAIN TUMOURS VIII – Melanocytic, Lymphoma, Histiocytic and Germ Cell Tumours.

System: Nervous

Causes: Cancer

Co-authors: Clinical Professor Lesley Cala and Clinical Associate Professor Peter Robbins

This module deals with four completely unassociated groups of brain tumours.

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Thursday, January 26, 2017
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MELANOCYTIC LESIONS

MENINGEAL MELANOCYTOSIS – 8728/0

Primary pigmented tumours of the leptomeninges are an uncommon group of conditions, and include pigmented meningioma, malignant melanoma, meningeal melanocytoma, melanotic schwannoma, and melanocytosis. The differential diagnosis is often confusing owing to their similar appearance on CT and MR studies. Additional diagnostic confirmation with electron microscopy and immunohistochemical analysis is often required when assessing biopsy or resection specimens. The biological behaviour, treatment, and prognosis of these lesions are different, so it is important to make the correct pathologic diagnosis.

Embryology: Current embryologic evidence suggests a common origin of melanocytes originating from the neural crest elements normally found within the basal layer of the epidermis and the leptomeninges covering the base of the brain and the brain stem. Consequently, the areas most commonly involved are the pons, cerebellum, cerebral peduncles, medulla, interpeduncular fossa, and inferior surfaces of the frontal, temporal, and occipital lobes.

Incidence: 1 : 100,000

Age: may be found in childhood as neurocutaneous melanosis.

Neurocutaneous melanocytosis (NCM) is a rare congenital neurological disorder characterized by abnormal aggregations of nevo-melanocytes within the central nervous system (leptomeningeal melanocytosis) associated with large or giant congenital melanocytic nevi

Clinically present as variably severe and progressive neurological impairment, sometimes resulting in death.

Prognosis of NCM

Asymptomatic NCM shows a normal life expectancy. Symptomatic NCM has a poor prognosis, though this can be extremely variable (from weeks to months).

Death can result from complications of hydrocephalus or from the development of melanocytoma or CNS melanoma.


35-year-old man with a history of remote closed head injury 9 years beforehand who presented with recurrent headache, cortical blindness, and numerous new neurologic deficits.

A, Axial noncontrast CT scan shows increased attenuation of the right temporal lobe, frontal lobes, suprasellar cistern, cerebellum, basal cisterns, dentate nuclei, and an area adjacent to the fourth ventricle (arrows).

B, Axial noncontrast CT scan obtained 4 years earlier shows no areas of increased attenuation in the parasellar regions.
C, Sagittal noncontrast T1-weighted MR image depicts a suprasellar mass along with areas of increased signal in the tuber cinereum (*black arrow*) and tectal region (*arrowheads*), consistent with T1 shortening from melanin. Note the subtle area of increased signal in the pons (*white arrow*).

D, Contrast-enhanced MR image shows marked basal cistern involvement (*arrows*).

E, Axial contrast-enhanced T1-weighted MR image of the brain shows enhancement of the basal meninges and intraparenchymal lesions of both temporal lobes (*arrows*).

F, Corresponding axial FSE T2-weighted MR image shows heterogeneous signal intensity in the parasellar region with decreased signal intensity from areas of melanin (*arrows*).

G, Sagittal non contrast T1-weighted MR image reveals a large, hyper intense, oblong, anterior intraspinal mass (*arrows*). Note subtle areas of increased signal intensity surrounding the adjacent spinal cord anteriorly and posteriorly (*arrowheads*).
Spinal axis of same patient:

**H**, Sagittal contrast-enhanced T1-weighted MR image of the cervicothoracic spine shows extensive meningeal enhancement (*arrows*) with mass effect and spinal cord compression at the C4–T1 level (*arrowheads*).

**I**, Sagittal FSE T2-weighted MR image reveals decreased signal intensity within the intraspinal mass caused by melanin deposits (*arrowheads*).

**J**, Axial contrast-enhanced MR image shows marked compression of the cervical spinal cord by the mass (*arrows*). C indicates cervical spinal cord.

**K**, Sagittal noncontrast T1-weighted MR image of the thoracic and lumbar spine shows increased signal intensity surrounding the conus medullaris (*arrows*).

**L**, Sagittal contrast-enhanced T1-weighted MR image of the thoracolumbar spine shows extensive intradural enhancement and an anterior intraspinal mass at the L5–S1 level.

**M**, Sagittal FSE T2-weighted MR image of the thoracic and lumbar spine shows decreased signal intensity in the intraspinal mass at the L5–S1 level (*arrow*).
Same patient - Microscopy

*N*, from a mass in the left middle cranial fossa. The neoplasm contains sheets of cells, many of which contain dark brown melanin pigment (*arrows*). The nuclei are large and homogeneous with prominent nucleoli (*arrowheads*). Mitotic figures were rarely observed in the neoplasm.

*O*, immunohistochemistry for vimentin. The tumour cells contain abundant intracytoplasmic staining for this intermediate filament, which is characteristic but not specific of melanocytoma (*arrowheads*). Other cells are darkly pigmented owing to melanin deposits (*arrows*).

*P*, For comparison, see a control section containing only melanin deposits in which the primary antibody against vimentin was omitted. Immunohistochemical staining for HMB-45 and S-100 is not shown here.

**Treatment:** surgical exploration to debulk the tumour mass and biopsy for confirmation of diagnosis. A ventricular drainage device may be needed if there is hydrocephalus. This may have a filter attached to prevent spread of melanocytes to the abdomen.

**MENINGEAL MELANOCYTOMA – 8728/1**

**Definition:** this is an uncommon benign circumscribed, slow growing dural tumour which is well-differentiated. The neoplastic cells are believed to be derived from leptomeningeal melanocytes. It is often solitary but can present as multifocal or disseminating along the arachnoid and dura mater.

**Sites:** the majority arise in the extramedullary, intradural compartment at the cervical and thoracic spinal levels and are compressed against the dura. In this location they can be associated with nerve roots and spinal foramina. A minority arise from the leptomeninges in the posterior fossa and supratentorial compartment. Meckel’s cave is also a site with a predilection for primary melanocytic neoplasms.
**Incidence:** rare. 1 case per million

**Gender:** some female preponderance.

**Age:** 45 – 50 years. Occurrence in children is very rare.

**Clinical presentation:** there is often a prolonged evolution of symptoms from 5 – 10 years. Spinal meningeal melanocytomas typically present with progressive pain, weakness and sensory deficits. Patients rarely present with subarachnoid haemorrhage.

**Microscopic:** On light microscopy, there are spindle, fusiform, epitheloid or polygonal cells. The cells have eosinophilic cytoplasm with variable content of melanin pigment. Mitotic figures are rare or absent and necrosis and haemorrhage are generally not seen. These features help in differentiating melanocytomas from metastatic or primary melanomas of the central nervous system. Electron microscopic studies and immunohistochemical staining allow for differentiation between melanocytoma and melanotic meningioma.

- Meningeal-based neoplasm formed by tight cellular nests or whorls with variable melanin pigment.

Collections of brown melanin pigment.
**Immunohistochemistry:** melanocytomas are strongly immunoreactive for markers of melanocytic differentiation, including S-100 protein, HMB-45 and Melan-A. Microphthalmia transcription factor, a nuclear transcription factor highly expressed in melanin producing cells, can be detected in melanocytomas and is useful when other markers are negative or equivocal.

Reticulin stains and immunohistochemical stains for collagen IV and laminin indicate the presence of basal laminar proteins around blood vessels but not around individual tumour cells in a melanocytoma.

Melanocytomas are not immunoreactive for epithelial membrane antigen (EMA) or cytokeratins.

**Ultrastructure:** electron microscopy can distinguish melanocytomas from melanotic meningiomas because melanocytomas lack the desmosomes and interdigitating cytoplasmic processes that are so characteristic of meningiomas.

Both premelanosomes and melanosomes can be found within the cytoplasm of melanocytomas, indicating that melanin is produced by the tumour, not just accumulated in the cell.

Individual tumour cells of melanocytomas lack a basal lamina surrounding them.

**Imaging:** The preoperative diagnosis of meningeal melanocytoma is often difficult, as the clinical and neuroradiological features of the tumour are non-specific.

**CT** - well-defined, isodense to hyperdense, homogenous, contrast enhancing lesion.

**MRI** appearance of meningeal melanocytomas is variable, depending on the amount of melanin content present.

- **T1:** isointense or hyperintense
- **T2:** isointense or hypointense
- **T1 C+ (Gd):** heterogenous enhancement
- **T2* GRE:** may show blooming of low signal

Images below are T1W pre and post contrast, and courtesy of Nau LG, Hise JH, Bauseman SC, Todd FD. AJNR 1991; 12 (Mar-April). The mass at the foramen magnum is obstructing CSF flow.
**Treatment:** Complete excision is the treatment of choice. However, this is often not possible as intra-operative haemorrhage may be severe.

**Prognosis:** Although classified as benign, meningeal melanocytomas may behave aggressively and a limited number may transform to malignant melanomas.

Local recurrence has been reported even after gross total removal. Due to the risk of tumour recurrence even after complete excision, adjuvant radiation therapy is advised in cases of both complete and incomplete resection.

**MENINGEAL MELANOMA – 8720/3**

**Definition:** is a melanoma arising in a focal site, unlike the diffuse meningeal melanomatosis.

**Sites:** may be solitary discrete neoplasms with a nodular growth pattern or as proliferations that diffusely involve the surface of the brain (melanomatosis)

**Incidence:** 6 cases per 100,000 per year

**Gender:** no difference in the sexes.

**Clinical presentation:** varies depending upon whether the tumour is a solitary mass or a sheet-like proliferation.

**Macroscopic:** grow as extra-axial masses or as diffuse sheets of malignant cells within the subarachnoid space. The lesions are grossly gray, brown or black. In either growth pattern, there is usually frank invasion of the underlying CNS parenchyma. Less commonly primary melanoma presents as intra-axial masses that can secondarily disseminate throughout the leptomeninges. Both nodular and diffuse growth pattern can involve the spinal cord, the posterior fossa and the supratentorial compartments. Nodular lesions show a slight predilection for the spinal cord and posterior fossa which is the most abundant source of precursor melanocytes.

**Imaging:** CT scan before and after contrast below is courtesy of Suranagi VV, Maste P, Malur PR. Asian J Neurosurg 2015 Jan-Mar; 10(1): 39-41. Tumour is in a right frontal parafalcine position and enhances markedly with contrast, showing internal areas of necrosis.
**MRI:** superficial forms show T1 signal hyperintensity in regions of involved leptomeninges and brain. Often show thickening and contrast enhancement of the involved leptomeninges. Contrast-enhancement and T1 hyperintensity often extends from the brain surfaces deeply within the sulci and may track along penetrating arteries. Hydrocephalus is common due to melanotic deposits obstructing CSF outflow or decreasing its absorption.

MRI features of nodular forms of melanoma demonstrate a solid mass that is generally based on the dura. T1W and T2W signal abnormalities may be seen depending on the amount of melanin present. Heavy melanin show greatest T1 hyperintensity and T2 hypointensity. The degree of contrast enhancement also varies.

In both forms rapid growth rate is suggested by the presence of vasogenic oedema in the adjacent brain. This will be seen as T2 hyperintensity.

**Microscopy:** CNS melanoma, like its cutaneous and systemic counterparts, is capable of demonstrating a wide spectrum of microscopic appearances, each of which has the potential to mimic a number of other neoplastic processes. Melanin production is variable and may be absent (amelanotic melanoma). One common pattern comprises pleomorphic and mitotically active polygonal tumour cells in diffuse sheets or papillae. The latter often result from areas of tumour necrosis, with persisting viable cells limited to perivascular cuffs, resulting in a pseudo-papillary pattern.

Distinction between primary CNS melanoma and metastatic involvement of the CNS by melanoma of cutaneous or systemic origin can be impossible on purely morphologic grounds, and requires careful clinical and imaging evaluation to exclude the possibility of a primary ‘occult’ melanoma arising outside the CNS. In general terms however, although primary and metastatic lesions show considerable histologic overlap, metastatic lesions as a group often show extensive necrosis, more obvious cytologic malignancy, higher mitotic indices, and higher MIB-1 labelling proliferating indices. A useful clue to the diagnosis of a primary process is the identification of a precursor leptomeningeal melanocytic lesion.

With respect to melanocytoma, melanoma generally comprises larger, more cytologically atypical cells, often arranged in loose nests or sheets with CNS invasion and/or necrosis. Bizarre, pleomorphic nuclei are common, and melanomas are more densely cellular and mitotically active, with higher mitotic rates and MIB-1 labeling indices. None the less, it is recognised that melanocytic neoplasms of the CNS represent a spectrum ranging from those which are clearly ‘low grade’ and well differentiated i.e. melanocytoma through to those which are frankly malignant – melanoma. A small, rare, but important group of intermediate primary CNS melanocytic lesions is recognised. These are characterised by the presence of some worrisome microscopic features (e.g. low level mitotic activity [one to three per 10 HPFs], slightly elevated MIB-1 labeling indices, sheet like growth and / or hypercellularity) but do not possess the degree of hypercellularity, mitotic rate, or anaplasia typical of melanoma.
Immunohistochemistry: images below of markers:
A. DOPA, B – HMB-45, C – S-100, D – vimentin

Treatment: surgical excision if possible.

Prognosis: a primary malignant melanoma of the leptomeninges can metastasize to remote organs.

Meningeal Melanomatosis - 8728/3

This is a rare variant of meningeal melanoma that seems to arise directly from melanocytes within the leptomeninges.

Despite the use of CT, contrast-enhanced MR imaging, and CSF cytology, the disease can be difficult to recognize. Meningeal melanomatosis may be radiologically and clinically confused with diffuse leptomeningeal neoplasms.

Clinical: example is a 68 yr old female with headache, vomiting, mental deterioration, and gait disturbance. Examination showed mental slowness, poor concentration and memory, a short-stepped gait, and lower limb weakness.

Imaging: Cranial CT scans revealed hydrocephalus with effacement of the cerebral convexity sulci and abnormal contrast enhancement in the right sylvian and frontoparietal fissures. See images and legends below, courtesy of Pirinia M-G, Nascaukuc Nm /Sakvu F, Tassinrieb CA, Zanellad L, Bacchinid P, Bertonid F, D’Erricoa A, Cortia B, Grigionia WF. AJNR 2003; 24: 115-118
At presentation, contrast-enhanced cranial CT scans show dilatation of the lateral (A) and third (B) ventricles, with effacement of the cerebral convexity sulci (in A). Abnormal contrast enhancement is present in the right Sylvian fissure (arrow in B) and in the right frontoparietal region.

Twelve months after the placement of a ventricular CSF shunt with a right parietal approach, cranial axial (C) and coronal (D) T1-weighted spin-echo MR images (TR/TE, 580/14) obtained after the intravenous administration of contrast show small lateral and third ventricles and diffuse dural and leptomeningeal enhancement.

Plain cranial CT scan obtained 1 month before the patient’s death shows tiny ventricles and symmetric areas of hypoattenuation (arrows) in the subinsular white matter and external capsules. This finding was probably due to neoplastic encasing of the penetrating arteries.

Microscopic: Spreading of neoplastic cells along subpial, perivascular, and Virchow-Robin spaces into the cerebral cortex. The cells are polygonal with a dusty cytoplasmic pigment.

Immunohistochemistry: The immunohistochemical findings were diagnostic of malignant melanoma. In particular, the neoplastic cells were strongly positive for S-100, vimentin, and HMB-45, but they were negative for glial fibrillary acid protein and cytokeratins.
Diffuse melanocytosis and melanomatosis involve the supra- and infra-tentorial leptomeninges and the superficial brain parenchyma and generally occur in the setting of dermatologic syndromes (e.g., neurocutaneous melanosis syndrome and nevus of Ota). Primary leptomeningeal melanomatosis is a rare, aggressive tumour and arises from melanocytes within the leptomeninges and carries a poor prognosis. This tumour is also referred to as a meningeal variant of primary malignant melanoma. The malignant melanocytes spread in the leptomeninges, into the Virchow-Robin spaces, and superficially within the brain substance.

**Treatment:** Following intracranial biopsy for diagnosis, patients may be offered radiotherapy. Others may receive intrathecal chemotherapy such as Interleukin-2.

**Prognosis:** is very poor. The average survival from time of diagnosis is 10 weeks. 7% of patients may be alive at one year from diagnosis but only 3% alive at 2 years.

**PRIMARY CNS LYMPHOMAS – PCNSL - (CNS lymphoma)**

**Overview:** Primary central nervous system lymphomas (PCNSL), by definition, arise within the CNS in the absence of prior or concurrent involvement of systemic sites. CNSL is now known to be a form of extranodal, high-grade lymphoma. It originates in the brain, leptomeninges, spinal cord, or eyes; typically remains confined to the CNS; and rarely spreads outside the nervous system.

The cells of origin are lymphocytes although there are no lymphatics in the brain tissue.

Drug delivery is impaired by the blood-brain barrier and cerebral toxicity limits the use of some available treatments.

**Incidence:** rare tumour accounting for only 2% of cerebral neoplasms.

**Classifications:** many have existed but currently the WHO classification is used internationally. This groups PCNSL into 3 groups: B cell neoplasms, T cell and NK cell neoplasms, and Hodgkin’s lymphoma.

**Types:** 90% of PCNSLs are diffuse large B-cell lymphomas (DLBCLs); the remaining 10% are poorly characterized low-grade lymphomas, Burkitt lymphomas, and T-cell lymphomas.

**Clinical:** Primary symptoms may result from local mass effect due to raised intracranial pressure, from ocular involvement, or from focal deposits on cranial or spinal nerve roots.

**Diagnosis:** the clinical and neuroimaging presentation of PCNSL can be varied and the differential diagnostic possibilities large, so no patient should be treated for PCNSL without definitive proof of diagnosis, either by vitrectomy, positive CSF cytology, or brain biopsy.

Furthermore, differences are found between the immunocompetent patient and the immunocompromised: 75% of immunocompetent patients have solitary lesions whereas a large percentage of the immunocompromised patients have multiple lesions.

In general terms, the diagnosis of large cell PCNSL is generally straightforward, and is not compromised by small (stereotactic) sample size. CSF cytology is often negative at presentation, but aids in documenting CNS recurrence. Immunohistochemical studies resolve potential confusion with anaplastic glioma or metastasis, and generally facilitate lymphoma classification and immunophenotyping. The majority of PCNSL are successfully diagnosed and classified in routinely
fixed and processed biopsy specimens, but flow cytometry, molecular and cytogenetic studies can play a critical role in diagnosis in some cases. Potential areas of diagnostic difficulty include polymorphous infiltrates, where inflammatory, infectious and other disorders may need to be distinguished from lymphoma (particularly in the immunocompromised), and rare histological subtypes of PCNSL. Small specimen size may limit conventional cytogenetic and flow cytometry studies, but PCR techniques to identify clonal B or T cell receptor gene rearrangements or specific translocations may potentially be applied to small fixed and processed tissue samples.

Another important consideration in the diagnostic workup of a patient with suspected lymphoma is that pre-operative steroid induced regression may lead to non-diagnostic biopsies.

**B CELL LYMPHOMAS**

**DIFFUSE LARGE B-CELL LYMPHOMA OF THE C.N.S. - 9680/3**

**Definition:** it is an extra-nodal non-Hodgkin’s lymphoma

**Sites:** supratentorial single lesions in 70% of patients and a predilection for lesions to lie deep in the cerebral hemisphere in structures adjacent to the ventricular system.

In AIDS patients, 85% display multiple lesions and found in 45% of non-AIDS patients.

**Incidence:** account for 90% of primary CNS lymphomas.

**Age:** Immunocompetent patients who develop PCNSL are predominantly older adults- PCNSL incidence peaks at age 57 years in immunocompetent populations, compared with a peak range of 31 to 35 years in immunocompromised patients

**Gender:** PCNSL tends to affect males more than females in both groups. This difference is more pronounced in the immunocompromised population (male-to-female ratio, 7:1) than in the immunocompetent population (2:1)

**Risk factors:** Congenital or acquired immunodeficiency is the only established risk factor for PCNSL. The HIV pandemic is the primary factor responsible for the increase in PCNSL incidence. Persons infected with HIV have a 3600-fold higher risk of PCNSL compared with the general population. HIV-related PCNSL is associated with a reduction in the number of circulating CD4+ cells, a factor linked to patient survival. With the introduction of highly active antiretroviral therapy (HAART), the proportion of HIV-infected persons with CD4+ cell counts less than 50 cells/mm³ has declined, and this has correlated with a reduction in PCNSL incidence in this population.

An increased PCNSL risk has been observed in organ transplant recipients receiving immunosuppressive drugs and in some autoimmune and immunomodulating diseases, as well as in patients with prior malignancies, implicating immune dysregulation as a risk factor for PCNSL

**Clinical presentation:** Headache, nausea, vomiting, epileptic seizures, disorders of speech and vision and focal neurologic deficits are the most common symptoms of brain lymphomas.

**Macroscopic:** varies greatly. The tumour can be solitary or multiple, well-demarcated or diffuse, firm or soft, friable, granular, centrally necrotic, focally haemorrhagic, grey-tan, yellow or indistinguishable from normal brain parenchyma.

AIDS patients tend to have more necrotizing lesions which may simulate abscesses with centrally pale and peripherally hyperaemic regions. Despite extensive necrosis, cysts are uncommon.
In the immunocompetent, tumours tend to have a homogeneous, non-necrotizing appearance, simulating other primary neoplasms.

**Imaging:** The dense cellularity of the tumour accounts for its isodense or hyperdense appearance on nonenhanced CT scan and hypointense appearance on long TR-weighted MR.

Almost all PCNSLs enhance homogeneously on CT and MRI. PCNSLs are assumed to be diffusely infiltrative at the time of presentation.

MRI below, courtesy of Siasios I, Fotiadou A, Fotakopoulos G, Ioannou M, Anagostopoulos V. J Clin Med Res 2015 Dec. 7(12): 1007-1012, shows on a FLAIR image - left, the oedema around a mass in the right occipital region. A T1W post contrast – right - illustrates the tumour itself.

**Differential diagnosis:** includes metastasis, glioma and toxoplasmosis, whereas in rare cases PCNSLs have signs of demyelinating disease.

**FLAG; Diagnosis:** is often established by stereotactic biopsy. As mentioned earlier, it is essential that corticosteroid treatment given to reduce associated cerebral oedema is not given prior to biopsy when ever possible. Pre-operative steroid induced regression may lead to non-diagnostic biopsies because steroid treatment induces apoptosis of the tumour cells, leading to the phenomenon of ‘vanishing’ or ‘ghost’ lesions.

See the CT scan post contrast images below taken 10 days apart – arrows indicate lymphoma bilaterally in the region of the basal ganglia on the left at admission and the almost disappearance of the lesions 10 days later after steroid treatment.
AIDS patients present an additional problem which is the possibility of the basal ganglia lesions being due to Toxoplasmosis. As steroids could have a very adverse effect upon an infectious process, one regime is to administer azithromycin for 10 days and then repeat the CT scan. The next image is a post contrast CT scan on admission with a left basal ganglia deposit plus surrounding oedema – arrows.
The post contrast CT scan above shows the deposit to have almost completely disappeared, so the deposit was due to toxoplasmosis, not lymphoma.

**FLAG:** If the lesion had remained unchanged, a decision would then have been made that it was lymphoma and steroids could be safely given. Whenever possible a stereotactic biopsy would be preferable.

**Microscopy:** Classically there is a perivascular distribution of neoplastic cells – see arrow below. These variably-sized collars of tumour cells surround blood vessels and are associated with perivascular reticulin deposition. Laminin, collagens type 3 and 4 and fibronectin have all been demonstrated in this reticulin network. Perivascular lymphocytes are most common around vessels of 15 µm in diameter. The reticulin network may appear open and not completely envelope tumour cells.
From perivascular cuffs, tumour cells infiltrate and invade neural parenchyma.

When tumour cells become confluent and a mass lesion forms, a pattern of geographic necrosis may also be seen, with perivascular islands of viable tumour cells surrounded by large regions of eosinophilic, necrotic tumour parenchyma (coagulative necrosis) – see below.

Image above courtesy of Russell and Rubinstein’s Pathology of Tumours of the Nervous System.

This pattern of necrosis differs from that seen in PCNSL treated with steroids. Biopsies that have been taken after steroid treatment, lipid-laden macrophages accompanied by lymphocytes and lymphoplasmacytoid cells infiltrate loose, pale necrotic zones with scattered pyknotic cells but without regions of coagulative necrosis.
There is a tendency for more cell-to-cell variability and pleomorphism noted in tumours arising in the immunocompromised when compared to those in the immunocompetent.

**Immunohistochemistry:** the tumour cells express CD19, CD20 and CD79a, whereas the majority express Bcl-6 and MUM1 and in some cases CD10 is expressed as well. The high mitotic activity leads to high MIB1 labelling indices, which can exceed 90%. Necrosis may also be noted in histopathologic analysis. CD 20 is a pan B-cell marker – see below.

There are 4 major variants of diffuse large B cell lymphoma:

**Centroblastic** - medium to large nuclei, oval to round vesicular nuclei with fine chromatin and membrane-bound nucleoli. Cytoplasm is scant.

**Immunoblastic** – have large centrally located nucleoli and appreciable amounts of basophilic cytoplasm.

**Anaplastic variants** – very large round, oval or polygonal cells with bizarre pleomorphic nuclei resembling Reed-Sternberg cells of Hodgkin lymphoma. This can mimic anaplastic carcinoma.

The 4th variant is the T cell/histiocyte rich variant.

This variant has less than 10% large neoplastic B cells, and are populated by non-neoplastic T cells with or without histiocytes.

Monotony of cell type may be helpful in assessment of diffuse large cell lymphomas arising in the immunocompetent but pleomorphism and polymorphic cell populations is the typical situation with immunocompromised patients.

Immunohistochemistry for germinal center–related antigens

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<tr>
<td>bcl-6</td>
<td>26/33 (79)</td>
<td>The bcl-6 protein is a zinc-finger transcriptional repressor encoded by the BCL-6 gene</td>
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<tr>
<td>CD10</td>
<td>6/32 (19)</td>
<td>CD10 is a marker that reflects GC origin in reactive lymphoid tissue and lymphomas</td>
</tr>
<tr>
<td>MUM1</td>
<td>31/32 (97)</td>
<td>MUM1 is a late GC/early post-GC marker</td>
</tr>
<tr>
<td>CD44</td>
<td>11/31 (35)</td>
<td>CD44 is expressed most strongly by post-GC mantle zone cells</td>
</tr>
<tr>
<td>vs38c</td>
<td>4/33 (12)</td>
<td>The presence of vs38c and CD138 denotes plasmacytic and/or post-GC differentiation</td>
</tr>
<tr>
<td>CD138</td>
<td>0/32 (0)</td>
<td>The presence of vs38c and CD138 denotes plasmacytic and/or post-GC differentiation</td>
</tr>
<tr>
<td>BCL-2</td>
<td>27/29 (93)</td>
<td>BCL-2 protein expression prevents cellular apoptosis and is downregulated by normal GC cells</td>
</tr>
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GC—germinal center; PCNSL—primary central nervous system lymphoma.

Molecular/genetic features

Gain of chromosome 18q and translocation t(14;18) are frequently found in B-cell non-Hodgkin’s lymphomas (B-NHL). Increased BCL2 transcription and BCL2 protein expression have been suggested to be the result of the gain. t(14;18) can be identified in the blood of healthy persons many years before they develop Non Hodgkin’s lymphoma so it is a pre B cell prognostic marker.

Pathogenesis of diffuse large B-cell lymphoma—see below. In the CNS there are also somatic hypermutations as well as chromosomal translocations, especially those involving the IgH and BCL-6 genes. TP53 mutations are rare in PCNSL. Drawing courtesy of Mrugala MM, Rubinstein JL, Ponzoni M, Batchelor TT. Curr Oncol Rep. 2009 Jan; 11(1): 73-80.

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<th>Gene</th>
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<tr>
<td>ECM family:</td>
<td>CNS tropism, B-cell migration, lymphoproliferation, cell differentiation, migration, angiogenesis, and metastasis</td>
<td>Aggressive tumor growth, high metastatic potential, poor prognosis</td>
</tr>
<tr>
<td>SPP1 and CH13L1</td>
<td>Expresed in tumor tissue and endothelium</td>
<td>Overexpression associated with aggressive tumor growth, decreased survival in patients treated with methotrexate</td>
</tr>
<tr>
<td>STAT5</td>
<td>Tumor suppressor gene, regulation of B-cell differentiation</td>
<td>Mutations associated with lymphomagenesis</td>
</tr>
<tr>
<td>PRDM1</td>
<td>Induction of cell growth arrest and stabilization of p53 protein</td>
<td>Deletion or promoter methylation can induce tumor growth</td>
</tr>
<tr>
<td>PI3K</td>
<td>Regulation of cell contact and adhesion</td>
<td>Shorter survival in patients with loss of expression</td>
</tr>
<tr>
<td>BCL-6</td>
<td>Transcriptional repressor, oncogene, malignant transformation of germinal center B cells</td>
<td>Overexpression associated with favorable prognosis</td>
</tr>
</tbody>
</table>

CNS—central nervous system; ECM—extracellular matrix.

Treatment: The recommended treatment for these patients includes chemotherapy with or without additional radiotherapy, whereas corticosteroids can be used in addition. Surgery is not recommended for the treatment of brain lymphomas and it is only performed in extreme situations.

Prognosis: PCNSL of DLBCL type is a highly aggressive tumour and although its prognosis is poor, about one-third of younger patients can hope for cure of the disease.

The disease has unfortunately a poor prognosis and patients are expected to survive for 3 - 6 months without treatment, whereas chemotherapy alone or in combination with radiotherapy may improve median survival time to 25 - 60 months. Younger patients (under the age of 60) and patients whose lymphoma does not affect meninges or the regions in proximity to ventricles have a better prognosis. The same applies to individuals whose immunity is normal. Concentration of serum lactate dehydrogenase (LDH) is an independent prognostic marker. Increased LDH and protein levels in CSF generally indicate a poor prognosis.

**INTRAVASCULAR LARGE B-CELL LYMPHOMA** – 9712/3 (Angiotropic lymphoma)

Definition: a disorder of large B-cell lymphomas characterized by exclusive or markedly predominant growth of lymphoma within vascular lamina and which has a predilection to involve the CNS and skin but can involve any organ system.

Age: usually affects elderly patients in their 6th to 7th decades of life.

Gender: male-to-female ratio of 1:2

Pathogenesis: The reason why lymphoma cells tend to stay in the intravascular space in IVL is a consequence of the absence of CD29 (β1 integrin) and CD54 (ICAM-1) surface ligands, which probably disable them from diapedesis across the endothelium.
Clinical presentations: varied. Reports detail mental status changes, dementia, aphasia dystonia, cranial nerve dysfunction, polyneuropathy, paraplegia, seizures, headache, cauda equina syndrome, ataxia. Extraneural features may be apparent especially skin plaques and nodules. Very aggressive tumour with short survivals.

Laboratory tests: A mild to moderate elevation of CSF protein is usually present.

Macroscopic: 50% are diagnosed at autopsy. Gross appearance includes areas of brain and spinal cord softening and infarction, haemorrhages or swelling and herniation – see specimen below. However, the involved areas may look normal.

Imaging: varied findings. May have single or multiple mass lesions, infarct areas, white matter abnormalities and meningeal enhancement on MRI and CT scans. Angiography (DSA), CT and MRI often show evidence of multiple vascular occlusions and stroke as nonspecific multifocal abnormalities.

MRI: T2/FLAIR: hyper-signal abnormalities in a dynamic pattern (resolution of some and the new appearance of others) – see below, courtesy of Assoc. Prof. Frank Gaillard, Radiopaedia.org, rID 37944.

DWI/ADC: restriction areas in a dynamic pattern

T1 C+ (Gd): a persistent mass-like enhancement may be noted in proximity to the T2 or DWI changes. Different patterns of parenchymal and meningeal enhancement may be seen.
**Microscopic:** Large lymphoma cells are seen in small and medium caliber blood vessels, with vesicular nuclei, prominent nucleoli and mitoses. Sometimes cells have anaplastic features. Intraluminal fibrin deposition may be present. See next two images.

![Microscopic image](image1)

**Immunohistochemistry:** Tumour cells express B antigens such as immunoglobulin light and heavy chains, CD5, CD19, CD20, CD22 and CD79a. Rarely intravascular lymphoma may have a T cell phenotype.

CD44, (Hermes 3 or homing receptor), an adhesion molecule, immunoreactivity is found in all studies of intravascular tumour cells.

**Molecular analysis:** Confirms immunoglobulin gene rearrangement. Rarely intravascular lymphoma may have a T cell phenotype, or in rare T cell cases clonal T cell receptor gene rearrangements.

**Differential diagnosis:** In the brain includes other forms of primary or secondary CNS tumours or infarcts.

**Treatment:** Chemotherapy and bone marrow transplant can induce clinical remission.

IVL is sensitive to systemic chemotherapy. However, the treatment still remains suboptimal due to the rarity of this disorder and the difficulty to establish a diagnosis in time.
**Prognosis:** IVL usually has a rapidly fatal outcome, with patient overall survival lasting only a few months.

**IMMUNODEFICIENCY-ASSOCIATED CNS LYMPHOMAS**

This includes AIDS-related diffuse large B-cell lymphoma, EBV-positive diffuse large B-cell lymphoma, post-transplant lymphoproliferative disorders and lymphomatoid granulomatosis.

**Definition:** lymphoproliferative disorders in patients with primary or acquired immunodeficiencies. **Primary immunodeficiencies** include Ataxia Telangiectasia and X-linked disorders such as Wiskott-Aldrich syndrome. The latter is eczema, thrombocytopenia and immunodeficiency. **Acquired immunodeficiencies** predominantly occur in the setting of infection with the Human Immunodeficiency Virus or arise following immunosuppressive therapy administered after organ transplantation.

The lymphoproliferations that occur with immunodeficiency are extremely heterogeneous. In part this reflects the diversity of the causal immune defect. The most striking clinical characteristic is the high frequency of extranodal disease. Frequently, these lymphomas are driven by viruses such as Epstein-Barr virus (EBV), although the lack of EBV in a proportion indicates that alternate pathways must also be involved in the pathogenesis.

**ACQUIRED - AIDS-RELATED DIFFUSE LARGE B-CELL LYMPHOMA (ARL)**

**Definition:** high grade, aggressive non-Hodgkin’s lymphoma.

**Incidence:** 4% people with AIDS have non-Hodgkin Lymphoma (NHL) at diagnosis and at least the same proportion develop NHL during the course of their illness.

**Types:** three types on the basis of areas of involvement

- Systemic NHL
- Primary central nervous system lymphoma (PCNSL)
- Primary effusion lymphomas ("body cavity lymphoma")

Systemic NHL is the most common variety of ARL, followed by PCNSL, which is less common but not rare and primary effusion lymphoma, which is a rare disease.

**Microscopic:** the most common variants are diffuse, large B-cell lymphoma and small, non-cleaved cell lymphoma, including Burkitt and/or Burkitt-like.

**Clinical features:** AIDS-related Burkitt lymphoma may develop in the presence of relatively sustained CD4+ counts.

Diffuse large B-cell lymphoma usually develops later in the course of the illness and in patients who have lower CD4+ counts.

**PCNSLs tend to occur at CD4 counts of less than 50/μl.**
PCNSL patients may present with headache, blurred vision, muscular weakness, sensory deficits, personality changes, depression, apathy, confusion, memory impairment, and cranial neuropathies. These findings may also occur with leptomeningeal involvement.

**Lymphoma** has become more common as the initial AIDS-defining condition.

There is a reduction in the overall incidence of AIDS-related NHL and higher CD4+ cell counts at presentation, presumably due to the effect of highly active antiretroviral therapy (HAART) therapy.

With the use of HAART therapy and effective treatment of opportunistic infections, both leading to longer life expectancy, the burden of NHL might be altered.

The prognosis is improving but it still remains poor.

**Etiology:** largely unknown; however, several factors play an important role in development of the disease. These include infections with viruses, namely, Epstein-Barr virus (EBV) infection and human herpes virus 8 (HHV-8) infection; continuous B-cell stimulation; and immunodeficiency.

**Systemic NHL** constitutes about 80% of all AIDS-related lymphomas (ARLs). These lymphomas are of the following varieties

- Burkitt lymphoma and Burkitt-like lymphoma
- Diffuse, large cell lymphoma, including centroblastic lymphoma, immunoblastic lymphoma, and plasmablastic lymphoma of the oral cavity

**Molecular pathogenesis:** NHLs are heterogeneous. Activation of c-myc occurs in all AIDS patients with Burkitt lymphoma. Inactivation of p53 is found in 50-60% of patients and EBV infection in 30-50%.

In centroblastic NHL, EBV infection is found in 30% of affected individuals. BCL-6 proto-oncogene is positive in 20% of patients

**Immunoblastic** lymphoma - EBV is positive in 90% of patients and latent membrane protein (LMP)-1 (EBV-encoded protein) is expressed in 65-75% of patients. EBV-positive lymphomas express LMP1, suggesting a pathogenic role of the virus in development of lymphomas. LMP1 is positive only in immunoblastic lymphomas. **Polymorphic** cells.

**Plasmablastic** lymphoma of the oral cavity - the malignant cells tend to grow in a cohesive manner. The cells are usually large, monomorphic, and have abundant cytoplasm with a peripherally placed nucleus. There is a single prominent nucleolus. EBV positive in 50%.

**Primary CNS Lymphomas** generally have immunoblastic histology. There is consistent infection of the tumour cells by EBV, with 90% of the patients expressing LMP-1, suggesting the importance of the virus in the pathogenesis of the tumour. Most of the patients have mutations of BCL-6, and they also express high levels of the BCL-2 protein. Expression of p27K1P1 and a high proliferative index are found in immunoblastic lymphoma.

**Immunoblastic lymphoma** has malignant lymphoma cells with plasmacytic features. The cells have large, solitary nucleoli and abundant cytoplasm. The tumour cells usually show strong cytoplasmic immunoreactivity with monoclonal antibody against syn-1.
The peak incidence for PCNSLs has varied over time and has been affected the most by introduction of HAART therapy. **The tumour is rare in immunocompetent individuals.** The incidence of PCNSLs is increased by 1000-fold in AIDS patients.

**Prognosis:** 3.5 months

**Imaging:** A PCNSL is typically a well-defined focal lesion on a head CT scan.

**AIDS-related PCNSLs** show a high degree of enhancement on CT scans following intravenous contrast injection. The enhancement is typically irregular, unlike that in seronegative patients with the same neoplasm. The difference might be attributable to central necrosis of the tumour in AIDS patients because of rapid growth when compared with non-HIV positive patients. MRI scanning improves the diagnostic yield.

Immunodeficient patients with PCNSL are often diagnosed with multifocal lesions, which are reported in 30%–80% of patients with AIDS-related PCNSL. Because many lesions exhibit necrotic regions, contrast enhancement is commonly irregular or peripheral, and ringlike enhancement is reported in up to 75% of cases. The basal ganglia and corpus callosum are frequently involved. Spontaneous haemorrhage in PCNSL lesions may be more frequent in AIDS patients than in non-AIDS patients.


Contrast-enhancing lesions on CT scans (A–D) in 4 patients with AIDS-related PCNSL. Note irregularly enhancing lesions in the right parietal lobe (A), right occipital lobe (B), and right periventricular white matter (C and D); most of the lesions show ring enhancement (A, B, and C)

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All patients with HIV and a lymphoma are recommended to have a lumbar puncture with microscopy and flow-cytometry performed to rule out CNS involvement.

**Staging:** Staging is not usually valuable for PCNSLs and thus is not indicated. The malignancy generally remains confined within the CNS.

**Treatment:** in the era of HAART, patients with AIDS-related lymphomas (ARLs) are generally being treated with standard or only slightly modified chemotherapy regimens. Autologous bone marrow and stem-cell transplantation approaches in lymphoma patients have been successful.

Addition of rituximab to EPOCH (etoposide, prednisone, vincristine [Oncovin], and doxorubicin hydrochloride [hydroxydaunorubicin hycrochloride]), CHOP, CODOX/MIVAC and other standard regimens is likely beneficial.
Steroids are often given when a symptomatic brain mass lesion is identified in patients with ARLs. These agents can shrink the tumour and also convert contrast-enhancing lesions into non-enhancing lesions.

**PCNSL** usually occurs in patients who have very low CD4 counts and who are severely immunosuppressed. The median CD4 count of such patients has been found to be as low 15/μL in some studies.

**Prognosis:** The tumour has a very bad prognosis. Pre-HAART studies have indicated a median survival of only 1-2.5 months for untreated patients with PCNSL.

Radiotherapy in combination with steroids has been the cornerstone of therapy, but median survival remains around 3.5 months. A high performance status is one of the most important prognostic factors in this patient population.

High-dose chemotherapy combined with whole-brain radiation therapy improves tumour response rates and survival compared with whole-brain radiation therapy alone.

High-dose methotrexate has been suggested as an alternative to radiation therapy for primary CNS lymphoma but patients who had a biopsy diagnosis had a median survival of 73 days only.

**EBV-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA – NOS**

[EBV – Ebstein-Barr Virus.]

Several studies had reported that EBV positive patients showed an inferior prognosis compared with EBV negative cases, especially the elderly group. The clinical course is often aggressive with a median survival of 2 years and an overall 5-year survival rate of approximately 25%. Many studies also showed the young patients of EBV positivity demonstrated poor outcome with traditional immunochemotherapy.

**CNS POST TRANSPLANTATION LYMPHOPROLIFERATIVE DISORDERS**

These may occur as either an isolated primary CNS lesion or as part of a multifocal process with systemic manifestations. Found in 2% of autopsied solid organ post-transplant patients but identified in 22% in some series. However, abnormalities from cerebrovascular events were present in more than 50%. The CNS is thought to account for about 25% of all extranodal post-transplant lymphoproliferative disorders.

**Types:** only monomorphic and polymorphic PTLD have been described in a brain location. The lesions are clonal so fall under the term PCNSL.

**Etiology:** most are EBV-related, although EBV-negative types have been reported.

**Sites:** monomorphic large cell morphology may be more common in primary CNS lesions. Polymorphic PTLD more often seen in disseminated disease with brain involvement.

**Clinical presentation:** the latency between transplantation and emergence of clinical abnormalities averages 1 – 3 years. However, the range reported is 3 months to more than 20 years.

**Imaging:** may simulate abscesses and are often multiple.
**Microscopic:** less than 5% of CNS PTLD are of T-cell origin. The rest are B-cell monomorphic.

**Immunohistochemistry:** most B-cell monomorphic demonstrate CD20 immunoreactivity.

**Treatment:** rarely patients who have their immunosuppressive drugs reduced show a clinical response but a few series show remission in up to 65%.

**Prognosis:** median survival is 26 months which is better than other PCNSL in immunocompromised. Other series, using radiotherapy have had survivals of up to 10 years. Most require radiotherapy, treatment with monoclonal antibodies, chemotherapy or a combination. In general, a CNS location for PTLD carries a poor prognosis.

**Predictors of lower survival are:** CNS location, low performance status, non-detection of EBV, T-cell origin, monoclonality, tumour at more than one site and treatment with chemotherapy.

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**LYMPHOMATOID GRANULOMATOSIS – 9766/1**

**Definition:** lymphomatoid granulomatosis is a distinctive type of malignant lymphoma associated with immunosuppression. There is an exuberant T-cell reaction in an EBV-associated B-cell lymphoproliferative disorder. T-cell component represents a prominent, polyclonal, reactive, T-cell infiltrate. It is best viewed as a T cell–rich, B-cell lymphoma.

**Sites:** the CNS or peripheral nerves are involved in up to 30%.

**Frequency:** a rare disease of unknown prevalence.

**Age:** most common in the 5th and 6th decade.

**Gender:** Male : Female = 2 : 1

**Racial:** no known racial predilection.

**Clinical presentation:** The clinical features of lymphomatoid granulomatosis reflect systemic multi-organ disease. Pulmonary involvement usually is present, while the skin (50%), nervous system (25%), kidneys, and liver are affected less commonly. The lymph nodes, spleen, and bone marrow usually are spared until late in the course of illness. Primary orbital involvement has been reported

- CNS may include mass lesions. Neurological manifestations, including mental status changes, ataxia, hemiparesis, and seizures, may occur.
- Peripheral nerve involvement may include distal sensory neuropathy or mononeuritis multiplex.
- Isolated neurological lymphomatoid granulomatosis has been reported

**Laboratory tests:**
- WBC count - Leukopenia (20%) and lymphopenia (33%) may be present.
- CD4 lymphocyte count may be low.
- Leukocytosis greater than 10,000 cells/μL is rare.

Hematocrit is normal or slightly elevated.
Erythrocyte sedimentation rate (ESR) has mild-to-moderate elevation but may be normal. Obtain renal and liver function studies. Findings are usually normal. Urinalysis results are usually normal. Delayed-type hypersensitivity and lack of anergy have been reported in more than 50% of cases.

**Etiology:** Apart from association with opportunistic disease and EBV, the etiology of lymphomatoid granulomatosis is unknown.

**Imaging:** CT scan shows high-density lesions. MRI lesions are isointense or hyperintense on T1-weighted images and hyperintense on T2-weighted images. Enhancement may be punctate and linear, a finding that can be relatively specific for inflammation of deep cerebral vessels.


A, Contrast-enhanced T1-weighted axial image shows an enhanced lesion from the splenium of the corpus callosum extending to the right parietal white matter. There is a small area of necrosis within the mass (arrow). Nodular and multiple punctate enhancements are seen in the white matter (arrowhead).

B, T2-weighted image (fast spin-echo sequence shows a hyperintense mass (arrow) and surrounding oedema.

C and D, Contrast-enhanced T1-weighted images show multiple punctate enhancements in the pons and cerebral white matter bilaterally.

E and F, T2-weighted axial image shows patchy hyperintense areas in the pons and cerebral white matter bilaterally (arrows).

G, Stereotactic biopsy specimen from the right parietal lobe shows small lymphoid cells, microglia, and macrophages, which were prominent in the perivascular space (arrow).
Contrast-enhanced T-weighted image 6 months after radiation therapy shows that the mass has almost disappeared.

**Microscopic:** Diagnosis by the histological triad comprising the following:

- Nodular polymorphic lymphoid infiltrate composed of small lymphocytes, plasma cells, and variable numbers of large atypical mononuclear cells
- ‘Angiitis’ due to transmural infiltration of arteries and veins by lymphocytes with associated vessel wall necrosis and acute and chronic inflammatory cells. Angiodestructive and angiocentric infiltrates are characteristic.
- Granulomatosis (central necrosis within the lymphoid nodules and not granuloma formation)

A combination of PCR and in situ hybridization show that most lymphomatoid granulomatosis cases have malignant B cells containing Epstein-Barr virus (EBV) RNA. The biology of EBV infection involves binding to the complement receptor CD21 on B cells, resulting in the continuous growth or immortalization of infected B cells in vitro. In vivo, polyclonal, B-cell proliferation occurs, but it usually is controlled by immune regulation involving cytotoxic T cells. In immunodeficient states, the host’s defenses may be unable to curb EBV-induced B-cell proliferation. In this regard, lymphomatoid granulomatosis is similar to EBV-associated post-transplant lymphoma.

**Perform analysis for cell phenotype,** clonality, and EBV infection. Despite the predominance of T cells, the malignant cells appear to be B cells, and the T-cell infiltrate is polyclonal. In general, the B-cell population is clonally expanded; however, oligoclonal populations have been identified in rare cases. A similar finding is described in post-transplant lymphoma and probably reflects an EBV-related phenomenon.

**Peripheral nerve involvement**: The infiltrate surrounds the nerve and causes spotty demyelination.

**Treatment:** Not well defined. Has ranged from observation to treatment with prednisone or chemotherapy. Spontaneous remission has been reported.

In view of the association of lymphomatoid granulomatosis with EBV and the similarity to post-transplant lymphoma, the use of antiviral drugs with minimal immunosuppressive therapy is advocated. More than 50% of patients with lymphomatoid granulomatosis respond to treatment.

**Prognosis:** Recurrence is usual and may include refractory disease or progression to high-grade lymphoma (13-47%). When lymphomatoid granulomatosis progresses to high-grade lymphoma, combination antilymphoma regimens are used, but response rates are poor at this stage - usually is progressive and fatal. 90% fatality rates at 5 years. The cause of death is usually extensive destruction of the pulmonary parenchyma, resulting in respiratory failure, sepsis, and, occasionally, massive haemoptysis. Poor prognostic indicators include an age younger than 30 years, neurological or hepatic involvement, leukopenia or pancytopenia, and anergy.

- Localized disease may respond to radiotherapy.
- Surgical resection of isolated pulmonary masses followed by chemotherapy has been associated with disease-free survival for at least 2 years.
- Other treatment options include ganciclovir, interferon alfa-2, or, depending on histologic grade, combination chemotherapy.
Complications

Haemoptysis, occasionally massive, may complicate cavitation of the diseased pulmonary tissue. Pneumothorax may occur. Opportunistic infections may develop.

Seizures, mental status changes, mononeuropathy, or diabetes insipidus may complicate progressive neurological disease.

Summary:
The clinical diagnosis of LG is difficult when the lesion is confined to the brain. Although radiologic findings in LG of the brain are quite variable, the presence of multiple punctate or linear enhancements that reside along the perivascular space on MR imaging suggests LG or other diseases affecting the vascular wall or perivascular space, such as sarcoidosis, primary angiitis of the central nervous system, and other granulomatous angiitis. Although less specific for LG, when ringlike enhancement or meningeal thickening and enhancement are observed on MR images, the possibility of LG should be considered in an appropriate clinical setting.

LOW GRADE B-CELL LYMPHOMAS OF THE CNS

Definition: CNS involvement is a rare and unexpected complication of indolent NHL – 3% of low-grade lymphomas, mainly after transformation to high-grade lymphoma-, which should be considered in the differential diagnosis of patients presenting with new neurological signs. This condition is treatable and some patients have a long clinical course.

Age: median age 59 years.

Clinical: a median Karnofsky performance status (ability to cope with everyday living tasks) of 70% is frequent. Can present with memory and visual disturbance. The clinical course may be variable and frequently more indolent than in classical PCNSL.

Imaging: Low-grade PCNSL may differ from classical high-grade PCNSL in its clinical features and radiological morphology.

MRI demonstrates a high intensity lesion on T2 weighted images with irregular enhancement by gadolinium.

Microscopic: may have B-cell or T-cell lymphoma. Evidence of active systemic indolent lymphoma is found in all patients. There is a diffuse perivascular infiltration of small atypical lymphocytes.

Immunohistochemistry: positive for CD20 and CD79a and positive for immunoglobulin heavy chain (IgH) rearrangement.

Treatment: may have complete tumour resection plus chemotherapy with methotrexate therapy. Some have whole-brain irradiation and can achieve complete remissions.

Prognosis: Although low-grade primary central nervous system lymphoma is considered relatively indolent, the literature suggests that intraparenchymal, low-grade primary central nervous system lymphomas are mostly progressive, and early treatment including irradiation may be a choice. Reports of an overall survival of up to 60 months.
MALT LYMPHOMA (mucosa-associated lymphoid tissue lymphoma) of the DURA – 9699/3

**Definition:** a subset of primary leptomeningeal lymphoma

**Sites:** typically located in the cranial vault. The anatomic location of dura mater involvement is variable, more frequent in hemispheric convexities, temporal-parietal and parietal-occipital dural surfaces, interhemispheric falx, tentorium, cavernous sinus and the cerebellopontine angle region. The second most frequent site of MALT lymphoma involvement intracranially is the glomus of the choroid plexus in the lateral ventricles, an ectodermal origin structure devoid of a blood brain barrier. Involvement by CT usually shows hyperdense asymmetrically bulky choroid plexus.

**Incidence:** very rare - account for < 1% of all CNS lymphoma

**Age:** most often found in middle aged individuals.

**Gender:** F : M = 5 : 1

**Clinical presentation:** Presentation is usually indolent with symptoms related to mass effect. Include dizziness, fainting spells, nausea, vomiting, memory impairment and blurred vision.

**Macroscopic:**
Unlike other PCNSL lymphomas which are usually of non-Hodgkin B-cell lineage, primary dural lymphomas tend to arise from mucosa-associated lymphoid tissue (MALT).

**Types:** plaque-like thickening of the dura which may trap and compromise cranial nerve function or a more nodular mass mistaken for a meningioma – see below..

**Imaging:** These tumours present as extra-axial lobulated/nodular masses, that may be either solitary or multiple.

**CT** - Due to high cellularity, these tumours are typically hyperdense and generally enhance vividly.

**MRI - T1:** isodense to grey matter

- **T1 C+** - vivid enhancement (usually homogeneous) and the brain tumour interface may be indistinct
- **T2** - iso to hypodense to grey matter and oedema common in the adjacent brain.
A,B  CT pre and post contrast show a hyperdense extra-axial lesion within the interhemispheric fissure with associated bilateral frontal subcortical vasogenic oedema and intense homogeneous enhancement after contrast.

C, D  MRI evaluation shows a T1 and FLAIR isointense lesion to grey matter with T2 hypointense behaviour and F. perilesional oedema.

G  the Gd-enhanced axial T1 image shows homogeneously intense enhancement.

H. The diffusion-weighted image shows lesion isointensity, while the apparent diffusion coefficient map shows moderate diffusion restriction (ROI 1) compared to normal grey matter (ROI 2).

I) Proton MR Spectroscopy shows a significant elevation of the choline peak with a choline / creatine ratio larger than 1, a mild decrease in N-acetyl-aspartate (NAA), and no lipid or lactate abnormalities.

**Microscopy of a local patient:** small round cell tumours
**Immunohistochemistry:** demonstrates the presence of CD20 +, CD79a +, Bcl-2 +, IgD, CD 3, CD43, K y λ, Ki 67:15%. Molecular analysis positive for monoclonality.

**Treatment and prognosis**

Primary dural lymphomas are non-aggressive and patients have excellent outcomes regardless of treatment. Anti-convulsant drugs and cortico-steroids may control a lesion but surgical resection can be curative.

**Differential diagnosis** is essentially that of other dural masses, including:

- meningioma
- dural metastases
- Erdheim-Chester disease
- Rosai-Dorfman disease

**T-CELL LYMPHOMAS**

**Definition:** There are many different forms of T-cell lymphomas, some of which are extremely rare. T-cell lymphomas can be aggressive (fast-growing) or indolent (slow-growing).

**Incidence:** less than 5% of primary CNS lesions.

**Sites:** most commonly in brain parenchyma; involvement of deep brain structures (basal ganglia, corpus callosum, brainstem, and/or cerebellum-36%). 30% have multiple lesions at diagnosis. Less common is leptomeningeal or spinal cord presentations. Isolated dural based lesions are also reported. May be supra – or infra-tentorial and single or multiple.

**Gender:** greater male preponderance.

**Racial:** more common in Asian countries.
**Microscopic:** most commonly large cell type and medium sized cell type, as well as a mixture of both of these types. May have a polymorphous background of small lymphocytes, eosinophils, plasma cells and epithelioid histiocytes.


**Immunohistochemistry:** tumour cells typically express T cell antigen CD4, but have an abnormal loss of other antigens such as CD7 and/or CD5.

Image below - staining with the T cell marker CD3 extensive involvement.

Staining of the brain biopsy with the B-cell marker CD20 shows it is absent.
**Subtypes:** cytotoxic/suppressor T cell lymphoma and anaplastic large cell lymphoma.

Immuohistochemistry of cytotoxic/suppressor T cell lymphoma – CD8 immunoreactivity, cytoplasmic granule proteins e.g. granzyme B, perforin and TIA and TCR beta gene rearrangement. This type is also known as T cell large granular cell and is more commonly associated with leukaemia.

**PRIMARY ANAPLASTIC LARGE CELL LYMPHOMA (ALCL)** – also called Ki-1 lymphoma - is characterized by large cells with abundant cytoplasm and pleomorphic nuclei which often show horseshoe shapes.

**Immunohistochemistry:** positive for CD30 (Ki-1) antigen typically along the cell membrane and in the Golgi region, as well as EMA and are negative for EBV.

**Molecular/genetic:** The majority show a characteristic translocation – t (2:5)(p23;35) that results in fusion of the anaplastic lymphoma kinase (ALK) gene (chromosome 2) with the nucleophosmin gene (chromosome 5). Other translocations may also be present. These result in overproduction of the ALK protein and its cellular distribution will vary according to the translocation.

In the most common - t(2:5) - ALK can be demonstrated in the cytoplasm, nuclei and nucleoli of tumour cells. ALK expression correlates with epithelial membrane antigen positivity, young patient age and favourable prognosis in systemic and CNS tumours.

Multiple reports have occurred of primary CNS anaplastic large cell lymphomas in both immunocompetent as well as immunocompromised patients.

**Clinical:** comparable to those of PCNSL in general. May present with seizures depending on location.

**Prognosis:** The median progression-free survival (PFS) is 22 months. The 2- and 5-year PFS are 45% and 22%, respectively.
In summary, TPCNSL is a rare disorder with characteristics at presentation and outcomes similar to that of PCNSL in general. Receipt of methotrexate (MTX) is an important factor that appears to influence survival.

**NK/T-cell lymphomas of the CNS**

**Definition:** Extranodal natural killer (NK)-/T-cell lymphoma (nasal type) is an aggressive lymphoma marked by extensive necrosis and angioinvasion, most often presenting in extranodal sites, in particular the nasal or paranasal sinus region. Other extranodal sites include the palate, trachea, skin, and gastrointestinal tract. Hemophagocytic syndrome may occur; historically, these tumours were considered part of lethal midline granuloma. In most cases, Epstein-Barr virus (EBV) genomes are detectable in the tumour cells and immunophenotyping shows CD56 positivity. Cases with blood and marrow involvement are considered NK-cell leukemia.

**Racial:** predilection for Asian and South American populations.

**Imaging:** This type of NHL is PET avid

**Microscopic:** Cytologically, neoplastic cells are small to medium-sized lymphoid cells possessing pale cytoplasm with azurophilic granules. Histopathologically, lymphoma cells may be admixed with a polymorphic population of small lymphocytes, plasma cells, eosinophils, and histiocytes, hence the old terminology “polymorphic reticulosis.” Lymphomatous infiltrate may show angiocentricity and angiodestruction, leading to coagulative necrosis. Marrow hemophagocytosis may occur. In aggressive NK-cell leukemia, circulating neoplastic cells can vary from large granular lymphocytes to frank blasts.

**Immunohistochemistry:** Neoplastic cells are surface CD3−, cytoplasmic CD3ε+, CD56+, cytotoxic-molecule positive, Epstein-Barr virus (EBV) positive, with germline T-cell receptor gene.

Lymphoma cells are typically CD2+, cytoplasmic CD3ε+, CD56+, and express perforin, granzyme B, and TIA-1. Neoplastic cells are invariably infected by Epstein-Barr virus (EBV) in a clonal episomal form, which is detected most reliably by in situ hybridization (ISH) for EBV-encoded RNA (EBER), constituting a diagnostic requisite. However, rare cases might be CD2+, CD3ε+, cytotoxic-molecule positive, EBV positive, but CD56−, and exceptional ones might show TCR gene rearrangement. These cases are rare, being included as the “T-cell” part of the WHO nomenclature of NK/T-cell lymphoma.

Quantification of circulating EBV DNA is an accurate biomarker of tumour load.

**Molecular pathogenesis**

Early studies showed specific karyotypic and genomic aberrations. Based on the observations that 6q21 is frequently deleted, genes residing in this region, including FOXO3, PRDM1, and HACE1, have been shown to be putative tumour-suppressor genes. The gene PRDM1 (alias BLIMP1) regulates the maturation, homeostasis, and proliferation of NK cells. Gene expression profiling has shown patterns different from normal NK cells and other T-cell lymphomas. Several oncogenic pathways are activated, including Notch-1, Wnt, JAK/STAT, AKT, and nuclear factor κB. In addition to gene expression profiling, microRNA expression profiling has also identified a distinct microRNA signature, leading to dysregulation of p53, cell-cycle, and MAPK signaling pathways. Recently, whole-exome sequencing has identified somatic-activating mutations of the JAK3 gene in 35% of NK/T-cell lymphomas, resulting in cytokine-independent constitutive JAK/STAT activation. These findings are important to clinicians as they may provide therapeutic opportunities targeting overexpressed
proteins including survivin and aurora kinase A or activated signaling pathways such as Notch-1 and JAK/STAT

Treatment: Traditional treatments for other aggressive types of lymphoma have shown unsatisfactory results in NK/T-cell lymphoma and the overall survival has historically been significantly worse than similarly staged aggressive lymphomas. CHOP which is the mainstay treatment for aggressive lymphomas produces inferior results in NK/T-cell lymphoma.

Recent advances and newer chemotherapy combinations have shown significant improvements. The use of chemotherapy which contains L-asparaginase in particular has had significantly better results. Similarly treatment with IMEP plus L-asparaginase achieves superior outcomes to treatment with IMEP alone.

In addition it has been shown that for higher risk patients, using radiation therapy before chemotherapy achieves superior results to giving radiation after chemotherapy.

Concomitant/sequential chemotherapy and radiotherapy is standard treatment. Radiotherapy alone is inadequate because of high systemic failure rate. For stage III/IV nasal, nonnasal, and disseminated lymphomas, systemic chemotherapy is indicated. Regimens containing L-asparaginase and drugs unaffected by P-glycoprotein are most effective. Hematopoietic stem cell transplantation (HSCT) is not indicated for early-stage nasal lymphomas. HSCT for lymphomas not in remission has poor results. In advanced-stage nasal, nonnasal, disseminated, or relapsed lymphomas, HSCT may be considered when remission is achieved. Prognostic modeling and EBV DNA monitoring may be useful in risk stratification for HSCT.

Prognosis: Serial plasma EBV DNA quantification is therefore important in the follow-up of NK/T-cell lymphoma patients in remission. It should be performed on a long-term basis, as the lymphoma is known to relapse after even decades of remission. Early stage disease has an excellent prognosis for overall survival. For late stage disease overall survival remains poor.

HISTIOCYTIC TUMOURS

Background: Two major classes of cells evolve in parallel from what is thought to be a common CD34-positive stem cell in the bone marrow: specialized antigen processing and scavenging cells – macrophages and specialized antigen presenting cells – dendritic cells. Langerhans cells represent an immature population of myeloid dendritic cells.

LANGERHANS CELL HISTIOCYTOSIS – 9751/3

Preferred term for a cluster of conditions :- histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schuller-Christian syndrome, Hashimoto-Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans cell granulomatosis, Langerhans cell (eosinophilic) granulomatosis, type II histiocytosis and nonlipid reticuloendotheliosis.

Langerhans cells are 10-15 µm in diameter, with grooved, folded, lobulated or indented nuclei and inconspicuous nucleoli. Birbeck granules – 200-400 nm are tennis-racket shaped and defining in these cells and shown with electron microscopy. A C-type lectin, langerin (CD207) is required for the formation of the granules. Langerin may be useful as a diagnostic marker of Langerhans cell histiocytosis. Also CD1a and S-100 protein.
Sites: 30% have bone disease and lung involvement is the next commonest site. Muco-cutaneous involvement is seen in 25% and CNS involvement in less than 15%. The most common parenchymal site in the CNS is involvement of the hypothalamic-pituitary region.

Incidence: Incidence is estimated at ~5 per million children, and 1-2 cases per million adults.

Age: primarily affects children with a median age of 5 years but a range of 15 days to 18 years. Adults up to 83 years have been reported.

Gender: There is a male predilection (M:F = 1.5:1)

Clinical: CNS - triad of exophthalmos, diabetes insipidus and lesions of membraneous bones. Also present with epilepsy and cerebellar dysfunction.

Macroscopic: infundibular thickening in 50%, hypothalamic mass lesions (10%) or infundibular atrophy (30%). Bone lesions in the craniofacial or skull bones are found in over 50%, dural-based masses in 30% and choroid plexus involvement occasionally. The pineal gland is cystic in 30% and pineal gland size over 10 mm is seen in 15%. The Virchow-Robin spaces are observed in 75%. Degeneration of the cerebellar dentate nucleus in 40% and in basal ganglia in 25%. Overall, the sites of involvement seem to correlate with those in which the blood-brain barrier is not complete. Viz: 3 types of lesions; circumscribed granulomas in the meninges and choroid plexus, granulomas involving the brain parenchyma, usually as an extension from the meninges or Virchow-Robin spaces and neurodegenerative lesions without granuloma, mainly affecting the cerebellum and the brainstem.

The granuloma in the choroid plexus and meninges are sharply demarcated from surrounding brain tissue and may be single or multifocal. Involvement of the meninges can cause diagnostic cells to be found in the CSF.

Imaging: infundibular lesions are typical but patients may present with lesions in cerebellar or cerebral hemispheres, pons and basal ganglia even in the absence of infundibular abnormalities.

A, Thickened, enhancing pituitary stalk in a 2-year-old girl with a 1-year history of LCH and new-onset diabetes insipidus

B, Coronal contrast-enhanced T1WI in a 6-year-old girl obtained 2 years after the onset of diabetes insipidus. Image shows a thickened pituitary stalk at the cranial portion, in the region of the median eminence

**Microscopic:** lesions show a polymorphic infiltrate with the general organization of a granuloma, consisting of CD1a+ Langerhans cells, foamy macrophages, multinucleated giant cells, lymphocytes, plasma cells and a large number of eosinophils. It is thought the Langerhans cells are clonal and the other cells are reactive. Young lesions have typical CD1a+ Langerhans cells and older lesions have predominantly foamy macrophages.

With granulomatous parenchymal involvement there is tissue destruction and the granulomas are surrounded by a much wider inflammatory zone in which mainly CD8+ T cells are present. A profound activation of microglia is noted in this wider zone, with loss of neurons and oligodendrocytes and striking astrogliosis. It can affect the entire brain and so can multiple sclerosis-like demyelination.

The neurodegenerative changes are thought responsible for many of the neuropsychiatric disturbances in the late stages of the disease.

**Image has CD1a cells.**

**Immunohistochemistry:** staining for S100 protein.

Treatment: drugs that cross the blood-brain barrier, such as cladribine, or other nucleoside analogs, such as cytarabine, are used for active CNS LCH lesions.

- Treatment of mass lesions with cladribine has been effective. Mass lesions included enlargement of the hypothalamic-pituitary axis, parenchymal mass lesions, and leptomeningeal involvement.
- Patients with LCH and mass lesions in the hypothalamic-pituitary region, the choroid plexus, the grey matter, or the white matter, may also respond to standard LCH chemotherapy. Treatment with vinblastine with or without corticosteroids for patients with CNS mass lesions; mainly pituitary demonstrated an objective response.

CNS neurodegenerative syndrome

Drugs used in active LCH, such as dexamethasone and cladribine, along with other agents, such as retinoic acid, intravenous immunoglobulin (IVIg), infliximab, and cytarabine with or without vincristine have been used in small numbers of patients with mixed results. Many of these agents may result in the complete or partial resolution of radiographic findings, but definitive clinical response rates have not been rigorously defined.

Perhaps the most important aspect of therapy for neurodegenerative disease is the early recognition of clinical neurodegeneration and institution of therapy. Studies combining MRI findings together with cerebrospinal fluid markers of demyelination, to identify patients who require therapy, even before onset of clinical symptoms, are currently underway in several countries.
Treatment Options for Childhood LCH that are No Longer Considered Effective

Treatments that have been used in the past but are no longer recommended for pediatric patients with LCH in any location include cyclosporine and interferon-alpha. Extensive surgery is also not indicated. Curettage of a circumscribed skull lesion may be sufficient if the lesion is not in the temporal, mastoid, or orbital areas. Patients with disease in these particular sites are recommended to receive 6 months of systemic therapy with vinblastine and prednisone. For lesions of the mandible, extensive surgery may destroy any possibility of secondary tooth development. Surgical resection of groin or genital lesions is contraindicated as these lesions can be healed by chemotherapy.

Radiation therapy use in LCH has been significantly reduced in pediatric patients, and even low-dose radiation therapy should be limited to single-bone vertebral body lesions or other single-bone lesions compressing the spinal cord or optic nerve that do not respond to chemotherapy.

**ROSAI-DORFMAN DISEASE**

Also known as Sinus histiocytosis with massive lymphadenopathy (SHML), is a rare benign histiocytic proliferative disorder which usually presents with bilateral painless cervical lymphadenopathy. CNS involvement is uncommon, and usually presents clinically and radiologically as a "meningioma"-like mass. Parenchymal examples are also described.

Rosai-Dorfman disease is due to over-production of a type of white blood cell called non-Langerhans sinus histiocyte. These cells then accumulate, most often in the lymph nodes, but may occur in other areas of the body and can lead to organ damage. The reason that these cells over-produce is not known, although many possibilities have been considered, including viral, bacterial, infection, environmental, and genetic causes.

**Definition:** occurs both as isolated, primary extranodal disease, as well as a manifestation of a more disseminated multiple disorder.

**Sites:** only 33% present solely with CNS involvement. Found in brain, spinal cord, sella turcica, dura, epidural space, orbit, globe and soft tissue and bony structures around the nervous system.

**Age:** from 5 years to adults in the 7th decade.

**Gender:** no difference between sexes

**Clinical:** Fever, leucocytosis with neutrophilia and polyclonal gammaglobulinaemia. A vast majority of patients (~80%) present with painless massive cervical lymphadenopathy. Headaches and seizures have been described when there is intracranial involvement.

**Imaging:** mimic meningioma. Are homogeneously or inhomogeneously enhancing and circumscribed, with variable oedema in the underlying brain. Rarely invasion of the dural venous sinuses occurs. The dural-based lesions are not only in the cranium but can also be extra- or intradural spinal cord locations presenting with cord compression or the cauda equina syndrome.

Primary parenchymal CNSA is more unusual than dura-based but presents as a circumscribed, enhancing mass. This group have solitary lesions.
CT central nervous system

- hyperattenuating meningeal-based mass showing contrast enhancement
- parenchymal oedema surrounding the lesion may be present

MRI CNS: meningeal based mass
- T1: isointense to grey matter
- T2: hyperintense to grey matter
- T1 C+ (Gd): homogenous enhancement

Images, T1W plus contrast, courtesy of Dr Basem Ikram Ibrahim, Radiopaedia.org, rID: 26346

Macroscopic: very firm consistency so can be hard to biopsy with a thin needle.

Microscopic: Histiocytes - abundant. Singular large round nuclei twice the size of resting lymphocytes. Prominent nucleolus. Abundant cytoplasm. Histiocytes may contain other whole cells: neutrophils, lymphocytes, plasma cells.

- The "eaten" cell is within a vacuole; thus, it should have a clear halo around it.
- Thought to be related to peripolesis; the attachment of a cell to another.
Immunohistochemistry: stains with S-100 and CD68. CD1a negative. Histological and immunohistochemical confirmation is essential for diagnosis. The histiocytes have bland nuclei, abundant cytoplasm and indistinct cell borders. Emperipolesis, usually of lymphocytes, is characteristic. The cells are S-100 protein and CD68 positive, and CD-1a negative. SHML may also exhibit atypical histologic features.

CNS Rosai Dorfman may be misdiagnosed as a nonspecific inflammatory process because CNS disease, as with other extra-nodal locations, may demonstrate atypical histologic features, e.g. the histiocytic component and emperipolesis may be obscured by other inflammatory cells.

Treatment: may require treatment with surgery, steroids, and/or chemotherapy. Rarely radiation therapy may be used. Chemotherapy may include vinblastine, 6-MP, methotrexate, thalidomide, or Gleevec. The ultimate goal of an overall treatment plan is to use as little treatment as possible to keep the disease under control and preserve quality of life.

Prognosis: Rosai-Dorfman does not usually threaten life or organ function. It is believed that 5% to 10% of patients have progressive disease that may damage tissue. However, for most patients, the disease is self-limited, and the outcome is good.

ERDHEIM-CHESTER DISEASE - 9750/1

Definition: is a rare systemic histiocytic disease of unknown aetiology, characterised by xanthogranulomatous infiltrates, and radiologically by symmetrical osteosclerosis of long bones. It represents a rare form of non-Langerhans cell histiocytosis. The diagnosis relies on the association of specific radiologic and histologic findings. Intracranial involvement is rare. The most frequent CNS manifestations are diabetes insipidus, cerebellar syndromes, orbital lesions, and extra-axial masses involving the dura.

Sites: This disease mostly affects long bones, but it can occur in the tissues behind the globe of the eye, kidney, skin, brain, lung, heart, pituitary gland, and a part of the retroperitoneum.
Age: Erdheim-Chester is a disease that most often becomes apparent in middle age, with an average age at onset of 53 years.

Gender: It can affect men and women with a slight male preponderance.

Clinical: The symptoms and course of the disease depend on the location and extent of the involvement of the internal organs. The most common presenting symptom is bone pain.

Pathology: Erdheim-Chester disease is a systemic lipogranulomatous disorder with infiltration by lipid-laden histiocytes (foamy macrophages), Touton giant cells and a variable amount of background fibrosis. S-100 nor CD1 are not detected, but CD68 is positive.

Both Erdheim-Chester disease and Langerhan cell histiocytosis may co-exist.

Imaging: Intracranial involvement of the dura, brain and pituitary are rare.

- meninges
  - dural accumulations, may mimic meningiomas, with enhancing soft tissue masses
  - T2 signal characteristics are somewhat different, as the accumulations in ECD are hypointense

Image – MRI T1W plus contrast, courtesy of Assoc. Professor Frank Gaillard, Radiopaedia.org, rID 2591 shows involvement of the meninges in the posterior fossa – arrows.

- brain: usually the hypothalamus; intraparenchymal masses in Erdheim-Chester disease appear nonspecific
- pituitary infundibulum: presenting with diabetes insipidus
**Diagnosis:** Erdheim-Chester is sometimes mistaken for Langerhans cell histiocytosis (LCH), as it may share the same clinical (exophthalmos, diabetes insipidus) or radiologic (osteolytic lesions) findings. However, a biopsy of the affected tissue differs in a number of ways from LCH and can establish a definite diagnosis. The histiocytic infiltrate lacks the features of LCH (is S-100 protein and CD1a negative, no Birbeck granules)

**Microscopic:** diffuse infiltration with large foamy histiocytes, lymphoid aggregates, fibrosis, rare Touton-like giant cells. Touton giant cells have a central ring of nuclei while the peripheral cytoplasm is clear due to accumulated lipid. These cells are formed by fusion of lipid containing macrophages.

**Immunohistochemistry:** The cells in ECD stain for the same proteins as juvenile xanthogranuloma but the clinical presentation and age is different. CD68 and Factor XIIa is positive. S100 is weak or negative and CD1a is negative.

Electron microscopy: lipid droplets are seen in the cytoplasm but no Birbeck granules.

**Treatments** have been used with limited success. These include steroids, immunotherapy, chemotherapy to control the over-production of cells, the use of radiation therapy, and/or surgery. While these treatments may control the symptoms and growth of the disease, there is no known “cure.” Surgical or percutaneous intervention for hydronephrosis, orbital or meningeal involvement is useful for symptomatic local disease.

**Prognosis:** Erdheim-Chester disease can be life-threatening with complications such as heart failure, severe damage to the lungs, and kidney failure. However, with treatment, there are patients who are able to live a near-normal life but some patients relentlessly progress. Pulmonary fibrosis and cardiac failure are the most common causes of death. Mortality rates are sketchy, but may be as high as 60%. Three year survival is about 65%

**HISTIOCYTIC SARCOMA – 9755/3 (previously Malignant histiocytosis)**

Rare and aggressive.

**Age:** found in childhood and adults. Mean age = 44 years.

**Clinical:** patients have systemic symptoms (fever, fatigue, loss of weight), skin infiltrates, and lymphadenopathy


Brain (A, B) and spinal (C, D) magnetic resonance imaging (MRI) of the patient.

(A) Brain FLAIR MRI showing high signal intensity in the left periventricular and deep white matter of the left parietal lobe.

(B) T1-weighted axial enhancement of the brain, showing subtle enhancement of the lesion.

(C) Sagittal T2-weighted spinal MRI, showing diffusely increased signal intensity lesion with mild cord enlargement in the lower level of C3 through the upper level of T5.

D) Sagittal T1-weighted MRI, showing patchy enhancement of the spinal cord.
**Micro:** can be monomorphic or polymorphic with neoplastic cells usually round to oval in shape with abundant eosinophilic cytoplasm. Cells large with many mitotic figures. Haemophagocytosis can be seen. Nuclei are large, round to oval and multinucleation may occur. Variable degrees of atypia may also be present, with nuclear irregularities. A background of reactive cells occurs and may be sometimes so dense as to mask the true identity of the tumour.
Cytologic and histologic features of the first cerebrospinal fluid (CSF) aspiration and biopsy of left parieto-occipital lesion.
(A) Central nervous system smear, showing a few large cells with abundant cytoplasm and large nuclei.
(B) The large cells in the solid sheet from the biopsy were similar to the cells in the CSF smear. Vessels are cuffed by mature lymphocytes.
C) A few bizarre cells, larger than the adjacent cells, were observed.
(D) The cells, including the bizarre cells, were positive for CD68, consistent with histiocytes.

**Immunohistochemistry:** makes the diagnosis. All the histiocytic sarcomas are positive for macrophage-related antigens and negative for antigens on B cells, T cells, myeloid cells, epithelial cells, and melanocytes. Tumours display one or more histiocytic markers, including CD 68 (KP1 or PG-M1), lysozyme, CD11c and CD14. Also CD163, the haemoglobin scavenger receptor has been used as a specific marker. T-cell receptor and immunoglobulin genes may be present in a germline configuration. Are positive for lysozyme and/or CD68, followed in frequency by CD11c, CD4, CD11b, CDw32, peanut agglutinin receptor, and CD13. Show expression of oncoprotein p53.

Recognition of these tumours is important clinically and requires assessment of clinical, morphologic, and immunophenotypic features, supplemented by analysis of T-cell receptor and immunoglobulin genes.

**Prognosis:** usually no survivals over one year.
**JUVENILE XANTHOGANULOMA (JXG)**

**Definition:** Juvenile xanthogranuloma, is a rare, non-Langerhans cell histiocytosis that is usually benign and self-limiting. Classified as a dendritic cell-related disorder.

**Sites:** It occurs most often in the skin of the head, neck, and trunk but can also occur in the arms, legs, feet, and buttocks. JXG can affect the eye, most commonly in young children with multiple skin lesions. Less commonly JXG may involve locations such as the lung, liver, adrenal gland, appendix, bones, bone marrow, pituitary gland, central nervous system, kidney, heart, small and large intestines, and spleen.

**Incidence:** The total number of patients with JXG is not known, but it may be higher than reported since this disease is sometimes misdiagnosed or may spontaneously improve in children.

**Pathology:** JXG involves the over-production of a kind of histiocyte called a dendritic cell (not a macrophage). These cells then accumulate and lead to various symptoms, depending on location. The cause of this disease is not known.

**Age:** JXG mainly affects infants and small children with an average age of 2 years, although it can also occur in adults of all ages.

Most of the time, it presents as a single skin lesion which varies in size, but children less than 6 months of age are more likely to have multiple lesions. **It occurs at birth in about 10% of patients**

**Gender:** more males are affected than females.

**Clinical:** When JXG occurs in adults, it tends to be more complicated and is not known to spontaneously improve. Skin lesions are self-limited and rarely require treatment in most patients. Those with large abdominal masses, liver, bone marrow, or central nervous system involvement may do well with treatment such as chemotherapy similar to that used for Langerhans cell histiocytosis.

Patient may be asymptomatic or present with seizures, ataxia, weakness.

**Microscopic:** Typical morphological presentation includes diffuse infiltration of the skin by histiocytes, multinucleated giant cells, with Touton cells, and foam cells admixed with lymphocytes and granulocytes, notably eosinophils. Foam cells can be distinguished by vacuolated cytoplasm and small round centrally located nucleus.

**Immunohistochemistry:** Immunohistochemical staining plays a key role in diagnosis of atypical cases of JXG. Macrophage markers, especially CD68, factor XIIIa and vimentin are positive. In some cases, an expression of protein S100 can be found, whereas CD1a is usually negative.

**Treatment:** The lesions grow slowly. Multisystem disease requires Langerhans cell histiocytosis-type chemotherapy. Surgical excision may occur for single lesions.

**Prognosis:** Can be fatal if massive hepatic or CNS involvement

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**CNS GERM CELL TUMOURS**

Includes germinoma, teratoma, yolk sac tumour, embryonal carcinoma, choriocarcinoma and mixed germ cell tumours.

**Background:** Account for 2% of all primary intracranial neoplasms. Most prevalent among Far-East Asians. Cohorts at greatest risk are children and adolescents. 90% are in patients under 20 years. Peak age 10–12 year olds. Congenital cases occur and these are usually teratomas or rarely mixed germ cell tumours of partially teratomatous composition. Teratomas account for more than 50% of foetal brain tumours. More frequent in males – 2.5 : 1, especially in pineal teratomas.

**Genetics:** Duplication of the short arm of chromosome 12 (i12p) is the most common anomaly described in adult-onset extragonadal germinomas. CNS teratomas have shown a high frequency of sex chromosome abnormalities, most commonly increased copies of the X chromosome. Recurring cytogenetic abnormalities commonly seen involve loss of 1p and 6q, alterations in the sex chromosomes, and rarely, abnormalities of 12p.
Deletion of 1p36 in 80%–100% of infantile malignant GCTs arising from testicular and extragonadal sites has been reported. A minority of tumours also show evidence for C-myc or N-myc amplification.

**Associated conditions:** Klinefelter syndrome — characterized by a 47 XXY genotype and physical anomalies such as underdeveloped testes and gynaecomastia. There is chronic elevation of serum gonadotrophins associated with the Klinefelter complex. Trisomy 21 "Down syndrome" has an increased risk of intracranial germ cell tumours. These are usually germinomas but a congenital teratoma of the pineal and an immature teratoma have been reported in this group.

**Sites:** 80% of CNS germ cell tumours arise in the suprasellar compartment (30%) or pineal region (50%). The tumours lie along a mid-line intracranial axis that traverses the 3<sup>rd</sup> ventricle. Other sites are the basal ganglia, cerebellopontine angle, lateral ventricles, cerebellum and corpus callosum. Germinomas are the most common type in the suprasellar region.

Congenital germ cell tumours can be massive causing skull rupture at delivery. The tumour can extend into the orbit and extracranial soft tissues — usually teratomas.

CNS germ cell neoplasia can be multifocal.

**Clinical:** symptoms vary depending upon the site of the tumour.

*Pineal region* tumours which cause obstructive hydrocephalus by compressing the aqueduct of Sylvius, will have symptoms of raised intracranial pressure such as headache, nausea, vomiting and blurred vision. Ocular movement disorders owing to pressure on the tectal plate especially palsy of upwards gaze and convergence (Parinaud syndrome). Infiltration of the periaqueductal gray matter may result in paresis of downwards gaze and ptosis. Can cause ataxia due to involvement of the superior cerebellar peduncles.

*Suprasellar compartment tumours* — often involve the infundibulum extending to the hypothalamic region and distorting the optic chiasm. Neurologic defects include visual disturbances (decreased visual acuity and narrowing of the visual field), diabetesinsipidus and pituitary failure (primary or secondary amenorrhoea and growth retardation) due to disruption of the hypothalamohypophyseal axis. Pituitary deficiencies can be also caused by tumour extension into the sella turcica destroying the gland. Precocious puberty may occur in boys, occasionally in girls.

**Pre-operative evaluation:** assessment of serum and CSF for α- fetoprotein and β- HCG. The pattern of marker elevation correlates with histologic subtype and immunohistochemistry. Increase in α fetoprotein levels are predictive of predominant yolk sac components and less frequently of immature teratomas. High β- HCG levels point to choriocarcinoma elements.

**Imaging:** is of limited value to predict the histologic composition of CNS germ cell tumours. CT: One exception is the case of a germ cell tumour displacing or engulfing an otherwise intact pineal gland. One may see a nodular cluster of punctate calcium deposits representing the native pineal. If the tumour has arisen from the pineal gland itself, the calcifications are displaced in a circular fashion around the pineal tumour. The non-teratomas are solid and contrast-enhancing on both CT and MRI. Thalamostriate germinomas are more prone to cystic change and intra-tumoral calcification, than pineal and suprasellar germinomas.
Germinomas are more likely to homogeneously enhance and present as diffuse periventricular growths in the absence of a pineal or suprasellar primary. MRI of a solid germ cell tumour are hypo to iso-intense on T1-weighted and iso- to hyperintense on T2W sequences. Choriocarcinomas may have haemorrhage. The imaging studies will confirm hydrocephalus and invasion of structures plus linear or nodular foci of contrast enhancement along ventricular surfaces or in the CSF space that represent CSF-borne metastases. 

Pre-natal ultrasound: may detect congenital brain tumours, many being germ cell tumours of the teratoma group.

Macroscopic: germinomas are usually soft or friable gray to tan-white and most are solid. Cyst formation and calcification are more common in thalamostriatial cases. Necrosis and haemorrhage suggest embryonal carcinoma and choriocarcinoma. Elements of yolk sac tumour may have gelatinous or myxoid change. If adipose tissue, bony spicules, chondroid nodules or cysts filled with mucus or greasy debris are found this favours teratomas. May even contain hair and teeth. Mature teratomas tend to be well circumscribed with non-infiltrative margins that enable complete surgical excision.

**GERMINOMAS**

**Age:** peak incidence 10 – 12 years of age.

**Incidence:** 3 – 5% of paediatric intracranial tumours but 0.4 – 1.0% in adults.

**Site:** most common tumour of the pineal region and account for 85% of intracranial germ cell tumours. Some cases have germinomas in the pineal and suprasellar region.

**Gender:** Pineal region: M : F = 22 : 1. Suprasellar region M : F = 1 : 1.3

**Imaging:** Germinomas are soft tissue density, enhancing masses. When present in the pineal region they appear to "engulf" the normal pineal tissue and can have associated central calcification, in contrast to pineocytomas, and pineoblastomas which are described as "exploding" the foci of calcification. Cystic components are commonly found in up to 45% of cases.

CT - the high cellularity results in a degree of hyperdensity compared to adjacent brain. Usually, the mass enhances brightly.

When in the floor of the third ventricle it is typically seen filling and expanding the infundibular recess and supraoptic recess. Imaging may, however, be normal initially and if the diagnosis is suspected clinically (e.g. idiopathic hypothalamic diabetes insipidus) then a close follow-up is required to identify potentially a very subtle abnormal pituitary stalk enhancement and thickening.

**FLAG:** In the paediatric population presence of calcification in the pineal region is a useful marker of an underlying tumour, as no calcification of the pineal is seen in children below the age of 6.5 and only 10% of children between 11 and 14 years of age.
MRI: demonstrates a soft tissue mass, typically ovoid or lobulated in contour, engulfing the calcified pineal gland with the following signal characteristics

- **T1**: isointense or slightly hyperintense to adjacent brain
- **T2**
  - isointense or slightly hyperintense to adjacent brain
  - may have areas of cyst formation
  - may have areas of haemorrhage (low signal)
  - have a predilection for invading adjacent brain (oedema)
  - central calcification appears low signal (engulfed pineal gland)
- **T1 C+ (Gd)**: vivid and homogeneous

MRI T1W with contrast – sagittal – courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID 6511 displays a vividly enhancing tumour in the pineal region which has obstructed the aqueduct causing hydrocephalus.

Another case of a pineal region germinoma with cystic change – MRI T1W with contrast, coronal view, courtesy of Ahmed Abd Rabou, Radiopaedia.org, rID 24296.
MRI T1W with contrast Image of suprasellar tumour with involvement of the pituitary stalk – courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID 17966. The supra-optic recess is obliterated - arrow.

Some cases may have a germinoma in the pineal region and also in the suprasellar region. In the MRI T1W sagittal view with contrast, courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, RId 2614 – Note the presence of two tumours - arrows.

**Microscopy:** the example demonstrates the classic microscopic appearances of germinoma. The large primitive neoplastic cells are mitotically active and arranged in lobules. There is an
accompanying chronic inflammatory cell infiltrate, which when pronounced, may potentially obscure the nature of the neoplasm. The accompanying infiltrate may have a granulomatous character, and if the neoplastic cells are obscured or not appreciated, granulomatous CNS conditions may be inappropriately considered.

**Immunohistochemistry:** placental alkaline phosphatase, c-Kit, and OCT4 are highly expressed in germinomas. Variation in expression is likely to be predictive of a five-year progression-free survival rate. In addition to being a diagnostic marker, OCT4 may also probably be a prognostic marker for intracranial germinoma. In the example above, the stain would not be taken up by the inflammatory lymphocytes etc. OCT4 is an 18-kDa POU-domain transcription factor encoded by the POU5F1 gene. Also known as OCT3, OTF3, and POU5F1, OCT4 is involved in the initiation, maintenance, and differentiation of pluripotent and germline cells during normal development.

**Treatment:** The mainstay of treatment is with radiotherapy which offers 85% long-term cure rate. Leptomeningeal seeding or spillage during surgery are thought to be poor prognostic factors. Imaging of the entire neuroaxis is therefore recommended before irradiation.

**Prognosis** is good, with over 90% 5-year survival with chemotherapy and radiotherapy.

**TERATOMA of the CNS**

This includes the mature – 9080/0, the immature – 9080/3 and malignant transformation variant 9084/3.

Tumour has tissue components resembling normal derivatives of more than one germ layer.

Immunophenotyping is not useful as teratomas mimic their somatic counterparts in antigens. An antibody panel including sub-type restricted markers may expose elements of germinoma (CD117/PLAP/OCT4-reactive) or yolk sac tumour (α-fetoprotein reactive).
MATURE TERATOMA – 9080/0

Composed of elements that have an adult level of differentiation in a small number. Most contain immature components. Intraspinal teratomas are mature throughout. Other components of the teratoma may be keratinized cellular material, glioneuronal islands, villous formations like choroid plexus, nodules of hyaline cartilage, osseous trabeculae, adipose tissue and bundles of muscle. Enteric and respiratory tissue can be present. It is a midline mass containing calcification, soft tissue, cysts and fat.

**Imaging:** the example is a CT scan of a 36 year old male who presented with headaches. Calcification – image (a) – white arrow. Fat – image (c) – white arrow. Sausage-shaped mass is present on image (d) – arrow – which has obstructed the foramina of Monro with resultant ventricular obstruction and hydrocephalus.

Differential diagnosis: central neurocytoma and SEGA (subependymal giant cell astrocytoma).

IMMATURE TERATOMA – 9080/3

Indicators of lesion immaturity are hypercellular stromal constituents resembling uncommitted foetal mesenchyme, glandular structures formed by crowded columnar cells evidencing the subnuclear vacuolization typical of developing gastrointestinal and respiratory epithelium, clefts lined by melanotic neuroepithelium like retinal differentiation, and primitive neuroectodermal elements that can assume neuroblastoma or ganglioneuroblastoma-like appearances, fashion rosettes of ependymoblastic or neurosensory type, and align in canalicular arrays mimicking the embryonic neural tube. Often shows mitotic activity. Clinically have malignant potential.
The photomicrograph above includes a mixture of immature tissue type. Neuroepithelial structures and pigmented epithelium are present, and there is a small focus resembling germinoma toward the bottom of the image.

**TERATOMA with MALIGNANT TRANSFORMATION – 9084/3**

Have been described as teratomas with somatic-type malignancy – spawning sarcomas of undifferentiated or rhabdomyosarcomatous type, leiomyosarcoma, squamous carcinomas and adenocarcinomas.

**YOLK SAC TUMOUR**

**Incidence:** rare tumour

**Sites:** pineal or suprasellar but can be other sites and often a large tumour.

**Imaging:** Images courtesy of Al-Masri AA, KhasawnehNH, Aladily TN. Ann Saudi Med 2011; 31 (3) : 298-300.

CT Precontrast transaxial images of the brain demonstrate high-density intra-axial para-midline left temporoparietal mass (star) with two foci of calcifications (arrow); perilesional oedema is seen as hypodensity.

Axial (a), coronal (b) and sagittal postcontrast T1WI MRIs of the brain for the same patient demonstrate homogenous enhancement of the lesion with surrounding vasogenic edema. The lesion appears off-midline and deforming the trigone of the left lateral ventricle.
Microscopic: this example demonstrates a loose microcystic and reticular pattern of proliferation of delicate spindly cells, which focally surround a blood vessel, to form a characteristic Schiller-Duval body.
A further example – arrows indicate the Schiller-Duval bodies which look a little like glomeruli.

**Immunohistochemistry:** cytoplasmic labelling of epithelial constituents and hyaline globular bodies for α-fetoprotein. This is a **marker antigen** normally synthesized by the primitive yolk sac endoderm as well as foetal hepatocytes and intestinal epithelial cells and is found in 100% of cases.

This marker is also useful for the identification of minor yolk sac tumour elements within germinal neoplasms of mixed composition and in distinguishing solid variants from embryonal carcinomas and germinomas. However teratomas may have glands of enteric type that also label for this antigen.

Epithelial components of the yolk sac tumour may be reactive for PLAP but are diffusely cytokeratin positive. Also positive for vimentin but negative for glial fibrillary acid protein (GFAP).

Yolk sac tumours do not label for β-HCG or human placental lactogen which are markers of trophoblastic differentiation.

**Treatment:** chemotherapy and sometimes additional radiotherapy in cases proven by biopsy.

**Prognosis:** yolk sac tumours, have a poor prognosis – one year or less, with reported survival rates ranging between 40% and 70%.

**EMBRYONAL CARCINOMA of the CNS - 90703**

**Definition:** A non-seminomatous malignant germ cell tumor characterized by the presence of large germ cells with abundant cytoplasm resembling epithelial cells, geographic necrosis, high mitotic activity, and pseudoglandular and pseudopapillary structures formation.

**Incidence:**
It is a relatively rare neoplasm and accounts for only 10% of all intracranial germ cell tumours.
Age: peak age 20 – 30 years

Pathology: It is an aggressive tumour and has a propensity to metastasize systemically. A component of embryonal carcinoma is often found in mixed germ-cell tumours, in which case it is usually the most aggressive component, and dictates prognosis. CSF and plasma AFP and b-HCG may be elevated, but this is not specific to this tumour.

Microscopic: it is formed by a population of large mitotically active cells, arranged in solid and trabecular cohesive arrangements.

FLAG: A detailed account of Embryonal tumours of the CNS is provided in the learning module titled Brain Tumours V- Choroid plexus and Embryonal Tumours. Pineoblastoma is discussed in Brain Tumours VI – Pineal, Sellar region and Pituitary Tumours.

CHORIOCARCINOMA of the CNS – 9100/3

This is the rarest and most malignant of the CNS germ cell tumours. It is highly vascular.

Sites: Common location is the pineal and the suprasellar region. Less common includes lateral ventricle, pituitary fossa, basal ganglia and septum pellucidum.

Incidence: 2 – 3% of all primary intracranial germ cell tumours.

Age: range 3 - 22 years of age (mean age, 11.8 years)

Gender: the male-to-female ratio of 6:1.
Clinical: clinical presentations are nonspecific, depending on the location of the tumours. Precocious puberty, which results from the production of HCG, is the most common specific symptom of PICCC occurring in males, especially in patients younger than 12 years of age.

Diagnosis: Correct pretreatment diagnosis is important for determining a therapeutic plan. HCG/β-HCG is a useful biologic tumour marker characteristic of choriocarcinoma. Markedly elevated serum HCG/β-HCG levels are strongly suggestive of choriocarcinoma or mixed GCTs with choriocarcinoma elements. A patient with a markedly elevated serum β-HCG level of >5000 very likely has choriocarcinoma.

Pathology: intratumoral hemorrhage and extraneural/CSF metastasis are common manifestations of PICCC, which are responsible for its poor prognosis. A combination of surgery, chemotherapy, and radiation therapy has improved survival. When the tumour is small enough to allow complete resection, surgery should be considered as the first line of therapy.

Correct pretreatment diagnosis is important for determining a proper therapeutic plan because PICCCs appear to have a mixed response to treatment. Because patients with PICCC are at high risk for intratumoral hemorrhage and extraneural/CSF metastasis, biopsy for histologic diagnosis is not recommended. Markedly elevated HCG/β-HCG levels are strongly suggestive of choriocarcinomas, though HCG/β-HCG elevations can occur with other GCTs containing syncytiotrophoblastic giant cells.

Imaging: PICCC is frequently seen as a solitary mass with heterogeneously increased attenuation on noncontrast CT scans – see below. Image courtesy of Lv X-F, Quia Y-W, Zhang XL, Han J, Quia SJ et al. AJNR 2010, 31 : 1994-1998. Although the presence of calcification has been described in several cases, it is usually not a dominant feature of PICCC

MR imaging:
The tumour has been described as an ovoid or irregular mass with a large haemorrhagic component. The presence of haemorrhage is a characteristic feature of PICCC. After the administration of contrast, the tumours usually show markedly heterogeneous enhancement.
Axial T1-weighted image demonstrates an isointense mass with some hyperintense areas (arrow). B, Axial T2-weighted image shows the heterogeneity of the lesion with marked hypointense (longer arrow), isointense, and hyperintense (shorter arrow) areas.

On T2-weighted images all lesions display heterogeneous hypointensity and hyperintensity. Correlating the MR imaging appearance and the microscopic findings, the heterogeneous signal intensity seen on MR images reflects the various components contained within the lesion, such as intratumoral haemorrhage, fibrosis, cysts, necrosis, or vascular proliferation. Frequent haemorrhage is seen in PICCC due to the fragility of vessels perfusing these trophoblastic tumours and due to the innate capacity of trophoblastic cells to invade and erode vessel walls. Marked strip-like or patchy areas of hypointense signal intensity on T2-weighted images correspond histologically to intratumoral blood products such as hemosiderin and fibrosis. On T1-weighted images, these foci of high signal intensity are assumed to correlate with small foci of haemorrhage.

On gadolinium-enhanced T1-weighted images, the heterogeneous, ringlike, and intratumoral nodular enhancement is extra. Heterogeneous and intratumoral nodular enhancement is most likely due to the sheet- or cordlike arrangement of the trophoblastic cells, which undergo vascular proliferation. The ring-like enhancement may be attributed to plentiful blood vessels on the peripheral rim of the tumor. Consequently, cystic necrosis is more likely to occur in the central area of the tumour. In most of the tumours, enhancement on T1-weighted images is seen in the isointense or slightly hyperintense areas on T2-weighted images.

**Microscopic:** choriocarcinoma is formed by an admixture of syncytiotrophoblast and cytotrophoblast. The syncytiotrophoblast (centre) is multinucleate with pale vacuolated eosinophilic cytoplasm. The surrounding cytotrophoblast is formed by smaller basophilic cells with distinct borders. Often associated with areas of haemorrhage, necrosis, fibrosis, and neovascularization.
Treatment: remains controversial because the tumour is highly resistant to standard treatment. Reported cases of successfully treated PICCCs using a combination of surgery, chemotherapy, and radiation therapy have occurred but the disease is usually fatal and there is no established treatment. Some recommend surgery as the first-line therapy when the tumour is small enough to resect completely.

Prognosis: The clinical outcome in patients with PICCC is very poor, which is probably due to their high risk for fatal haemorrhage and their propensity for extraneural/CSF metastasis. Such extraneural metastases usually occur in the lung in one-third of patients. The median survival time is 22 months and the 1- and 2-year survival rates are 61.2% and 49.8%, respectively.

FLAG: serum HCG/β-HCG levels should be sought for diagnosis and biopsy of these highly vascular tumours avoided.

MIXED GERM CELL TUMOURS - 9085/3

The term is applied to germinal cell neoplasms exhibiting any combination of the histologic entities described in pure form above. Pathologists specify what components are in the mixed tumour as it can have a bearing on management and prognosis. An immunohistochemical panel must include antibodies to each of the possible components.

ACKNOWLEDGEMENTS:

Pathology images: those not individually acknowledged in the text have as their source PathWest Laboratory Medicine WA.

Radiology images: those not individually acknowledged in the text have as their source Sir Charles Gairdner Hospital, The Queen Elizabeth II Medical Centre.

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