PATHOLOGY OF TUMORS OF THE CENTRAL NERVOUS SYSTEM
MHD – Neuroscience Module

Ewa Borys
Assistant Professor, SSOM
Department of Pathology, LUHS

Objectives

1. Become familiar with basic classification of CNS tumours
2. Understand how patients present
3. Know the common tumours in children and adults
4. Know familial tumor syndromes involving CNS

Introduction

• 1-2% of all malignant neoplasms
• 2nd most common malignancy in childhood (after hematologic) and the most common solid cancer of childhood
• 85% occur within the brain – 15% in the spinal cord
• Adults - 70% supratentorial
• Children - 70% infratentorial, typically in the cerebellum
Central nervous system tumors are unique in many ways

- The distinction between a "benign" and "malignant" tumor is less evident than in other sites
  - Glial tumors with benign histology will infiltrate the brain and can be fatal, when located in an area where surgical resection is not possible
- Surgical resection is restricted because of the functional anatomic considerations
  - E.g. removal of a lesion in the motor area will leave the patient permanently paralyzed
- Benign lesions can have fatal outcome because of the location

Tumor Growth

- Expansile:
  - Sharp border between tumor and surrounding tissue
  - E.g. metastatic carcinomas
- Infiltrative
  - Single tumor cells percolate through brain parenchyma and surround normal structures
  - E.g. glioblastoma

Tumor Spread

- Primary CNS tumors rarely metastasize outside of the CNS
- Subarachnoid spread is common in some types of CNS tumors (e.g. medulloblastomas)
- Cerebrospinal fluid cytology is useful in:
  - Metastatic carcinomas (meningeal carcinomatosis)
  - Medulloblastomas
Clinical Signs and Symptoms

- Compression of adjacent structures
- Local brain invasion
- Increased intracranial pressure
- Determined by tumor type and location

Clinical Signs and Symptoms

- **Headaches** – common manifestation, due to an increased intracranial pressure
  - more common in infratentorial tumors
  - change in prior headache pattern
  - headache worsening with change in body position (e.g. bending over)
  - worse at night
- **Nausea and vomiting** (due to increased ICP)
- **Seizures**
  - More common in supratentorial hemispheric tumors
- **Syncope**
  - A significant rise in ICP can temporarily cut off cerebral perfusion leading to loss of consciousness (e.g. colloid cyst of the third ventricle)
- **Cranial nerve palsies** (skull base tumors)
- **Focal neurologic deficits**
- **Cognitive dysfunction** (confusion, memory loss)
- **Infants**: the head enlarges, fontanelles bulges and the head circumference increases.

Diagnosis

- **CT or MRI**
- **Biopsy:**
  - Frozen section including smears
  - Paraffin sections
  - Immunohistochemistry
  - Molecular studies
Prognostic factors

• Patient characteristics
  – Age
  – Physical status
  – Comorbidities
  – Extent of surgical resection

• Tumor characteristics
  – Location and histologic type
  – Proliferative capacity
  – Molecular features (may override histology)

Treatment

• Surgery (LOCATION!)
  – Resection vs biopsy
  – Goals: diagnosis, reducing the mass effect, can be curative

• Radiation therapy
  – External beam radiation including whole brain radiation
  – Stereotactic radiosurgery

• Chemotherapy
  – Temozolomide
  – Alkylating agents
  – Steroids
  – Anticonvulsant therapy

Classification

• PRIMARY - tumors arising from the brain parenchyma or its coverings

• METASTATIC - secondary tumors which spread to the brain through bloodstream
  – Can be either intra-axial or extra-axial
I. PRIMARY CNS TUMORS

1) Tumors arising in the parenchyma
   a) Gliomas
      a) Astrocytoma
      b) Oligodendroglioma
      c) Ependymoma
   b) Neuronal and mixed neuronal-glia tumors
      a) Central neurocytoma
      b) Ganglioglioma
      c) Dysembryoplastic neuroepithelial tumor (DNET)
   c) Embryonal tumors
      a) Medulloblastoma
      b) Primitive neuroectodermal tumor (PNET)
      c) Atypical teratoid/rhabdoid tumor (AT/RT)
2) Tumors arising from the coverings
   a) Meningioma
   b) Hemangiopericytoma
   c) Chondroma
   d) Leiomyoma
   e) Osteoma
   f) Hemangioma
   g) Lipoma

3) Tumors of Pituitary Gland
   a) Pituitary adenoma
   b) Craniopharyngioma

4) Tumors of Pineal Gland
   a) Germinoma
   b) Pineocytoma

5) Tumors of Cranial and Peripheral Nerves
   a) Schwannoma
   b) Neurofibroma
   c) Malignant Peripheral Nerve Sheath Tumor (MPNST)

Histological grading

- Means of predicting biological behavior of a neoplasm
- Key factor in the choice of therapy
Histological grading

- WHO grading is widely used:
  - **Grade I**: tumors with low proliferative potential and possibility of cure with surgical resection alone
  - **Grade II**: infiltrative tumors that often recur despite low level of proliferative activity
    - Some progress to higher grade
  - **Grade III**: clearly malignant, RT/chemo
  - **Grade IV**: malignant with rapid pre- and postoperative course and fatal outcome

ASTROCYTOMA

- The most common glioma
- Can occur anywhere in the brain
- All age groups effected
- Clinical symptoms depend on location and grade

Pilocytic astrocytoma
(Juvenile pilocytic astrocytoma)

- **WHO grade I**
  - Most common glioma of children and adolescents
  - Slow growing with low proliferative potential
  - Possibility of cure with surgical resection alone
Pilocytic astrocytoma

- Cerebellum and brain stem of children and young adults
- MRI: discrete, contrast enhancing mass without surrounding cerebral edema

Classic finding: cystic mass with mural nodule (solid/cystic)

Pilocytic astrocytoma – solid and cystic mass in cerebellum

BIPHASIC ARCHITECTURE: COMPACT AND MICROCYSTIC AREAS
DIFFUSE GLIOMAS

- **WHO grading scale:**
  - **GRADE II** - Infiltrative in nature and despite low level proliferative activity; often recur and progress to higher grade
  - **GRADE III** - Malignant tumors, but without microvascular proliferation or necrosis. Usually receive adjuvant radiation and/or chemotherapy.
  - **GRADE IV** = GBM (Glioblastoma), most malignant astrocytoma; rapid progression and a fatal outcome.

Glioma Grading

- **Glioma Grading**
GLIOBLASTOMA

- Malignant (high-grade) astrocytoma
- Most common malignant brain tumor in adults
  - 15% of intracranial neoplasms
  - 50% of primary malignant brain tumors
  - Incidence 3-4 cases per 100,000
- Usually in older adults but any age can be affected
- Short time from first symptoms to diagnosis (<3 months in 68%)
- Arises in cerebral hemispheres and is diffusely infiltrating
  - "Butterfly lesion"
  - Gliomatosis cerebri

MRI, axial T1:
peripherally-enhancing mass with surrounding edema and mass effect
(compression of the lateral ventricle and midline shift)

“Butterfly” glioma

GLIOBLASTOMA

Gross specimen, axial view:
- Large mass with poorly defined borders
- Areas of yellow necrosis
- Reddish-brown hemorrhage
- Mass effect on the lateral ventricles and midline shift
GLIOBLASTOMA

• Histologic features:
  – Pleomorphic malignant astrocytes
  – Many mitoses
  – Endothelial cell hyperplasia
  – Areas of necrosis with pseudopalisading of cells at the periphery
  – Tumor cells GFAP positive

PSEUDOPALISADING NECROSIS
OLIGODENDROGLIOMA

- Rare malignant tumor of oligodendrocytes
- Better prognosis than astrocytoma
- Most frequent in the **frontal lobe**
- Due to frequent cortical involvement most patients present with **seizures**
- Characteristic intratumoral **calcifications** on **CT**

OLIGODENDROGLIOMA

**CT:**
intratumoral calcifications

- **Secondary structures:**
- perinuclear halos
- “fried egg” appearance
- chicken-wire capillary pattern

Secondary structures:
perineuronal satellitosis
Rosettes

- Spoke-wheel arrangement of cells around central core – resembles rose windows found in gothic cathedrals
- Central hub may be an empty lumen or space filled with cytoplasmic processes
- Cytoplasm of each of the cells in rosette is wedge-shaped with apex directed toward central core
- Nuclei of the cells in rosette are peripherally positioned and form a ring around the hub

Rosettes in **medulloblastoma** have central core composed of delicate neuropil fibrils (Homer – Wright rosettes)

Rosettes in **retinoblastoma** have cells arranged around empty lumen (Flexner-Wintersteiner rosettes)

**Perivascular pseudorosette** (ependymoma): halo of tumor cells surrounds blood vessel

**True ependymal rosette:** halo of tumor cells surrounds empty central lumen
**Ependymoma**

- Arises from ependymal cells
- Most frequent in children but can present at any age
- 4th ventricle most common site
- In adults usually spinal
- Imaging: discrete, exophytic, contrast enhancing

---

**Fourth ventricular mass (T1 post-contrast)**

Initial presentation with signs and symptoms of raised intracranial pressure is common, particularly with tumors in the fourth ventricle

---

**Ependymoma in lateral ventricle**
Ependymoma perivascular pseudorosettes: tumor cells surround a blood vessel

True ependymal rosettes: tumor cells surround central lumen

**Medulloblastoma**
- Arises from undifferentiated neuroectodermal cells
- Highly malignant tumor in cerebellum of children
- Spread along the CSF pathways
- Sensitive to radiation therapy
Medulloblastoma
MRI: discrete, contrast-enhancing mass in fourth ventricle

Medulloblastoma: nodular fleshy tumor in fourth ventricle

Sheets of undifferentiated cells ("small blue cells") with scanty cytoplasm and dark staining nuclei
Homer-Wright rosettes (tumor cells surrounding neuropil)
MENINGIOMA

- Extra-axial (outside of brain parenchyma)
- Arises from arachnoid cells
- Usually benign tumor of middle aged adults, more common in females
- Often asymptomatic but may present with seizures or focal neurologic deficits
- Multiple in NF2
- Resection usually curative
- +/- Radiation

Meningioma

MRI (T1 post-contrast): well circumscribed superficial mass with bright contrast enhancement

Gross: discrete globular solid mass attached to the dura

Dural attachment ("tail")
Meningioma

Psammoma bodies (laminated calcifications)

Whorls

Fascicles in fibroblastic variant: elongated cells with collagen deposition.

Syncytial appearance: tight clusters of meningothelial cells without discernible cell borders.

Schwannoma

• Benign tumor of Schwann cell origin
• Involves cranial or spinal nerves (extra-axial)
• Common at cerebellopontine angle and VIII cranial nerve (“acoustic neuroma”)
  – Loss of hearing and tinnitus
  – Actually arises from vestibular portion of the VIII cranial nerve which carries balance = should be called vestibular schwannomas
• Bilateral acoustic neuromas found in NF2

Globular well circumscribed mass in cerebellopontine angle. Yellow coloration due to lipid accumulation, focal hemorrhage.
Primary CNS lymphoma

- Most are **diffuse large B-cell lymphomas (DLBCL)**
- Older adults (60-80s)
- **Immunodeficient** patients are at increased risk
  - EBV-related
- Single or multiple lesions, most are supratentorial
- Present with cognitive dysfunction, psychomotor slowing and focal neurological deficits
- Worse prognosis than systemic DLBCL
Metastatic carcinoma

- Much more common than primary brain tumors
- Lung > breast > melanoma > kidney > GI tract
- Most common primaries with “meningeal carcinomatosis” (CSF spread): lung and breast
- Frequently multiple
- Multiple tumor masses suggest metastatic carcinoma

MRI:
Ring-enhancing sharply demarcated lesions at the border of cortex and white matter

Metastases most often appear at the border of the grey and white matter in the distribution of the middle cerebral artery.
Bilateral hemorrhagic brain metastases from lung carcinoma

Hemorrhagic brain metastases:
- Lung
- Melanoma
- Renal cell carcinoma
- Choriocarcinoma

FAMILIAL TUMOR SYNDROMES

- Neurofibromatosis (NF)
  - NF type 1
  - NF type 2
- Tuberous sclerosis
- Von-Hippel-Lindau
- Sturge-Weber
- Li-Fraumeni
- Cowden
- Turcot
- Gorlin (Naevoid basal cell carcinoma syndrome)
NEUROFIBROMATOSIS TYPE 1 (NF 1)

- Von Recklinghausen disease
- Gene on 17q11.2
  - Neurofibromin-GTPase activating protein
- CNS and PNS are most commonly involved:
  - Neurofibromas, MPNST, acoustic schwannomas, optic nerve gliomas (pilocytic astrocytoma),
  - Plexiform neurofibroma is pathognomonic of NF 1
- Extraneural manifestations:
  - Café-au-lait spots
  - Axillary and inguinal freckling
  - Lisch nodules (pigmented hamartomas of iris)
  - Osseous lesions (sphenoid wing dysplasia, scoliosis)
  - Tumors

Multiple cutaneous neurofibromas

Large café au lait spot
Plexiform neurofibroma: tumor involves multiple nerve fascicles
- "Bag of worms" on gross exam
- Micro: enlarged nerve fascicles with spindle cells and abundant mucin

NEUROFIBROMATOSIS TYPE 2 (NF 2)

- Gene on chromosome 22q12
  - Tumor suppressor gene
  - Merlin (schwannomin) – a cytoskeletal protein
- Schwannomas
  - Occur in younger patients than sporadic ones
  - Bilateral vestibular schwannomas are a diagnostic hallmark
- Multiple meningiomas
- Gliomas – usually spinal ependymomas

Bilateral cerebellopontine angle tumors
**Tuberous Sclerosis**

- Hamartomatous lesions involving multiple organs
- Two genes: TSC1 (9p) - hamartin and TSC2 (16p) - tuberin
- Classic triad:
  - Adenoma sebaceum
  - Seizures
  - Mental retardation
- CNS lesions:
  - Cortical tubers
  - Subependymal hamartomas, including subependymal giant cell astrocytoma (SEGA).
- Other tissues:
  - Facial angiofibromas (adenoma sebaceum), subungual fibromas, hypomelanotic macules ("ash-leaf spots"), shagreen patches on the forehead, cardiac rhabdomyomas, renal angiomyolipomas, pulmonary lymphangiomyomatosis

**Facial angiofibromas ("adenoma sebaceum"): multiple flesh-colored papules**

**Tubers** (glioneuronal hamartomas): foci of cortical pallor and blurring of grey-white junction

**SEGAs:** subependymal nodules – can lead to hydrocephalus
Von Hippel-Landau Disease

- VHL tumor suppressor gene on chromosome 3p
  - Protein in ubiquitin-ligase complex that targets transcription factor hypoxia-inducible factor (HIF) for degradation
  - Tumors show loss of VHL and express HIF which drives the expression of VEGF and other growth factors
- Lesions:
  - hemangioblastomas of CNS and retina
  - pheochromocytoma
  - pancreatic cysts
  - renal cell carcinoma (metastatic RCC is the leading cause of death)
  - endolymphatic sac tumor (middle ear)

Hemangioblastoma

- Closely arranged thin-walled capillaries with little intervening parenchyma
- Can produce erythropoietin - secondary polycythemia

Multiple cerebellar hemangioblastomas
Li-Fraumeni syndrome

• Germline mutation in TP53 tumor suppressor gene on ch. 17p13
• Lesions:
  – Soft tissue sarcomas
  – Osteosarcomas
  – Breast cancer
  – Brain tumors – children
    • Medulloblastoma
    • Choroid plexus tumors
    • Ependymomas
    • Astrocytomas (middle age)
  – Adrenocortical carcinoma

Quiz

1. Which are more common primary or metastatic brain tumors?
2. What histologic finding distinguishes GBM from lower grade astrocytomas: mitoses, cellular pleomorphism, necrosis, cellular density?
3. What is the most common primary brain tumor in adults?
4. What are 2 examples of CNS tumors where CSF sampling may help with the diagnosis?
5. Which brain tumor contains psammoma bodies and progesterone receptor?

Questions?
Answers

1. Metastatic tumor
2. Necrosis
3. Meningioma
4. Medulloblastoma and meningeal carcinomatosis
5. Meningioma