Clinical Application of Pathology

BRAIN TUMOURS IX – Mesenchymal, non-meningothelial tumours

System: Nervous

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LIPOMA – 8850/0 – WHO grade I

Lipomas, angiolipoma, hibernoma and primary intracranial liposarcoma comprise the family of fatty lesions and tumours of the CNS.

**Definition**: congenital tumour. The mass is thought persistence and maldifferentiation of the meninx primitiva (subarachnoid space precursor).

**Sites**: 85% are found, along or near the midline. Lipomas have a predilection for occurring in the ventral brain stem, dorsomesencephalic cisterns and supratentorial cisterns i.e. the subarachnoid space and cisternal location.

The tumour is found in 50% in the pericallosal cistern, 20% in the ambient, quadrigeminal plate and chiasmatic cisterns, 12% in the cerebellopontine angle or internal auditory canal and 7% only along the convexities of the brain.

**Other sites**: rare intradural cervical lipomas that can extend into the posterior fossa and multiple intracranial lipomas.

Lipomas have also been reported in the choroid plexus, interpeduncular cistern, septum pellucidum, Sylvian fissure and pineal region. Those found in the interpeduncular/suprasellar region often contain bone – called osteolipomas.

**Incidence**: Found in 1:1700 individuals. 2.5% of all patients studied by CT scan. Found in 0.46% in all autopsies.

**Associated conditions**: include other parenchymal malformations in 55%. Also incorporation of intracranial vessels and nerves within the lipoma is found in 35%.

Associated with agenesis of the corpus callosum, frontal bone defects (frontonasal dysplasia), abnormal vasculature, aneurysms, cranial nerve duplication, hypertrophic nerve fibres. Lipoma can be associated with genetic syndromes.

**Age**: paediatric group range is 2 months to 13 years. Tend to present however in the 2nd or 3rd decade of life as the lipoma is slow growing.

**Gender**: equal in the sexes except for lipomas of the cerebellopontine angle which are twice as common in males as in females.

**Clinical**: varies depending upon associated conditions. Symptoms associated with corpus callosum lipomas were seizures, mental deficits, hemiparesis, diencephalic syndrome and hydrocephalus.

Sleep apnoea is reported with lipomas of the tectal plate, vertigo and tinnitus with lipoma of the cerebellopontine angle, endocrine disturbances or blurred vision and headaches with osteolipoma of the tuber cinereum and obstructive hydrocephalus with lipoma of the quadrigeminal plate.

**Macroscopic**: Pericallosal lipomas are of 2 types: tubulonodular and curvilinear.

The tubulonodular type is usually found anteriorly within the pericallosal cistern, form early in embryogenesis, are large, round or cylindrical and associated with more severe anomalies of the corpus callosum, frontal bones, and surrounding soft tissues and bone.
The curvilinear lipoma occurs more posteriorly, form later in embryogenesis, are usually smaller than the tubulonodular type and form thin, ‘ribbon-like’ structures. Often asymptomatic and not associated with severe anomalies.

**Imaging:** CT and with MRI – lipomas have a bright signal of fat. No contrast enhancement.

MRI – lipomas are hyperintense on T1W images and relatively hypointense on T2W.

Ultrasound can diagnose lipomas of the corpus callosum as early as 26 weeks gestation. Some are surrounded by curvilinear calcification or contain punctuate calcifications.

One must distinguish lipomas from lipomatous differentiation in other tumours such as cerebellar liponeurocytomas and primitive neuro-ectodermal tumours.

**MRI:** T1W sagittal – courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID 2655 and rID:4716s a lipoma in the quadrigeminal cistern – arrow on left and in the suprasellar area – arrow - right.

Lipomas in the pericallosal cistern: **curvilinear type - arrow** – courtesy of Assoc.Prof. Frank Gaillard, Radiopaedia.org, rID : 15969. Note the corpus callosum is present.
Lipoma of the pericallosal cistern – Tubulonodular type – MRI FLAIR coronal - left image and axial T2 right image – see arrows. Images courtesy of Paresh K Desai. Radiopaedia.org, rID: 6587.

Note this patient has agenesis of the corpus callosum and the lateral ventricles are splayed apart.

On CT scan, the lipoma is of very low attenuation, less than CSF. Image courtesy of Wael Namattalla. Radiopaedia.org, rID 7973 shows a lipoma of the tectal plate – see arrow.
Macroscopic image of a lipoma in the tuber cinereum on the left - arrow and microscopy of the lipoma on the right. The fat cells occupy the lower half of the image.


**Treatment:** intracranial lipomas are often chance findings and asymptomatic, and even when associated with symptomatic malformations (e.g. callosal dysgenesis) they usually require no treatment. Attempts at resection have had relatively high morbidity with little benefit. Treatment of seizures or hydrocephalus is necessary if these are present.

**SPINAL LIPOMAS**

Asymptomatic small collections of fat have been reported in the filum terminale in 6% autopsies.

Spinal cord lipomas – 1% of all intraspinal tumours.

**Gender:** equal in males and females.

**Age:** present in 2nd or 3rd decade although present at birth. Grow slowly.

**Types:** intradural/extramedullary lipomas of the spinal cord are uncommon – usually in cervical and upper thoracic spine.

Spinal cord intradural/intramedullary lipomas – rare – found in dorsal aspect of the thoracic spine and midline.

Holocord lipomas – when intramedullary spinal cord lipomas affect nearly all levels of the cord.

**Associated conditions:** spina bifida occulta.
Lipomyelomeningocele – when there is benign fat in conjunction with spinal dysraphism. Found associated with syringomyelia, tethered spinal cord, dermal sinus tract, dermoid tumour, diastematomyelia and neurenteric cyst.

**Gender:** Female : Male = 1.5 : 1

**Clinical:** if untreated at birth, symptoms develop such as motor weakness and sensory changes in the lower limbs, bladder incontinence and pain.

**Microscopic:** lipomatous portion is made up of mature adipocytes.

**Prognosis:** only 30% improve motor function after surgery and only 7% improve bladder function.

Comparison with intradural/intramedullary lipomas which have a better prognosis.

**Lipomas of the filum terminale without spinal dysraphism**

**Imaging:** 90% can be seen on CT and MRI T1W- arrow on the image below.

![Image of MRI T1W arrow](image)

**ANGIOLIPOMA -8861/0 – WHO grade I**

**Sites:** occur within the spinal canal where these are predominantly extradural and also intracranially.

**Types:** infiltrating and non-infiltrating.

**Age:** the spinal type is most frequent in the 40 – 50 year age group.

**Gender:** the spinal type is more common in women.
**Clinical:** may present acutely from vascular complications such as haemorrhage, thrombosis, vascular engorgement or vascular steal. Pregnancy can precipitate symptoms from spinal and intracranial angiolipomas.

**Pathology:** non-infiltrating spinal tumours are epidural and dorsal especially in the thoracic region. The infiltrating type are more common in the anterior epidural space and can infiltrate adjacent soft tissues and also vertebral bodies.

**Imaging:** MRI – have the presence of large hypointense foci on T1W images corresponding to the vascular component. Non-fatty elements enhance vividly. The MRI images are T1W post contrast and using fat saturation sequence from 2 patients, courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID : 28242 and rID : 33244.

**Microscopic:** composed of mature adipocytes and vascular structures.

**Treatment:** surgical removal. The infiltrating type can be difficult to remove.

**Prognosis:** good. Recurrence has not been reported and most patients have a near complete or complete recovery.

**PRIMARY CNS LIPOSARCOMA**

**Incidence:** extremely rare. Have to be distinguished from metastatic disease, as liposarcomas are the second most frequent to metastasize to brain. These metastases especially those to dura or cavernous sinus should be distinguished from chordomas with extensive vacuolization which are called chordomas with lipomatous changes.

**Sites:** reported in the cerebello-pontine angle.

**Types:** there are several microscopic subtypes of liposarcoma, all characterized by a proliferation of neoplastic mesenchymal cells, some having the morphological characteristics of “lipoblasts”.

**Age:** mean age 12 years but range 6 – 17 yrs.
Clinical: Duration of symptoms prior to diagnosis is short - range 3–7 days). 35% patients had an underlying diagnosis of neurofibromatosis Type 1 (NF1).

Pathology:: show a variable mitotic rate, haemorrhage and necrosis.

Genetic: myxoid and round cell liposarcomas share t(12;16)(q13;p11)

Lipoblasts are characterized by the presence of one or more well circumscribed and defined cytoplasmic lipid droplets – see arrow below - which typically deform or indent the cell nucleus.

Treatment: surgery to achieve either subtotal or total resection. Sometimes local recurrence is treated with radiotherapy – up to 60 Gy and concomitant etoposide may be administered. The etoposide is given prior to and after the radiotherapy.

Prognosis: following resection there can be rapid regrowth and patients often die within a year. Median time for survival is 5 years but there is a range of 2.0 - 18 years.

MIXED LIPOMA with other MESENCHYME elements.

e.g. liponeurocytoma – WHO grade I –II. First described in 1978.

Liponeurocytomas are rare and slow-growing tumours located predominantly in the cerebellum. Cerebellar liponeurocytoma are a distinct entity from medulloblastoma in terms of prognostic, epidemiological and clinical aspects. Indolent behaviour.

Micro: Characterized by many lipidized cells found in clusters or scattered between small neoplastic cells. See below.
Immunohistochemical staining has demonstrated that both neuronal and glial differentiation is present. Mitotic activity is generally low in these lesions.

**Treatment:** surgical resection.

**HIBERNOMA – 8880/0 – WHO grade I**

**Definition:** are rare tumours composed of brown adipose tissue

**Sites:** cases reported in a parasagittal location, in the intradural, extramedullary plane extending from L3 to L5. And also at C7

**Age:** usually occur between 20 and 40 years.

**Gender:** slightly more common in women.

**Types:** typical (most common), myxoid, lipoma-like and spindle cell variants.

**Macroscopic:** well encapsulated and slightly dark yellow to red-brown in colour and are extramedullary and intradural

**Imaging:** MRI -Although they present as brown fat, the imaging characteristics on T1- and T2-weighted images demonstrate high signal intensity but slightly less than that of the subcutaneous fat. On MR imaging, the flow voids of feeding vessels may be identified.

On fat suppression sequences, there may be incomplete fat suppression because of the heterogeneous content of the mass and relatively decreased amount of lipid compared with adipose tissue.

**PET scan:** FDG-PET: FDG avid, although practically this has not been shown to help differentiate from malignancy.

**Microscopic:** composed of brown adipose tissue, considered an immature form. Multivacuolar adipocytes and brown fat cells with granular eosinophilic cytoplasm are interspersed with univacuolar adipocytes. Hypervascularity combined with abundant mitochondria give hibernomas their colour.
Immunohistochemistry: positive for S-100 protein like normal fat cells.

Mixed hibernomas/lipomas are more common than pure hibernomas.

Molecular/genetic: If cytogenic analysis shows an 11q13 translocation, it helps with a diagnosis of hibernoma over liposarcoma.

Treatment: surgical resection – easily separated from the surrounding tissue.

Prognosis: recurrence is rare as these are benign tumours.

CHONDROMA – 9220/0 – WHO grade I

Definition: A benign well circumscribed neoplasm arising from the hyaline cartilage in soft tissue or bone. It is characterized by the presence of chondrocytes.

Sites: skull base, dura, brain parenchyma, within the ventricles.

Origin: those which are extradural are thought to arise from embryonic cartilage rests along the basilar cynchondroses. Those related to the dura are totally ensheathed by layers of dura or attached to the subdural surface of the dura or falx.

Age: peak in 3rd decade but range reported is 15 months – 60 years.

Gender: equal in both sexes

Clinical: varies depending upon location.

Associated conditions: Ollier’s disease which also has multiple chondromas extra-cranially.

Maffucci syndrome

Previous trauma to the skull.

Imaging: CT scan – are hyper or hypodense or mixed. Minimal contrast enhancement and this is only present in the substance of the tumour as a rule.

- Angiography: vascular mass displacing adjacent cortical vessels
• MRI and CT – images with legends courtesy of Brownlee RD, Sevick RJ, Rewcastle NB, Tranmer BI. AJNR 1997; V. 18.

A. Contrast enhanced coronal CT shows a left parasagittal extraaxial mass with a hyperdense periphery and relatively hypodense central core.

B. MRI T1W coronal shows the mass to be predominantly hypointense, greater in the central core. There is a small focus of signal hyperintensity laterally between the tumour and the brain – arrow.

C. MRI T1W coronal contrast enhanced – shows a rim of enhancement – arrowhead and minimal enhancement of the tumour itself – arrow.

D. MRI T2W axial – bottom row left image – shows hyperintense signal centrally – arrow with a hypointense periphery containing punctate foci of hyperintensity – arrowhead.

E. – bottom row right image- lateral view of a digital subtraction angiogram from a left common carotid artery injection. The lesion itself is avascular and displaces adjacent cortical vessels. There is some effacement of the superior sagittal sinus adjacent to the lesion – arrow.

Macroscopic appearance: see below image F – fresh specimen was firm with a granular irregular appearance. The surface adjacent to the brain is illustrated in an axial plane.

Image G – gross specimen cut in the coronal plane appears white with a thick, dense outer rim of mature hyaline cartilage – arrowhead and a delicate central core – arrow – of less dense extracellular material.

Microscopic appearance: Image H - shows mature hyaline cartilage with scattered lacunes containing single chondrocytes – arrowheads surrounding a core of less dense extracellular material – curved arrows. Several thin-walled vessels lined by endothelium – arrows – were present within the extracellular material in the core of the tumour.
I, Microscopic section shows the fibrous capsule (arrowheads) containing small vessels of different calibre and wall thickness (arrows) surrounding the tumour.

J, Microscopic section shows a small focus of adipose tissue (arrow) that was present on the surface of the tumour adjacent to the brain.

K, Anatomic drawing of the location and microscopic features of the intracranial chondroma. The tumour was located between the dura and the brain, adjacent to the falx cerebri (arrow). It minimally compressed the surface of the brain (not depicted) and was weakly adherent to the superior sagittal sinus (arrowheads).

A local patient with chondroma:

Microscopic appearance of a dural based chondroma. Bland, widely separated chondrocytes lie in an abundant hyaline basophilic extracellular matrix.
Treatment: surgical excision.

Prognosis: Intracranial chondromas are circumscribed masses of well-differentiated, cytologically benign hyaline cartilage. They tend not to invade or destroy the surrounding parenchyma and there is little tendency for sarcomatous change. Total excision is frequently possible and is curative, with no recurrence reported on long-term follow-up.

CHONDROSARCOMA – 9220/3 – WHO grade III

Definition: a rare malignant tumour of the skull base.

Incidence: comprise only 0.2% of all intracranial neoplasms.

Types: variants include the conventional, hyaline and myxoid, (which is the commonest), dedifferentiated, mesenchymal and clear cell types. All except the conventional type are extremely rare within the skull and will not have detail provided here.

Sites: most of the conventional type arise in the vicinity of the clivus with 66% centred in the petro-occipital junction, 28% in the spheno-occiput, 6% in the spheno-ethmoid complex.

Clinical: patients present due to mass effect on adjacent brain, brainstem, cranial nerves. Symptoms may be over a long period of time such as 5 years.

Age: mean is in the 4th decade but it can occur at any age from children to the elderly.

Gender: slight female preponderance F : M = 1.3 : 1

Pathology: arise only in bones that form from the process of enchondral ossification so in the cranium, all chondrosarcomas develop in the skull base. Is the second most frequent primary sarcoma of the skull base. Chordoma is the most frequent.

Associated conditions: only 2.5% have a pre-existing condition such as Ollier disease, Maffucci syndrome, or multiple hereditary exostoses which predisposes the patient to chondrosarcoma.

Macroscopic: unlike chordomas, the conventional chondrosarcoma may arise lateral to the midline.

The tumour is bulky, consisting of nodules of gray to tan-white tissue that ranges from firm and gritty to mucinous. They grow with an infiltrative pattern, replacing the normal marrow elements, surrounding pre-existing cancellous bone and permeating the vascular channels within the cortical bone. So they frequently transgress the cortex and form a well-delineated soft tissue mass.

Imaging: there is a destructive, intramedullary, radiolucent mass with scattered punctate densities on plain skull radiographs. There may be bone expansion, endosteal scalloping and thickening of the cortex. Aggressive neoplasms may have large radiolucent areas with ragged margins and cortical destruction with a large soft tissue mass.

MRI shows the cartilage dark on T1 and hyperdense on T2. The non-mineralized and mineralized components of the tumour are well seen on CT scans.

On technetium bone scans chondrosarcomas show avid uptake of the isotope.

CT scan – axial non-contrast, courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org; rID 41937 - shows a densely calcified mass adjacent to the right greater wing of sphenoid.
MRI

- **T1**: iso- to slightly hypointense for chondrosarcoma of the base of skull
- **T2**: very high intensity in nonmineralised/calcified portions
- **T1 C+ (Gd)**
  - most demonstrate heterogeneous moderate to intense contrast enhancement.
  - enhancement can be septal and peripheral rim-like corresponding to fibrovascular septation between lobules of hyaline cartilage.

MRI – **T1W plus contrast** – courtesy of Assoc.Prof Frank Gaillard, Radiopaedia.org; rID 5421, displays a mass with irregular internal contour adjacent to the sphenoid wing with marked contrast enhancement in the non-mineralised component of the tumour.

MRI – **T2 weighted** – a different patient – showing a very bulky tumour on the left side, related to the left sphenoid wing with a very high intensity in the non-mineralised component of the tumour.

Courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org; rID 6069
Microscopic: varying degrees of cytologic atypia, determined by an assessment of the nuclear characteristics of the tumour cells and the extent of multinucleation.

Chondrosarcomas demonstrate a permeative and infiltrative growth pattern. Here, entrapped and remodeling anatomical bone is surrounded on all sides by formations of a chondrosarcoma.

Higher power field to demonstrate the basophilic hyaline character of the matrix in this chondrosarcoma. The neoplastic chondrocytes lie in lacunar spaces. Entrapped and remodeling
anatomical bone is present at the top.

The neoplastic chondrocytes in **hyaline chondrosarcoma** reside within lacunar spaces and are surrounded by hyaline matrix. The cytoplasm may be clear or eosinophilic and is usually scant and retracted around the nucleus. The matrix frequently mineralizes which manifests as irregular purple granules and in some tumours, focal enchondral ossification may occur. Areas of necrosis may be present. In the example below, there is an invasive pattern of growth in bone is again illustrated. The cartilaginous nature of the tumour is appreciable, pleomorphic tumour cells lie in lacunar spaces amidst chondroid matrix. See image below.

![Image of hyaline chondrosarcoma](image)

Neoplastic cells that seem to float in a frothy mucinous matrix are characteristic of **myxoid chondrosarcoma**. The tumour cells are stellate with elongated cytoplasmic processes that closely approach or even contact the processes of nearby cells. This gives a honeycomb-like network of interconnecting strands and cords of cells. Matrix surrounds chondrocytes. See image below, courtesy of Russell and Rubinstein’s Pathology of Tumors of the Nervous System. The myxoid matrix occasionally mineralizes and there enchondral ossification is common.
Mixed hyaline and myxoid chondrosarcoma contains variable amounts of both matrices which may merge with or are sharply demarcated from one another.

**Immunohistochemistry:** Positive for S100 protein and vimentin but negative for keratin.

**Molecular biology:** t (9;22)(q22-31; q11-12): TEC/CHN and EWS genes.

**Treatment and Prognosis:** They are relatively slow growing but locally aggressive. Metastatic disease is uncommon. Local resection is often the treatment of choice. Radiotherapy may sometimes be employed although sensitivity is thought to be minimal.

**OSTEOCHONDROMA – 9210/0 – WHO grade I**

**Definition:** an extremely rare tumour which is an exophytic bony protrusion covered by a cartilaginous cap, with a predilection for the skull base (which has multiple synchondroses).

**Incidence:** 0.1 – 0.2% of intracranial tumours.

**Sites:** tumours on the convexity dura have also been described. Symptomatic tumours have been reported at the skull base, dural convexity, sella turcica, occipital condyle, clivus, and cerebellopontine angle. The tumour can also present as a craniofacial lesion.

**Clinical:** Osteochondroma might become symptomatic due to the mechanical irritation of cranial nerves, soft tissues, or vascular compression, injury, or fracture.

**Macroscopic:** Usually, skull osteochondromas are solitary; however, multiple skull exostoses have been described in Proteus syndrome. This syndrome presents with mental retardation, multiple central nervous system anomalies, hemimegalencephaly, macrodactyly, osteochondromas, and soft tissue tumours.

**Associated conditions:** multiple lesions might be seen in association with other mesenchymal tumours like Maffucci and Ollier syndromes.


(a) T1-weighted axial MRI of the craniocervical junction at the level of the foramen magnum shows considerable cord compression due to a lesion (arrow) on the right side of the occipital bone.

(b) 3D reconstructed CT scan at the same level confirms the bony nature of the lesion (arrow).
(c) The tumour contains both membranous and cortical bone.

**Macroscopic:** An osteochondroma typically is formed by a stalk of mature bone and marrow, with a covering cap of cartilage. The histology demonstrates the proliferating cap of cartilage of this exostosis overlying cancellous bone. The cartilage cap may be lined partly at its surface by a thin layer of fibrous tissue. Some crowding of chondrocytes within the cartilaginous matrix is evident and enchondral ossification is present at the interface of the cartilage and bone.

**Microscopic:** osteochondroma is typically formed by a stalk of mature bone and marrow, with a covering cap of cartilage. Enchondral ossification is present at the interface of the cartilage and bone. See below.
**Immunohistochemistry:** large deletion of 8q; and an additional small deletion of the other allele of 8q that contains the EXT1 gene. FISH analysis of the cartilage cap, perichondrium, and bony stalk shows that these homozygous EXT1 deletions are present only in the cartilage cap of osteochondroma.

**Treatment:** surgery is warranted because these lesions are resistant to chemoradiotherapy.

**Prognosis:** these tumours are pathologically benign and complete excision often results in long-term cure. However there is less than a 1% chance of malignant transformation to a chondrosarcoma, with solitary osteochondroma and 5-10% risk with multiple hereditary exostoses.

**OSTEOMA – 9180/0 – WHO grade I**

**Definition:** are benign mature bony growths, seen almost exclusively in bones preformed in membrane (e.g. the skull).

**Sites:** most common locations include: paranasal sinus osteoma, skull vault osteoma and mandibular osteoma.

**Age:** peak 30 – 50 yrs

**Gender:** M : F = 2 : 1

**Clinical:** usually asymptomatic. They may be incidentally identified as a mass in the skull or mandible, or as the underlying cause of sinusitis or mucocele formation within the paranasal sinuses. When they are multiple, Gardner syndrome should be considered.

**Pathology types:** composed of mature bone. Three histological patterns are recognised

1. **ivory osteoma**
   - also known as eburnated osteoma
   - dense bone lacking haversian system
2. **mature osteoma**
   - also known as osteoma spongiosum
   - resembles 'normal' bone, including trabecular bone often with marrow
3. **mixed osteoma**
   - mixture of ivory and mature histology

**Imaging:** ivory osteomas appear as very radiodense lesions, similar to normal cortex, whereas mature osteomas may demonstrate central marrow.

Image below left, is a CT scan photographed on bone windows, of an ivory osteoma arising from the right orbital roof. Courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID 4063. Image on the right is also a CT scan photographed on bone windows and shows a mature type of osteoma, arising from the left orbital roof. Courtesy of Ruslan Esedov, Radiopaedia.org, rID 10646.
Treatment and prognosis: Osteomas are benign and only require excision if they cause adjacent complications (e.g. mucocoele formation) or mass effect (functional or cosmetic impairment).

OSTEOSARCOMA – 9180/3 – WHO grade III

Definition: it is a primary mesenchymal malignancy of bone in which the neoplastic cells synthesize and secrete the organic components of bone matrix, which may or may not undergo mineralization.

Incidence: in the skull the tumour accounts for 1-2% of all osteosarcomas.

Types: 3 biological groups

(a) conventional high grade osteosarcoma and its histological subtypes – 80%

(b) intramedullary well-differentiated osteosarcoma – 1% – usual type in the skull

(c) surface osteosarcomas – juxtacortical- 10%

10% are secondary and arise in a diseased bone such as chronic osteomyelitis in the appendicular skeleton but in the skull secondary osteosarcomas account for 27-47% of this type of tumour.

FLAG: the current goal is to distinguish low grade or well-differentiated osteosarcomas from high grade tumours because the high grade require chemotherapy for adequate treatment.

Site: most develop in the cranial vault and osteosarcoma of the skull base is rare.

Age: 60% osteosarcomas develop in patients under 25 years and 40% develop in patients more than 40 years. However, in the skull, tends to occur in the 3rd or 4th decade of life.

Gender: in the skull - almost equal in the sexes with a slight female preponderance. In the extra-cranial locations there is a male preponderance (1.6:1)

Associated conditions: previous radiation, Paget disease, bone infarction, pre-existing benign tumours, chronic osteomyelitis, metallic implants.
Associated genetic syndromes:

- Rothmund-Thomson syndrome (mutation of chromosome 8q24.3, encoding a DNA helicase).
- Bloom syndrome (mutation of chromosome 15q26.1 encoding a DNA helicase)
- Werner syndrome (mutation of chromosome 8p11 encoding a DNA helicase)
- Li-Fraumeni syndrome (mutation of chromosome 17p13 encoding p53 (tumour suppressor gene) and retinoblastoma gene (mutation of chromosome 13q14 encoding a transcription regulator)

Conditions associated with the development of secondary osteosarcoma:

- Prior radiation for tumours such as retinoblastoma, rhabdomyosarcoma, medulloblastoma, astrocytoma, craniopharyngioma, meningioma, pituitary adenoma and Paget’s disease.
- Radiation induced osteosarcoma occurs an average of 15 years later.
- Osteosarcoma only occurs in 1% of Paget disease.

Clinical: symptoms are often of less than one year duration. Depending upon location, there may be symptoms and signs of raised intracranial pressure, headaches, cranial nerve deficits, vision disturbances and difficulties walking.

Macroscopic: appearance varies depending on the subtype. Tumours with abundant mineralized bone are tan-white, gritty and hard but non-mineralised cartilaginous components are glistening, gray and may be mucinous if the matrix is myxoid or rubbery if hyaline type. Fibroblastic variants are white and leathery.

Areas of haemorrhage and cystic change are common producing a spongy mass. Intramedullary involvement is gross, with destruction of the overlying cortex forming a soft tissue component which displaces the periosteum peripherally. Invasion of the underlying brain parenchyma is common.

Surface osteosarcomas are broad based and rigidly attached to the underlying cortex, well-demarcated from the soft tissues.

Juxtacortical tumours (parosteal osteosarcoma) is solid, tan-white, hard and gritty but may have a gray firm glistening hyaline cartilage cap or soft areas representing fibrosarcoma. High grade juxtacortical osteosarcomas periosteal and high grade surface type may be dominated by cartilaginous tissue or hard areas mixed with fleshy regions.

Imaging: the intramedullary high grade tumours are poorly defined, destructive, mixed lytic and blastic masses that extend into the adjacent tissue, compressing and invading adjacent neural tissue.

CT and MRI define the anatomic extent of the tumours.

Surface osteosarcomas have a broad base of attachment to the underlying cortex.

Parosteal tumours are usually mushroom-shaped and densely mineralized. Show radiolucent areas or a lobulated contour with little or no periosteal reaction.
Periosteal osteosarcomas are fusiform, mainly lucent, frequently associated with a periosteal reaction in the form of Codman’s triangle and perpendicular linear striae radiate from the underlying bone.

High grade surface osteoblastic osteosarcomas frequently have a fine cloud-like pattern of mineralization.


Axial CT scan (C and D) without contrast, showed irregular calcification and low attenuation areas (bone window setting).

MRI showed a large mass arising from the postero-temporal aspect of the skull on the left side. There was a calcified hemorrhagic part of the mass with marked vascularity of the tumour (E T1W, F (T1W plus contrast) and G (T2W).

Microscopic: most are high grade and grow with a permeative pattern replacing the marrow space, surrounding and eroding pre-existing bony trabeculae of the diploic space and filling and expanding haversian systems of the inner and outer tables.

In osteoblastic foci, the malignant cells have an osteoblastic phenotype and are large pleomorphic and polyhedral or spindle shaped. Nuclei are hyperchromatic, central or eccentric, and may contain prominent nucleoli. Cytoplasm is eosinophilic and variable in volume. The tumour cells are intimately related to the surface of the neoplastic bone.

The neoplastic bone is woven, varies in quantity and is deposited as primitive, disorganized trabeculae that produce a coarse lacelike pattern or broad large sheets created by coalescing trabeculae.
Neoplastic cartilage, if present, is usually hyaline. The malignant chondrocytes demonstrate severe cytologic atypia and are found in lacunar spaces in hyaline matrix or float singly or in cords in myxoid matrix.

Fibroblastic foci have malignant spindle cells arranged in a herringbone or storiform pattern. The degree of atypia is variable but is often severe. Mitoses are numerous and abnormal forms are common.

The telangiectatic variant has numerous cystic spaces filled with blood. The malignant cells and bone matrix are found in the cyst walls.

Surface and intramedullary well-differentiated osteosarcomas are composed of a mild to moderately cellular bland spindle cell component that is intimately associated with long trabeculae or round islands of woven bone that may look like Paget’s disease. The tumour grows with an infiltrative pattern, replacing the marrow space and surrounding pre-existing bony trabecular that serve as scaffolding for the deposition of tumour bone.

Periosteal and high grade surface osteosarcomas have the features of conventional chondroblastic and osteoblastic osteosarcomas respectively.

The diagnostic feature of osteogenic sarcoma is the presence of a sarcomatous stroma forming both osteoid and mineralised bone matrix. Sheets and aggregates of mitotically active and anaplastic mesenchymal cells are interrupted by osteoid and mineralised bone. The osteoid has an amorphous and deeply eosinophilic appearance and is rimmed by the tumour cells. The osteoid is randomly and haphazardly oriented, and the extent of its production may vary throughout the tumour.

High power examination shows the extent of variation in nuclear morphology and widespread mitotic activity in the tumour cell population.
Osteosarcoma may demonstrate a wide spectrum of appearances. Osteoblastic (by definition malignant cells form bone/osteoid) areas shown above may be accompanied by fibroblastic, chondroblastic, telangiectatic, or small cell patterns.

**Immunohistochemistry:** commonly expressed antigens – vimentin, osteocalcin, osteonectin, S-100 protein, actin, smooth muscle actin, neuron specific enolase and CD99. Some also stain with antibodies to keratin and epithelial membrane antigen J.

Osteosarcoma is usually negative for stain with antibodies to Factor VIII, CD31 and leucocyte common antigen.

**Molecular/genetic:** cytogenetic abnormalities are found in 70% of osteosarcomas but have not been useful predicting diagnosis or prognosis.

**Treatment:** high grade osteosarcoma is treated with surgical excision, chemotherapy and radiation.

Low grade tumours usually treated solely with surgical removal plus radiation.

**Prognosis:** 5 year survival for high grade osteosarcomas is 50%. Many die of the local effects of the disease. Development of metastases is uncommon.

**DESMOID-TYPE FIBROMATOSIS – 8821/1 – WHO grade I**

**Definition:** Desmoid-type fibromatoses (DTF) are defined by the World Health Organization as clonal fibroblastic proliferations that arise in the deep soft tissues and are characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize.
**Types:** Fibromatoses may be classified as superficial or deep type based on location. Although superficial and deep fibromatoses share similar histologic morphology of a fibroblastic proliferation, superficial-type fibromatoses occur at palmar, plantar, or penile locations as opposed to deep-seated, visceral and extra-abdominal axial locations (i.e. chest or abdominal wall) of the deep-type or desmoid-type. CNS cases have been intracranial and dural-based.

**Incidence:** 2 – 4 / million per year. Superficial-type fibromatoses are more frequent than desmoid-type.

**Gender:** abdominal types more frequent in women and others tend to occur more frequently in males.

**Age:** 15 – 60 years. Rare in the elderly and children.

**Sites:** DTF can be extra-abdominal, abdominal, and intra-abdominal fibromatoses. Extra-abdominal fibromatoses more commonly occur on the chest, shoulder, back, thigh and head and neck. Abdominal fibromatoses arise typically from the rectus or internal oblique muscles and fascia in young pregnant or parous women. Intra-abdominal fibromatoses involve the mesentery or pelvis, and may be sporadic or associated with Gardner syndrome.

**Genetic/associated conditions:** The majority of DTF arise sporadically but others may be associated with germline mutations acquired in an autosomal dominant manner, such as Familial Adenomatous Polyposis (FAP) syndrome. FAP, which is caused by mutations in the adenomatous polyposis coli (APC) gene on chromosome 5, predispose patients to development of colorectal polyps that often progress to carcinoma. A variant of FAP, called Gardner syndrome is associated with extraintestinal manifestations such as DTF, as well as osteomas and epidermal cysts. Approximately 10% of these patients are affected by DTF.

Gardner fibromas are benign soft tissue lesions that are histologically similar to DTF, and represent precursor lesions. They occur in infants and children, and 45% of patients with Gardner fibroma develop DTF. Other hereditary syndromes include the autosomal dominant inheritance of hereditary desmoid disease (HDD), also known as familial infiltrative fibromatosis, are related to APC gene mutations.

**Clinical:** presentation depends on the location of the tumour.

**Macroscopic:** firm and display a white, whorled cut surface which may be poorly circumscribed.

Infantile fibromatosis with intracranial manifestation in a 3-year-old boy.

A–D, Axial T2-weighted images and sagittal T1-weighted images with and without contrast enhancement depict a tumour in the infratemporal and pterygopalatine fossa extending through the oval foramen into the middle cranial fossa and the right pre-pontine cistern.

The signal intensity is more heterogenic as compared with CT scans. On the T2-weighted images (A, B) the signal intensity was intermediate between muscle and fat and the tumour was markedly hypointense relative to brain parenchyma.

On the unenhanced T1-weighted image (C) the tumour was iso- to slightly hyperintense relative to muscle but slightly hypointense relative to brain parenchyma and strongly enhanced with contrast (D). Contrast enhancement was particularly pronounced intracranially (arrow).

**Microscopic:** DTF are composed of spindle-shaped fibroblastic cells that express the intermediate filament vimentin but lack expression of epithelial markers. The location, cellular morphology, and immunoprofile of these tumours suggest that they derive from mesenchymal sources. However, the exact cell origin of DTF is unclear yet. Recent evidence demonstrates that DTF are derived at a cellular level from mesenchymal stem (progenitor) cells.

A proliferation of bland appearing spindle-shaped fibroblasts in a collagenous stroma with infiltrative borders. Mitoses are rare and no atypia is seen. Keloid-like collagen or extensive hyalinization may be present.
Fibromatoses form poorly circumscribed, infiltrative masses, comprising spindle fibroblastic cells amongst variable amounts of stromal collagen (which may be keloid-like). Some mitotic activity may be observed, but no overt cytologic anaplasia is evident.

**Immunohistochemistry:** expression of estrogen receptors ERβ, progesterone receptor (PR), and androgen receptor (AR) in DTF found that the majority express ERβ but not ERα. Androgen receptor (AR) expression was detected in DTF and testosterone was found to have the ability to regulate beta-catenin protein level and proliferation rate in DTF.

DTF stain positive for vimentin and variably positive for smooth muscle actin or other muscle-specific markers. Rare cells may also be positive for S100 protein. Nuclear staining for β-catenin by immunohistochemistry is positive in at least 80% of sporadic DTF, with some studies demonstrating 98% nuclear staining. β-catenin is extremely useful in distinguishing DTF from other spindle cell neoplasms.

**Molecular biology:** both types involve aberrances of the Wnt signaling pathway, but the superficial-type generally lacks the β-catenin and APC gene mutations associated with DTF.

85% of DTF result from sporadic point mutations in the CTNNB1 gene which encodes β-catenin. *Point mutations of CTNNB1 (such as T41A, S45F, S45P)* lead to mutated β-catenin that is resistant to degradation by a complex comprised of APC, axin, and glycogen synthase kinase-3β. As a result, β-
catenin accumulates in the cytoplasm, translocates to the nucleus, and aids in activation of Wnt signaling pathway target genes involved in tumorigenesis.

Germline mutations in the tumour suppressor gene APC have also been described in DTF.

APC forms part of a complex which targets β-catenin for degradation. When APC is mutated, this complex does not form properly leading to β-catenin accumulation and thus increased transcription of Wnt signaling pathway target genes. Germline mutations of APC are associated with FAP, an autosomal dominant condition characterized by thousands of colonic polyps which can progress to colon cancer. The occurrence of DTF in FAP patients is roughly 10%. These patients are at increased risk for DTF as one APC allele is already mutated and if a sporadic APC mutation occurs, they become susceptible to the development of DTF. APC mutations have frequently been found in sporadic cases as well, with more than 400 mutations identified, 95% of which result in a truncated APC protein. APC is a large protein, with most DTF-causing mutations occurring between codons 1445-1578 (of 2843 total codons). Reports of severe desmoid phenotypes such as those associated with Hereditary desmoid disease (HDD) result from APC truncation at the 3' end beyond codon 1578.

**Trisomy 8 and Trisomy 20, as well as loss of 5q** (location of the APC gene) has been associated with DTF.

**Treatment:** surgical excision if possible. If not radiotherapy and chemotherapy may be used.

**Prognosis:** DTF are locally invasive, but non-metastatic. Local DTF recurrence rates after initial management range from 20-40%. Current research is focused on identifying prognostic indicators with sporadic DTF- have identified age (< 37 years-old), large size of the tumour (> 7 cm), and extra-abdominal location as being associated with poor prognosis.

**FIBROSARCOMA – 8810/3 – WHO grade III**

**Incidence:** very rare. 1% of all intracranial neoplasms.

**Age:** 3 – 63 years.

**Clinical:** varies depending on location. May present with seizures.

**Imaging:** tumour is fairly circumscribed and enhances vividly with contrast. Images of CT courtesy of Chopra R, Bhardwaj M, Premsagai IC. Rare Tumours 2010 Mar 31; 2(1) : e3. CT scan on admission revealed a Duramater-based contrast enhancing space occupying lesion in the left frontal region.

**Microscopic:** have a fascicular herringbone architectural pattern but little or no collagen production. There is overall uniformity of the spindle cell population, prominent vimentin positivity, and the presence of pericellular reticulin fibre network.
**Immunohistochemistry:** exhibit immunoreactivity only for vimentin.

**Associated conditions:** simultaneous occurrence of fibrosarcoma and meningiomatosis is well known.

Fibrosarcomas can occur in the setting of a pre-existing glioma, particularly post radiotherapy.

**Treatment:** surgery and if necessary intracavitary radiotherapy.

**Prognosis:** recurrences are local and survival correlates with grade :- 5-year survival rate of 52%.

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**MALIGNANT FIBROUS HISTIOCYTOMA – 8830/3 WHO grade III**

*(Undifferentiated pleomorphic sarcoma)*

**Definition:** the term malignant fibrous histiocytoma (MFH) refers to a group of pleomorphic sarcomas which shows no line of differentiation. The term undifferentiated pleomorphic sarcoma (UPS) is the preferred terminology.

**Incidence:** Intracranial UPS/MFH is an extremely rare tumor. It can originate in the central nervous system or arise as a metastasis from a primary extracranial tumor.

**Microscopic:** this example demonstrates the heterogeneous microscopic appearances of malignant fibrous histiocytoma. There are intersecting fascicles of spindle cells, surrounded by fibrous stroma and arranged in a “cartwheel” or storiform arrangement. Markedly pleomorphic areas are evident, with numerous bizarre multinucleate giant cells interspersed throughout.
Immunohistochemistry: Generally only vimentin is always expressed in MFH/undifferentiated pleomorphic sarcoma. May be focally positive reactivity for CD68.

MFH has been associated with hematopoietic diseases such as non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and malignant histiocytosis.

Imaging: CT typically reveals a nonspecific, large, lobulated, soft-tissue mass of predominantly muscle density, with nodular and peripheral enhancement of solid portions. Central areas of low attenuation may be present, corresponding to myxoid regions, old haemorrhage, or necrosis. Fat attenuation is not observed in the tumours; this fact can be useful in distinguishing undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (MFH) from some well-differentiated liposarcomas.

**MRI** signal characteristics of pleomorphic sarcoma/MFH are not specific, and the true histologic nature of the tumour cannot be ascertained by imaging alone. However, MRI is useful for determining extent of the tumour. Image below, courtesy of Sarrami AH, Setareh M, Afshar-Moghaddam N, Izadinejad M, Saadatnia M. J Res Med Sci 2011 Jul; 16(7): 968-973. See small and oval shaped lesions in the anterior and peripheral aspects of the pons and left cerebellar hemisphere as hypersignal on T2W sequence.

A single intraparenchymal enhancing lesion with a central necrotic area and peripheral edema in the parenchyma may be another morphological type.

Clinical: will vary depending upon location.
Treatment and Prognosis:

Early and complete surgical removal using wide or radical resection is indicated because of the aggressive nature of the tumour.

Prognosis is very poor.

SOLITARY FIBROUS TUMOUR OF THE DURA/HAEMANGIOPERICYTOMA – 8815/0/1/3

WHO grade I, II and III

Background: Apart from meningioma, several benign or low grade mesenchymal tumours may be found in the dura or leptomeninges. Although rare tumours, the most common examples include chondroma, haemangioma, lipoma and solitary fibrous tumour, the last, SFT, being the most common. The 2016 WHO Classification has put solitary fibrous tumour of the dura and haemangiopericytoma in the same group, considering that the two entities represent extremes of a single tumour type. Haemangiopericytoma is the most malignant and would be WHO grade II or III.

SOLITARY FIBROUS TUMOUR of the DURA - WHO grade I

will be discussed first.

Age: Most cases occur in adults in the 5th decade but there are some reports in children.

Sites: There may be some increased predilection for spinal localization, including intramedullary cases. A dural tail sign is uncommon although there is often a broad based dural attachment. This confuses it with the diagnosis of meningioma.

Incidence: 1% of intracranial tumours.

Gender: males preponderance.

Clinical: depends upon the site.

Macroscopic: it is a dural based lesion in the cranium and spine (thoracic and lumbar).

A, Noncontrast CT shows a heterogenous hyperattenuated multilobulated tumour in the left middle cranial fossa.

B, Contrast-enhanced CT, intense but heterogeneous contrast enhancement is noted.

C, T1-weighted axial MR image, a large lobulated mass is seen in the left paraclinoid portion to the tentorium.

D, T2-weighted axial MR image reveals 2 different signal intensity portions of the mass, hyposignal intensity and hypersignal intensity to gray matter.

E and F, Gadolinium-enhanced T1-weighted axial and coronal MR images show marked and heterogenous enhancement. The tumour is partially implanted on the surface of the tentorium (arrows).

G, Selective injection of the left internal carotid artery (capillary phase); the tumour is supplied at its periphery by pial branches.

H, Selective injection of the left external carotid artery; there is tumour blushing with dysplastic dilation of the tumour vessels. There is no demonstrable significant arteriovenous shunt or early venous drainage.

**Microscopic:** non-encapsulated with well-defined ‘expansile’ interface with adjacent brain or spinal cord. Cellular monomorphic groups of undulating spindle-shaped cells are present – see below -, arranged in a patternless fashion in a fibrous stroma - (or in poorly formed fascicles which have abundant band-like deposition of hyaline collagen fibres and prominent vascularity).
The vessels are commonly branching. – Ectatic vessels with irregular outlines are a distinctive feature – see below.

The nuclei are oval to elongated with delicate chromatin, with inconspicuous nucleoli and lack pseudoinclusions.
**Immunohistochemistry:** diffusely strongly reactive for CD34, BCL-2, cd99 and STAT-6. Also scattered factor XIIIa positive cells. Negative for EMA.

**Treatment:** surgical removal

**HAEMANGIOPERICYTOMA – WHO grade II**

**Definition:** this is a highly cellular and vascularized mesenchymal tumour with a characteristic monotonous low power appearance and well developed, thick walled branching ‘staghorn’ vasculature. It is almost always attached to dura with a high tendency to recur and to metastasize.

**Incidence:** less than 1% of intracranial tumours.

**Gender:** M : F = 1.5 : 1

**Clinical:** depends upon the site. One cannot distinguish it from a meningioma on imaging.

**Macroscopic:** solid, well demarcated tumour with a tendency to bleed. Globoid, slightly lobulated and firm. The cut surface is fleshy, grey to red brown or haemorrhagic with many visible vascular spaces.

**Imaging:** there is often a well demarcated lytic lesion of adjacent bone and a sharply demarcated tumour with a narrow base of dural attachment. Hypervascularity on angiography. There is a smooth or a nodular margin and it enhances intensely with contrast. There may be oedema in the underlying brain. There is a lack of calcification.

**MRI** – isointense to gray matter, multiple flow voids and adjacent brain oedema.

Image courtesy of Assoc. Prof. Frank Gaillard. Radiopaedia.org, rID 4326.

**MRI T1W sagittal with contrast.** Shows a tumour in the supratentorial compartment with narrow base of dural attachment and vivid heterogeneous enhancement.

Another example, also courtesy of Assoc. Prof. Frank Gaillard, in the posterior fossa.
MRI – T2W axial. Arrow indicates a flow void created by a large vessel. Several smaller vessels seen end-on along the right side of the tumour. The tumour mass, mostly to the right of midline, is isointense to grey matter.

MR spectroscopy – there is a high level of myoinositol. Alanaine peak is absent, which would be present in a meningioma.

DWI – intermediate restricted diffusion (less than meningioma).

Minimum ADC -1100 ( +/- 130) x 10^6 mm^2/s.

Angiography: it is usual for the external carotid artery branches, internal carotid artery and vertebral arteries to supply the mass. It is highly vascular and the arteries have a corkscrew appearance. There is a fluffy tumour stain and a lack of early draining veins. This is used for pre-operative embolization and to assess involvement of the dural venous sinuses.

Microscopic: The tumour is highly cellular, mitotically active. The cellularity is uniform, unlike meningioma. Monomorphous composed of packed tumour cells with little intervening fibrosis. Cytoplasm is scant and the cell borders are indistinct. The nuclei are round to oval, with moderately dense chromatin and inconspicuous nucleoli, lacking pseudo-inclusions seen in meningioma. Nuclear atypia is present and mitotic activity is variable – see below.

Cellular Solitary Fibrous Tumour (“Haemangiopericytoma) – Hypercellular spindle cell neoplasm with mitotically active cells and variably prominent vasculature.
**Treatment:** Surgery and radiotherapy.

**ANAPLASTIC HAEMANGIOPERICYTOMA – WHO grade III**

This tumour shows a high degree of mitotic activity (at least 5 mitoses per 10 HPF and/or necrosis plus haemorrhage). There is moderate to high nuclear atypia in the cellularity.

There is a rich network of reticulin fibres, typically investing individual cells which is most characteristic. There are numerous slit-like vascular channels lined by flattened endothelial cells. There are thin-walled and branching vascular spaces called “staghorn sinusoids”. Necrosis is uncommon. Calcification and psammoma bodies are not seen. It may invade and destroy adjacent bone, without evidence of a hyperostotic reaction.

**Immunohistochemistry:** STAT 6 is the important new marker for SFT/HPC. 85% are positive for vimentin which shows the vascular network. Also positive in nearly 100% cases for CD 34. This accentuates vascular and cell elements. See below. Images courtesy of Bahoran Singh Rajput. Slide Share Jan 13th 2016.

Reticulin is present around each cell. – see below
Also positive for factor XIIIa (85-100%) in individual scattered cells. Leu 7 positive in 70%. There is focal immunoreactivity for EMA.

Histogenesis: fibroblastic in nature.

**Differential diagnosis:** from meningioma and solitary fibrous tumour (WHO grade I).

**Prognosis:** of WHO grade II and III. Local recurrences are inevitable. Metastases occur to bone, lungs, and liver.

HAEMANGIOBLASTOMA – 9161/1 – WHO grade I

**Definition:** a slowly growing, highly vascular tumour which can occur in sporadic form or in association with Von Hippel-Landau disease (VHL).

**Sites:** in adults occurring in cerebellum, brain stem or spinal cord. When in association with VHL the haemangioblastomas may be multiple and affect the brain stem, spinal cord, nerve roots as well as the cerebellum.

**Incidence:** accounts for 2% of all intracranial tumours and 25% are associated with VHL disease.

**Age:** 20 – 29 year age group in those with VHL disease but a peak in the 4th decade for sporadic.

**Gender:** more common in males.

**Clinical Presentation:** symptoms are caused by impeded CSF flow causing hydrocephalus and raised intracranial pressure. The tumour produces erythropoietin which causes secondary polycythaemia.

**Macrosopic:** well circumscribed, highly vascular red nodules, often seen in the wall of a large cyst. May appear yellow due to high lipid content.

**Imaging:** shows a contrast enhancing mass with an associated cyst in 75% of cases.

**CT** – image courtesy of Hani Al Salam. Radiopaedia.org, rID: 12925
**MRI** – courtesy of Subash Thapta. Radiopaedia.org, rID 40570 – T1W plus contrast illustrates the cystic component with a contrast enhancing nubbin attached to the lateral wall.

**Angiography:** the images below show the circumscribed extremely vascular tumour – see black arrow with a sustained tumour blush.
**Microscopic:** histologically comprised of stromal cells and vascular cells which are large and vacuolated. There are 2 types: cellular and reticular. Haemorrhage may be seen in the tumour. The adjacent tissue reacts especially in the cyst or syrinx walls. The tumour edge is well demarcated and infiltration rarely occurs. The stromal cells are the neoplastic component, with variable sized nuclei dispersed amongst a rich capillary vasculature. Most characteristic are numerous lipid-containing vacuoles resulting in clear cell morphology as illustrated here.

Another patient, courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 15136
**Immunohistochemistry:** the vascular element shows rather typical endothelial cell staining with positive reactions for CD31, *Ulex europeus* agglutinin 1 and factor VIII related antigen.

Stromal cells show a variety of antigenic reactivities but do not resolve the elusive histogenesis of this cell. Neuron-specific enolase is strongly and diffusely immunoreactive in the stromal cells. This antigen distinguishes haemangioblastoma from metastatic renal cell carcinoma which is NSE negative but usually positive for epithelial membrane antigen and cytokeratins. Stromal cells have been reported to be immunoreactive for several neuropeptides and CD56 while being positive for synaptophysin and negative for chromogranin and neurofilament proteins.

Strong GFAP immunoreactivity is typically observed in reactive astrocytes adjacent to and entrapped within haemangioblastomas and in the gliotic walls of cystic tumours. S-100 immunoreactivity also reported and vimentin is strongly expressed by stromal cells and by the endothelial elements.

Erythrocyte-type glucose transporter protein (GLUT) is strongly immunoreactive in the endothelial cells of haemangioblastomas but not in the vascular element of metastatic renal cell carcinomas. GLUT is negative in stromal cells of haemangioblastomas but intense tumour cell membrane reactivity is found in renal cell carcinoma. Also stromal cells of haemangioblastomas are strongly immunoreactive for inhibin A with moderate to weak reactivity.

Transthyretin and transferrin are positive in 50% of haemangioblastomas. Epidermal growth factor receptor (EGFR) shows a strong cell membrane pattern in most stromal cells, while the vascular element and adjacent cerebellum are negative. Ezrin is iso immunoreactive for stromal cells. Also CD44 positive in stromal cells.

VEGF is positive in scattered stromal cells but typically shows strong reactivity of endothelial cells comprising the vascular element. Immunohistochemical staining for Ki67 (MIBI) shows few labelled nuclei consistent with the low proliferation rate of this tumour.

**Molecular/genetic:** haemangioblastoma is the commonest cause of death in VHL, so early gene analysis in this group is recommended to identify patients at risk.

**Treatment:** asymptomatic, noncystic lesions may be followed conservatively but cystic lesions in any location have a high risk of becoming symptomatic due to progressive growth of the cyst.

**Prognosis:** known to recur repeatedly but even after incomplete removal there may be a long delay before recurrence such as 14 years from the first operation.

**HAEMANGIOMA – 9120/0 WHO grade I**

**Definition:** it is a benign intraosseous skull neoplasm with predominantly vascular and some avascular components.

**Sites:** 20% of intraosseous haemangiomas are found in the skull and 30% in the vertebrae. The commonest sites are frontal and temporal and less commonly occipital, parietal or sphenoid. Rare in the flat bones.

**Incidence:** rare. Only 0.2% of all osseous tumours.

**Age:** commonest in the 4th decade.
Gender: more common in males 2:1.

Types: As an intraosseous haemangioma, skull vault angiomas are classified as venous, cavernous, or capillary type, according to their predominant vascular network. Histologically, it demonstrates hamartomatous vascular tissue within endothelium, but may also contain fat, smooth muscle, fibrous tissue, and thrombus.

Clinical: are benign slow growing neoplasms which rarely require treatment except when located in the sella region (cavernous angioma) where hypopituitarism and visual field defects may be a sequela.

Macroscopic: 1–4 cm size. Usually solitary but may be multiple. Have well circumscribed margins.

Imaging: Plain radiographs – sharply marginated expansile lesion which may have a thin peripheral sclerotic rim. There may be a honeycomb or sunburst appearance pattern. Image courtesy of Roberto Schubert, Radiopaedia.org, rID 17314

CT – non contrast shows the sharply marginated expansile lesion with a thin sclerotic rim in one third of cases. The inner and outer table are intact. The tumour may deform the overlying soft tissues. The lesion may have a spoke-wheel appearance or soap bubble appearance. Image courtesy of Chris O’Donnell, Radiopaedia.org, rID : 26876.
**MRI** - T1W – often isointense to brain but small lesions may appear hyperintense due to any fatty tissue within it. Large lesions are hypointense secondary to the presence of thickened trabeculae. It can be haemorrhagic and the MR signal will depend on the stage of the haemoglobin.

T2W – mixed intensities. Often hyperintense due to the slow flow or pooling of blood.

T1W plus contrast shows marked enhancement – see below.

Image courtesy of Fakhry Mahmoud Ebouda, Radiopaedia.org, rID : 31623

**Angiography:** shows hypervascular, delayed persistent blush giving a ‘cluster of grapes” appearance. Superselective embolization may be used to devascularize the tumour to reduce intraoperative bleeding and procedural morbidity. The angiogram below is courtesy of Politi M, Romeike BFM, Papanagiotou P, Nabhan A, Struffert T, Feiden W, Reith W. AJNR 2005; 26 : 2049-2052. It shows in A (mid-arterial) and B (capillary phase), the rich vascularity of the tumour, which is fed by the right middle meningeal (black arrow) and by branches of the superficial temporal artery (white arrow).
**Microscopic:** Image courtesy of Kang DW, Choi CH. J Korean Neurosurg Soc 2009 Nov; 46 (5) : 484-487, shows a proliferation of slit-like blood vessels lined by endothelial cells and filled with red blood cells.

![Microscopic Image]

**Treatment:** surgical removal, radiotherapy or embolization pre-surgery

**Prognosis:** if complete resection can be achieved, taking a clear margin of uninvolved bone, recurrence is very uncommon.

**EPITHELIOID HAEMANGIOENDOTHELIOMA – 9133/3 – WHO grade III**

**Definition:** Epithelioid haemangioendothelioma (EHE) is an extremely rare vascular tumour. It occurs around medium to large venous structures.

**Age:** all ages

**Gender:** 66% are male.

**Imaging:** associated with peritumoral vasogenic oedema and homogenous contrast enhancement in uni-focal cases.


a) Brain computed tomography scan showed multiple small intra-axial nodules with slightly high density. (b) Magnetic resonance imaging demonstrated that the signal of the nodules was hypointense to isointense on the T1-weighted image. (c) The magnetic resonance T2-weighted image revealed significant oedema around multiple nodular lesions showing hypointensity. (d) The magnetic resonance susceptibility-weighted image showed numerous low-intensity spots, indicating old haemorrhages. (e) Magnetic resonance T1-weighted image with gadolinium enhancement demonstrated little enhancement in most lesions but a weak enhancement in some nodules (arrow).
**Microscopy:** several patterns but the commonest type in the CNS displays cells arrayed in cords or branching patterns and embedded in variable amounts of myxoid or fibrohyaline stroma. The stroma is a distinctive feature and seems to be present in the majority of intracranial cases. It consists of rounded or slightly spindle-shaped eosinophilic endothelial (epitheloid) cells with rounded nuclei and prominent cytoplasmic vacuolisation.

Image (A) shows diffuse cellular proliferation, fine vascular channels, haemorrhage and haemosiderosis. 
(B) cells with a round and slightly coarse nucleus and a large volume of clear cytoplasm including large and small balloon-like lesions and erythrocytes. 
(C) immunostaining for CD31 revealed significant staining of the cell membrane and cytoplasm. 
(D) MIB-1 labelling index < 3% in the tumour cells.

Markers: strong immunoreactivity for CD 31, CD34 and factor VIII-associated antigen.

Electron Microscopy: features include intracellular and intercellular lumens, basal lamina, well-developed junctional complexes, pinocytic vesicles, cytoplasmic intermediate filaments and Weibel-Palade bodies. The latter are the storage granules of endothelial cells and release two molecules, von Willebrand factor and P-selectin.

Molecular description: t(1;3)(p36.3;q25) in some cases (involves PAX7)

Treatment: surgical resection as often uni-focal.

Prognosis: Favorable prognosis with complete resection; may recur or seed neuraxis; deaths are rare.

ANGIOSARCOMA – 9120/3 – WHO grade III

Definition: are rare malignant neoplasms of vascular endothelial cell origin, etiology unknown.

Age: from 2 weeks to 72 years. Mean age is 38 years

Gender: male preponderance – 66%

Sites: cerebral hemispheres but may occur in the meninges.


Axial T2-weighted MR image demonstrating a mildly heterogeneously hyperintense mass extending from the left middle cranial fossa (white arrowhead) through the left greater sphenoid wing into the left orbit (outlined black arrowhead). The axial T1W with contrast-middle image - demonstrates identical findings (white arrow and outlined white arrowhead, respectively) and heterogeneous enhancement of the mass. The coronal T1W contrast image demonstrates the mass extending downward and medially into the pterygoid recess of the left sphenoid sinus (outlined black arrows).
**Microscopic:** is a malignant vasoformative neoplasm. The example demonstrates the infiltrative and destructive pattern formed by vessels which are lined by the malignant endothelial population.

There may be a well-differentiated pattern with irregular vascular channels and intraluminal papillae but poor differentiation in solid areas.

Another example, courtesy of Baldovini C, Martinoni M, Marucci G. Case Reports in Pathology 2013; 2013(article ID 603671)
(a) the tumour is composed of pleomorphic, epithelioid cells with prominent nucleoli and atypical mitotic figures.  
(b) shows necrotic areas  
(c) neoplastic cells are strongly positive for CD31  
(d) and cytokeratin.

**Immunohistochemistry:** also focally positive to factor VIII-related antigen and *Ulex europaeus* agglutinin I

**Treatment:** surgical resection followed by chemotherapy and radiotherapy.

**Prognosis:** is poor - 5-year survival is 12%. No correlation has been found between the histological features and the growth and biological behaviour of the tumour.

**KAPOSI’S SARCOMA – 9140/3 – WHO grade III**

**Definition:** is a vascular malignancy that occurs in elderly patients of Mediterranean, East European or Middle Eastern descent, in endemic forms in sub-Saharan Africa and in HIV-infected patients and in other immunosuppressed patients. Human herpesvirus-8 (HHV-8) is the initiating agent in all forms. The lesions on the skin and elsewhere metastasize to brain.  
**Incidence:** rare. Most cases of Kaposi sarcoma in Australia are found in people who are HIV positive.  
**Gender:** more common in men than women.

**Clinical: Epidemic (AIDS-related) Kaposi sarcoma (KS)**

The most common type of KS in the United States is *epidemic* or *AIDS-related KS*. This type of KS develops in people who are infected with HIV virus which causes AIDS.

A person infected with HIV i.e. HIV-positive does not necessarily have AIDS.

The virus can be present in the body for a long time, often many years, before causing major illness. The disease known as AIDS begins when the virus has seriously damaged the immune system, which results in certain types of infections or other medical complications, including KS. When HIV damages the immune system, people who also are infected with a certain virus (the *Kaposi sarcoma associated herpesvirus* or *KSHV*) are more likely to develop KS.

KS is considered an “AIDS defining” illness. This means that when KS occurs in someone infected with HIV, that person officially has AIDS (and is not just HIV-positive).

In the United States, treating HIV infection with highly active antiretroviral therapy (HAART) has resulted in fewer cases of epidemic KS. Still, some patients develop symptoms of KS in the first few months of HAART treatment.

For most patients with HIV, HAART can often keep advanced KS from developing. Still, KS can still occur in people whose HIV is well controlled with HAART. Once KS develops it is still important to continue HAART.

In areas of the world where HAART is not easy to obtain, KS in AIDS patients can advance quickly.
Classic (Mediterranean) Kaposi sarcoma

Classic KS occurs mainly in older people of Mediterranean, Eastern European, and Middle Eastern heritage. Classic KS is more common in men than in women.

Patients typically have one or more lesions on the legs, ankles, or the soles of the feet. Compared to other types of KS, the lesions in this type do not grow as quickly, and new lesions do not develop as often.

The immune system of people with classic KS is not as weak as it is in those who have epidemic KS, but it may be weaker than normal. Getting older can naturally weaken the immune system. When this occurs, people who already have a KSHV (Kaposi sarcoma associated herpesvirus) infection are more likely to develop KS.

Endemic (African) Kaposi sarcoma

Endemic KS occurs in people living in Equatorial Africa and is sometimes called African KS. KSHV (Kaposi sarcoma associated herpesvirus) infection is much more common in Africa than in other parts of the world, so the risk of KS is higher. Other factors in Africa that weaken the immune system (such as malaria, other chronic infections, and malnutrition) also probably contribute to the development of KS, since the disease affects a broader group of people that includes children and women.

Endemic KS tends to occur in younger people (usually under age 40). Rarely a more aggressive form of endemic KS is seen in children before puberty. This type usually affects the lymph nodes and other organs and can progress quickly.

Endemic KS used to be the most common type of KS in Africa. Then, as AIDS became more common in Africa, the epidemic type became more common.

Iatrogenic (transplant-related) Kaposi sarcoma

When KS develops in people whose immune systems have been suppressed after an organ transplant, it is transplant-related KS. Most transplant patients need to take drugs to keep their immune system from rejecting the new organ. But by weakening the body’s immune system, these drugs increase the chance that someone infected with KSHV (Kaposi sarcoma associated herpesvirus) will develop KS. Stopping the immune-suppressing drugs or lowering their dose often makes KS lesions go away or get smaller.

Macroscopic: primary lesion on the gum, photo courtesy of Mark MacGill, MNT 20th April 2016.

MRI of the brain at control after 26 days of anti-Toxoplasma treatment. A. On Axial FLAIR T2-weighted images the lesions are hyperintense, with hypointense halo and surrounding oedema. B. Diffusion-weighted imaging of the lesions showed restricted diffusion. C. On unenhanced Axial T1-weighted images the lesions signal is heterogeneous. D. On enhanced Axial T1-weighted images faint lesions enhancement are depicted.

Diagnosis: biopsy of a skin lesion.

Staging: The immune status is assessed using a blood test known as the CD4 count, which measures the number of white blood cells called helper T cells.

I0 (good risk): CD4 cell count is 150 or more cells per cubic mm (mm$^3$).

I1 (poor risk): CD4 cell count is lower than 150 cells per mm$^3$. 

**Histological findings in blood-borne brain lesion.**

A. The multiple haemorrhagic nodules showed whorls of spindle-shaped cells and neovascularization with small-vessel proliferation characteristic of Kaposi’s sarcoma. B. Tumour cells invaded brain parenchyma through perivascular space. C. Neoplastic nodules showed haemorrhagic necrosis with pigmented macrophages. D. The neoplastic cells show strong cytoplasmic staining for CD34.

**Microscopic of a local example:** tumour is formed by fascicles of spindle cells, with slit-like spaces and extravasated red blood cells.
**Treatment:** Kaposi's sarcoma is usually a localized tumour that can be treated either surgically or through local irradiation including skull irradiation. Chemotherapy with drugs such as liposomal anthracyclines or paclitaxel may be used, particularly for invasive disease. Antiviral drugs, such as ganciclovir, that target the replication of herpesviruses such as KSHV have been used to successfully prevent development of Kaposi’s sarcoma although once the tumour develops these drugs are of little or no use. For patients with AIDS-KS, the most effective therapy is highly active antiretroviral therapy to reduce HIV infection. AIDS patients receiving adequate anti-HIV treatment may have up to a 90% reduction in Kaposi’s sarcoma occurrence.

**Prognosis:** 5-year survival now is 70%. Often, people with KS die from diseases related to HIV and AIDS, and not the Kaposi sarcoma itself.

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**CNS LEIOMYOMA – 8890/0 – WHO grade I**  
**And CNS LEIOMYOSARCOMA – 8890/3 – WHO grade III**

**Definition:**  
Leiomyoma and leiomyosarcoma are smooth muscle tumours (SMTs) that more commonly involve the uterus, soft tissue, lung, and gastrointestinal tract. These neoplasms rarely involve the CNS, but they are becoming more prevalent in the acquired immunodeficiency syndrome (AIDS) population.

**Pathology:** They arise from the mesenchymal cells of the dura mater or cerebral blood vessels.  
**Coinfection with Epstein-Barr virus (EBV) appears to be necessary for development of these neoplasms, and they are commonly referred to as EBV-associated SMTs.** The mechanism of tumorigenesis has not been elucidated, but is postulated to result from infection and neoplastic transformation of smooth muscle cells by the virus.  
It has been hypothesized that in the setting of immune compromise, high EBV viral titres at the time of primary infection allowed infection of tissue types that would not normally be infected under normal physiologic conditions. These neoplasms have also been identified in post-transplantation and other immune-compromised patients. It has been reported that EBV-associated SMTs are the second most frequent neoplasm in human immunodeficiency virus (HIV)–positive children.  
Symptoms vary depending on tumour location, and the tumours may be found as an incidental finding at imaging or autopsy.

Leiomyoma and leiomyosarcoma should be included in the differential diagnosis of dural-based masses in AIDS patients.

**Imaging**  
CT shows an isoattenuating dural-based lesion that may contain calcification. At MR imaging, the lesions are hypo- to isointense on T1-W images and iso- to hyperintense on T2-W imaging. Avid enhancement after administration of contrast material is typically seen, and these lesions share many imaging characteristics with meningiomas. Case reports have described these lesions as being hypovascular at angiography, unlike meningioma.

(c)Axial T1-weighted MR image shows an isointense mass centered in the region of the right cavernous sinus.  
(d) Coronal T2-weighted MR image shows an isointense mass that appears to encase and mildly narrow the internal carotid artery.  
(e) Postcontrast T1-weighted MR image with fat saturation shows avid enhancement.  
— see below.
**Microscopic:**
Histologic evaluation of *leiomyosarcoma* reveals densely packed neoplastic spindle cells with blunt ends and abundant mitotic activity. The mitotically active spindle cells are arranged in intersecting fascicles – see example below.

*(Leiomyoma* is composed of fascicles of bland smooth muscle cells. No mitotic activity or nuclear anaplasia. Nuclei have rounded rather than pointed ends-cigar-shaped nuclei.)*

**Immunohistochemistry:**
*Leiomyosarcoma* demonstrates positivity for smooth muscle actin, myogenin (a muscle-specific basic-helix-loop-helix transcription factor), and desmin (a major intermediate filament protein necessary for structural integrity and function of muscle).
**EBV-associated leiomyoma** in a 53-year-old woman with diabetes and hepatitis C who presented with worsening right-sided headache and diplopia.

(a) Photomicrograph with smooth muscle actin stain highlights the neoplastic spindle cells.

(b) Photomicrograph shows a spindle-cell neoplasm with cigar-shaped nuclei.


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**Treatment:** The main form of treatment for leiomyosarcomas is surgical excision and removal of the entire tumor and surrounding tissue. Depending upon the location of the primary tumor, surgical procedures may also include the use of certain reconstructive techniques. Surgical options are dictated by the size, location and spread of a tumor.

Standard therapy may often include postoperative radiation to help treat known or possible residual disease. If initial surgery is not an option due to the specific location and/or progression of the malignancy, therapy may include radiation alone. Radiation therapy preferentially destroys or injures rapidly dividing cells, primarily cancerous cells.

**Prognosis:** live up to 2 years.
MYOFIBROBLASTOMA – 8825/0 – WHO grade I
Also called inflammatory fibrosarcoma, plasma cell granuloma, inflammatory pseudotumour, inflammatory myofibroblastic tumour (IMT)

**Definition:** Myofibroblastoma is a benign and rare mesenchymal neoplasm composed of spindle cells in clusters and fascicles, with interspersed bands of hyalinized collagen. Plasma cells, lymphocytes and eosinophils may also be present.

**Background:** Broadly speaking, ‘inflammatory pseudotumour’ refers to a group of conditions characterised by a tumefactive proliferation of myofibroblastic spindle cells accompanied by lymphoplasmacytic infiltrates. First recognised in the lung, and increasingly in extrapulmonary sites, including the CNS, these lesions have variously been referred to as ‘plasma cell granuloma’, inflammatory myofibroblastic tumours (IMT), ‘inflammatory fibromyxoid tumour’ and ‘inflammatory fibrosarcoma’ (amongst others).

Initially regarded as a post inflammatory and reactive process, these conditions are now recognised to range from the benign and self-limiting, to neoplasms with the capacity for locally aggressive growth, recurrence and, on rare occasions, malignant behaviour. A subset of ‘inflammatory pseudotumours’ appears to be reactive and related to various and related to various infectious agents, including Epstein-Barr virus and human herpesvirus-8. Hepatic and splenic examples appear to represent EBV-related follicular dendritic cell proliferations/neoplasms, though EBV does not appear to play a major role in the pathogenesis of IPST at other sites. Other ‘inflammatory pseudotumours’ appear to be reparative in character; examples include the clinically benign myofibroblastic proliferations resembling nodular fasciitis in sites such as the lower urogenital tract.

Inflammatory myofibroblastic tumours (IMT), previously regarded as synonymous with IPST, represent neoplastic myofibroblastic proliferations. The clinical behaviour of this group includes the capacity for locally aggressive growth, vascular invasion, and rarely malignant transformation. Some IMTs have clonal rearrangements of the ALK gene and expression of ALK protein which can be detected immunohistochemically.

**Sites:** multiple sites throughout the body, including the CNS with the majority of the masses being in the breast.

**Incidence:** very rare in the CNS, all attached to the dura.

**Age:** between 9 and 70 years.

**Gender:** slight female preponderance

**Clinical features:** 30% of the systemic cases have fever, growth failure, malaise, weight loss, anaemia, thrombocytosis, polyclonal hyperglobulinaemia and a raised erythrocyte sedimentation rate. The symptoms disappear with removal of the tumour. CNS cases have headache and, depending on the size of the mass, features of raised intracranial pressure.

**Macroscopic:** circumscribed but not encapsulated. Consist of a white-tan mass with whorled fleshy or myxoid cut surface. May show focal haemorrhage, necrosis or calcification.

A. T1W – mass is hypointense,  B. T2W has mixed intensity,  C. T1W plus contrast – shows a ring-like enhanced boundary of the mass and  D. study 24 months post op. shows no recurrence.

**Differential diagnosis:** of meningeal myofibroblastoma includes other spindle cell neoplasms of the meninges, such as solitary fibrous tumours/haemangiopericytomas, fibrous meningiomas.

**Microscopic:**

- Myofibroblastic and fibroblastic spindle cells with inflammatory infiltrate of lymphocytes, plasma cells, eosinophils, histiocytes
- Background of abundant blood vessels
- Mixture of 3 patterns:
  - Resembling nodular fasciitis with elongated myofibroblasts containing abundant eosinophilic cytoplasm and vesicular nuclei, loose myxoid stroma with neutrophils, lymphocytes and eosinophils, but few plasma cells;
  - Cellular with spindled myofibroblasts and fibroblasts in more compact stroma, arranged as islands surrounded by fibromyxoid stroma with prominent plasma cells and mitotic figures;
  - Densely hyalinized stroma with few spindle cells, few plasma cells or lymphocytes
- May have ganglion-cell like myofibroblasts
- All 3 patterns have no nuclear pleomorphism, no atypical mitotic figures
- **Malignant behaviour:** associated with highly atypical polygonal cells with oval nuclei, prominent nucleoli, Reed-Sternberg like cells, atypical mitotic figures

The histological appearances are polymorphous – a myofibroblastic spindle cell proliferation and an accompanying inflammatory infiltrate are the principle constituents. Three basic histological patterns of extrapulmonary IMT were described by Coffin et al. These include a myxoid vascular pattern with inflammatory areas resembling nodular fasciitis or granulation tissue, a compact spindle cell pattern with intermingled inflammatory cells resembling fibrous histiocytoma, and a
hypocellular fibrous pattern with dense plate-like collagen resembling a scar or fibromatosis. The relative proportions of these various patterns may vary from one example to another, and also within the same lesion. The inflammatory components of plasma cells, lymphocytes and eosinophils are haphazardly scattered throughout the stroma. Plasma cells often predominate in the infiltrate, but are polyclonal in nature. In general, necrosis, granulomata and abscesses are not seen in IMT.

Image courtesy of Mark R Wick, PathOutlines 2016 Sept 12 shows spindle cells evident on this HP image.

Also an example of a myofibroblastoma which shows spindled myofibroblastic cells plus an inflammatory infiltrate.
Immunohistochemistry:

Positive Stains

- Vimentin (diffuse, strong), usually alpha smooth muscle actin, muscle specific actin and calponin
- ALK1 / p80 in 40%, but not specific
- Keratin and desmin in 1/3

Negative Stains

- S100, CD117, HHV8
- CD34, h-caldesmon

Electron Microscopy Description

- Myofibroblastic cells and activated fibroblasts

Molecular / Cytogenetics Description

- Clonal abnormalities of 2p23 including t(2;5)(p23;q35) involving ALK and NPM
- Also t(2;17)(p23;q23) involving ALK and CLTC and t(2;19)(p23;p13.1) involving ALK and TPM4
- Associated with ALK deregulation and younger patients

Treatment: surgical excision.

Prognosis: 25-35% recur. Some reports of metastases but this could be multiple primary sites.
RHABDOMYOMA 8900/0 – WHO grade I
And RHABDOMYOSARCOMA – 8900/3 – WHO grade III

Definition: suspected to be of embryonal origin as there is a prevalence in children, often midline and overlap with ectomesenchymomas.

Sites: adult examples of primary rhabdomyosarcomas may differ in origin from the paediatric and are more likely to be present in lateral brain locations and be supratentorial.

Incidence: primary rhabdomyosarcomas of the brain are exceedingly rare.

Types: primary rhabdomyosarcoma is less common than metastatic rhabdomyosarcoma.

The metastatic type occurs by haematogenous spread in 2% of paediatric patients with systemic rhabdomyosarcomas.

Localized CNS extension often develops in patients with parameningeal primaries in the middle ear/mastoid, nasopharynx, paranasal sinuses, parapharyngeal region or the pterygopalatine/infratemporal fossa. Survival after detection of CNS involvement is less than one year but removal of the metastasis has slightly improved survival.

Age: 2/3 to 3/4 of cases occur in infants and children.

Site: predilection for the posterior fossa in paediatric cases. The frontal lobe is the most common supratentorial location.

Primary meningeal examples occur but more often parenchymal variants extend into the meninges and disseminate within the C.S.F. Systemic metastases have also been reported.

Macroscopic: tumours are sharply demarcated from the surrounding brain or may be haemorrhagic.


A. CT non contrast shows a partially calcified mass in the pineal.
B. MRI axial T1W plus contrast shows heterogenous enhancement of the mass.
C. MRI T1W sagittal non contrast.
**Microscopic:** primary rhabdomyosarcomas are of the embryonal type. Most tumour cells are small and undifferentiated with irregular hyperchromatic nuclei and scant cytoplasm. Myoblastic differentiation is shown by cells with plump or spindle-shaped eosinophilic cytoplasm or strap-like cells with cross-striations. Differentiation may be more advanced in posterior fossa variants.

In the example below, which is a pleomorphic rhabdomyosarcoma, the neoplastic rhabdomyoblasts have irregular deeply staining nuclei. The larger rhabdomyoblasts have well defined and distinctly eosinophilic cytoplasm but with cytoplasmic cross striations not easily discerned here. Cross striations are seen on the next case.

![Image](image_url)

Image courtesy of Scott Kilpatrick. Medscape Mar 9th 2016

Embryonal rhabdomyosarcoma is evidenced by a variable cell population consisting of small, round tumour cells with hyperchromatic nuclei and of large, polygonal-shaped tumour cells with abundant eosinophilic cytoplasm, which often contains diagnostic cross striations (arrow – see above).
**Immunohistochemistry:** Tumour cells may show immunoreactivity for muscle markers such as myosin and muscle-specific actin. Myoglobin staining is more often restricted to differentiating rhabdomyoblasts and immature muscle fibres.

**Electron microscopy:** Identifies actin and myosin filaments, along with Z-band material in the cytoplasm.

The diagnosis of RMS may be missed unless electron microscopic and specific immunohistochemical studies are applied to "undifferentiated" or "primitive" CNS tumours.

**Associated conditions:** Rare reports of a lumbar spinal cord case in a 5 year old with spina bifida and of one arising in a pineal teratoma. Other reports associated with chronic cerebral paragonimiasis, hypomelanosis and hyperplastic choroid plexus.

**Treatment:** Postoperative chemotherapy and craniospinal radiation may improve the anticipated poor prognosis of patients treated with surgery and radiation alone.

**EWING SARCOMA/PNET – 9364/3 – WHO grade III**

Primitive neuroectodermal tumour (PNET) -9473 - pertaining to brain tumours has been deleted in the 2016 WHO Classification of Brain Tumours.

9364/3 applies to a tumour of the soft tissues or bone. Discussion of extraosseous intracranial Ewing’s sarcoma will follow.

**Incidence:** Extremely rare intracranially.

**Age:** Usually over 20 years but can occur in younger patients.

**Clinical:** Headache, raised intracranial pressure and possibly a palpable soft tissue mass extruding through the skull vault.


Preoperative CT scan of the brain of an 11 year old girl showed a rounded, well-defined, heterogeneously hyperdense, enhancing lesion in the left temporoparietal region, with a mass effect and destruction of the left temporal bone extending into the scalp, suggesting the possibility of meningioma. No evidence of calcification was noted within the lesion.

![CT scan of the brain](image)

**MRI:** Preoperative MRI of the brain showed a left temporal lesion, hypointense on T1, heterointense on T2, with heterogenous enhancement – see below.
Ewing’s sarcoma/PNET is a prototype of the “small round cell” tumour group. It is composed of sheets of small cells with high nuclear to cytoplasmic ratio. The cytoplasm is scant, eosinophilic, and usually contains glycogen, which is detected by periodic acid Schiff stain and is diastase degradable. The nuclei are round, with finely dispersed chromatin, and have one or more tiny nucleoli. - See example below. Occasional rosette formation is also seen. Ewing Family of Tumours (EFT) does not produce any matrix. This tumour frequently undergoes necrosis and the residual viable cells show a “peritheliomatous” or a perivascular distribution. Rarely, Ewing Family of tumours (EFT) tumour cells can be large with irregular nuclear membrane and prominent nucleoli.

Ewing’s sarcoma is formed by sheets of closely packed primitive cells, divided into collections of irregular size by thin fibrovascular septae. The tumour cells are characterised by small round but slightly irregular nuclei and lack distinct cytoplasmic borders. Small areas of necrosis within the tumour and “smearing” of nuclear chromatin may be evident.

A prototypic small round cell tumour, Ewing sarcoma must be distinguished from numerous other malignancies which may present with a ‘small round blue cell’ appearance.
**Immunohistochemistry:** EFT cells show membranous expression of CD99 or MIC2 – see left image below and antibody against FLI1 – right image below -, which is centered in the nucleus of the tumour cells has been shown to be specific for EFT. Depending on the degree of neuroectodermal differentiation, the tumour cells may also express neuron-specific enolase (NSE), synaptophysin, and S-100 protein.

**Differential diagnosis of the immunohistochemistry:**

Immunohistochemistry is essential for diagnosis as the family of small round cell tumours is rather large and includes non-Hodgkin lymphoma, neuroblastoma, rhabdomyosarcoma, mesenchymal chondrosarcoma, blastemal component of Wilms tumour, and rarely in DSRCT. Other tumours can also show small round cells and these are osteosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumour, and melanoma.

Although CD99 shows strong membrane positivity in EFT, it can also be positive in other tumours viz. lymphoblastic lymphoma, rhabdomyosarcoma, synovial sarcoma, mesenchymal chondrosarcoma, blastemal component of Wilms tumour, and rarely in DSRCT. A panel of immunohistochemical stains is employed to arrive at a definitive diagnosis.

CD99 (coded on short arm of X and Y chromosome is consistently expressed in Ewing/PNET, but not pathognomonic)., FLI1, and NSE would be positive in ES/PNET. Non-Hodgkin lymphoma would express the lymphoid markers, i.e., CD45RB, CD3, CD20, and TdT; neuroblastoma would be positive for neuroendocrine markers (synaptophysin, chromogranin); rhabdomyosarcoma would be positive for skeletal muscle markers viz., desmin, myogenin, myo-D1, and myoglobin; and synovial sarcoma would also express pancytokeratins, EMA, BCL2, and calponin.

**Molecular Genetics:**

The EFT in 85% of cases is associated with translocation t(11;22)(q24;q12). This fusion of EWS gene on 22q12 with the FLI1 gene on 11q24 results in a chimeric fusion transcript EWS-FLI1. Type 1 (exon 7 of EWS to exon 6 of FLI1) and type 2 (exon 7 of EWS to exon 5 of FLI1) are the two types of typical translocation sites. In another 10–15% of cases, the translocation t(21;12)(22;12) resulting in EWS-
ERG (Ets-related gene) fusion is seen. The remainder of 1–5% of the cases shows translocations, which involve fusion of EWS gene and a member of ETS family of transcription factors. The resulting translocations are EWS and ETV1 (Ets variant 1) (t(2;22)(p22;q12)), EWS and E1AF (Ets variant 4 – ETV4/E1A enhancer binding protein) (t(17;22)(q21;q12)), and EWS and FEV (t(2;22)(q33;q12)). More complex translocations have also been described.

Translocations involving EWS gene are observed in other tumours. EWS is fused to ATF1 (activating transcription factor 1) in malignant melanoma of soft parts, WT1 (Wilms tumour 1) in intra-abdominal DSRCT, CHOP in myxoid liposarcoma, and CHN in myxoid chondrosarcoma. In addition, EWS-like gene, TLS/FUS, is involved in tumour-associated gene fusions in myxoid liposarcoma and acute myeloid leukaemia.

**Treatment, prognosis:** in the past surgical and irradiation therapy resulted in <10 % 5 years survival.

The current combined high-dose irradiation and chemotherapy and only limited surgical intervention has much better results: 85% local control and 75% 5 years survival can be achieved.

The radiological changes can regress but if there are again lytic lesions, that is suspicious for relapse. Soft tissue extension is a bad prognostic sign. The prognosis of Ewing (skeletal type) is better than soft tissue PNET (extraskeletal type). Ploidy can have prognostic value (diploid is better).

**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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