XI. TUMORS OF THE NERVOUS SYSTEM

XII. NEUROCUTANEOUS SYNDROMES

GOALS AND OBJECTIVES:

At the end of this learning activity participants should be able to:

- Compare and contrast diffusely infiltrating astrocytomas and pilocytic astrocytoma
- Identify tumors commonly affecting children and discuss their typical localization and prognosis
- Discuss the most common primary sites of tumors metastatic to the CNS and discuss the typical gross pathologic presentation of metastatic tumors in the brain
- Compare and contrast the pathology of neurofibromatosis type 1 and type 2

ABSTRACT

Tumors of the nervous system are either primary or metastatic (approximately 50-50%). In children CNS tumors represent 20% of all cancers. Primary CNS tumors very rarely metastasize outside the CNS. At the same time it is estimated that nearly 25% of cancer patients develop CNS metastasis. The location of tumors in the CNS is a very important determinant of morbidity and mortality. The most common primary CNS tumors are astrocytomas. Neurocutaneous syndromes (phacomatoses) represent a group of inherited diseases characterized by the development of hamartomas and neoplasms throughout the body with particular involvement of the nervous system and skin. Many are inherited in an autosomal dominant pattern and have been linked to tumor suppressor genes.

KEYWORDS: astrocytoma, glioblastoma multiforme, medulloblastoma, meningioma, schwannoma, neurofibromatosis, tuberous sclerosis

XI. CNS TUMORS

- Are either primary or metastatic (approximately 50-50%)
- Annual incidence:
  10 to 17 per 100,000 persons for intracranial tumors
  1 to 2 per 100,000 persons for intraspinal tumors
- In children (< 15 years) CNS tumors represent 20% of all cancers
- In children a majority of tumors (70%) are infratentorial (in the posterior fossa)
- In adults a majority of tumors (70%) are supratentorial
- Generalizations about primary CNS tumors:
  - very rarely metastasize outside the CNS
  - location very important determinant of morbidity and mortality

PRIMARY CNS TUMORS

Can be classified according to their presumed cell of origin:
- **Gliomas**, that include:
  - Astrocytomas: e.g. fibrillary (diffuse) astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, pilocytic astrocytoma
  - Oligodendrogliomas: oligodendroglioma, anaplastic oligodendroglioma
  - Ependymomas: ependymoma, anaplastic ependymoma
- **Neuronal tumors**: e.g. gangliocytoma, cerebral neuroblastoma
- **Poorly differentiated (embryonal) tumors**: e.g. medulloblastoma
- **Meningiomas**: meningioma
- **Nerve sheath tumors**: schwannoma, neurofibroma
- **Adenohypophyseal tumors**: pituitary adenoma

PRIMARY CNS TUMORS – cont.

- Primary CNS tumors: ~ 60% astrocytic, ~ 17% meningeal, ~8% nerve sheath
- WHO system assigns histological grades to primary CNS neoplasms: grades I to IV (grade IV most malignant)
ASTROCYTOMAS

Diffusely infiltrating astrocytic tumors:

- Diffuse infiltration of brain parenchyma
- Inherent tendency for malignant progression
- Shared genetic abnormalities
- Diffuse astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), glioblastoma multiforme (WHO grade IV)

“Other” astrocytic tumors:

- More circumscribed
- Low potential for malignant progression
- Different genetic profile
- Most common: pilocytic astrocytoma (WHO grade I)

DIFFUSE ASTROCYTOMA

- Mean age at biopsy: 34 y
- Cerebral hemispheres
- p53 mutation (~ 75%)
- Overexpression of PDGF-A and its receptor (~ 60%)
- Median survival: 7-8 years

ANAPLASTIC ASTROCYTOMA

- Mean age at biopsy: 41 y
- Cerebral hemispheres
- Molecular genetics: as in diffuse astrocytoma plus disruption of tumor suppressor genes including:
  - Rb alterations (~ 25%)
  - LOH 19q (50%)
- Median survival: 2-3 years with therapy
GLIOBLASTOMA MULTIFORME

- Cerebral hemispheres, brainstem in children
- **Secondary GBM:**
  - mean age: 45 y
  - 1 - 10 y clinical history
  - p53 mutation and others as in AA
  - plus others: i.e. DCC loss of expression
- **Primary GBM:**
  - mean age 55 y
  - short clinical history
  - EGFR amplification, overexpression
  - other: MDM2, p16, Rb, PTEN
- Median survival: 9-12 months with therapy

GRADING OF DIFFUSE ASTROCYTIC TUMORS
BY WHO (2000)

- Three-tiered system (II - III - IV)
- Criteria: cellularity, nuclear atypia, mitotic activity, microvascular proliferation, necrosis
- In practice:
  - if microvascular proliferation and/or necrosis present: grade IV = GBM
  - high cellularity, atypia, mitotic activity:
    - grade III = AA

PILOCYTIC ASTROCYTOMA

- Typically affects children, young adults: most common glioma in children
- **Cerebellum, optic nerve, thalamus, basal ganglia, cerebral hemispheres, brainstem**
- Cyst-mural nodule
- Who grade I, malignant transformation rare
- No p53 inactivation
OLIGODENDROGLIOMA

- Presumed cell of origin: oligodendroglia
- Comprise 2.5 to 3.5% of all primary intracranial tumors
- Most common during the 5th-6th decades
- Median survival: 5-10 years
- Molecular genetics: majority show LOH 1p, 19q
- Infiltrative tumors histologically comprised of tumor cells with round nuclei and perinuclear halos (“fried egg”)
- WHO grade II tumors
- Malignant degeneration to anaplastic oligodenrogliomas = WHO grade III

EPENDYOMAMA

- Presumed cell of origin: ependymal cells
- Relatively common in children, also occur in adults
- Intra- or paraventricular location
- Posterior fossa in children, spinal cord in adults most common
- Median survival: 5-10 years
- Grossly well demarcated tumors, histologically showing dense cellularity, perivascular pseudorosettes, ependymal rosettes
- WHO grade II tumors
- Malignant degeneration to anaplastic ependymoma = WHO grade III

MEDULLOBLASTOMA

- Malignant cerebellar neoplasm (WHO grade IV) with peak incidence in the 1st and 2nd decades
- Densely packed round to carrot-shaped nuclei, frequent mitoses
- Frequently express neuronal markers as synaptophysin
- Often seeds in the subarachnoid space
- Late systemic metastases can occur
- Dismal prognosis without therapy
- With therapy (aggressive surgical resection, radiation, 50-60% long term survival)
Neuropathology V
Tumors of the Nervous System; Neurocutaneous Syndromes

MENINGIOMA
• Tumors of meningothelial cells, ~17% of CNS tumors
• Usually present after the 3rd decade as dura-based mass
• Most represent WHO grade I lesions and can be cured by surgical resection
• Exhibit a wide spectrum of histology, including the common meningothelial and fibrous patterns
• Characteristic histologic features: whorls, psammoma bodies

SCHWANNOMA
• 8% of intracranial tumors, most common intraspinal tumor
• Derived from Schwann cells that provide the myelin sheath of axons in the peripheral nervous system
• Most intracranial schwannomas are derived from the VIII. cranial nerve (acoustic schwannomas) and are at the cerebellopontine angle
• WHO grade I tumors
• Histology: Antoni A and B patterns, Verocay bodies

METASTATIC CNS TUMORS
• Represent 50% of CNS tumors in hospital patients
• ~ 25% of cancer patients develop CNS met
• Lung, breast, melanoma primaries most common
• Choriocarcinoma: rare tumor with high likelihood of metastasizing to the brain
• Prostatic carcinoma: common tumor almost never metastasizing to the brain
• Ovary, Hodgkin’s disease also very rarely metastasize to the CNS
• Gray/white matter junction is the most common site
• Gross and microscopic demarcation from brain typical
• Often multiple separate foci in CNS
XII. NEUROCUTANEOUS SYNDROMES (PHACOMATOSES)

- Group of inherited diseases characterized by the development of hamartomas and neoplasms throughout the body with particular involvement of the nervous system and skin
- Many inherited in an autosomal dominant pattern and have been linked to tumor suppressor genes
- Will discuss neurofibromatosis types 1 and 2, tuberous sclerosis here: these are considered familial tumor syndromes

NEUROFIBROMATOSIS TYPE 1

- Autosomal dominant disorder, frequency: 1 in 3000
- Neurofibromas (plexiform and solitary), gliomas of the optic nerve, pigmented nodules of the iris (Lisch nodules), cutaneous hyperpigmented macules (café au lait spots)
- Neurofibromas are benign tumors that also occur in the absence of NF-1 and only very rarely undergo malignant degeneration. In NF-1 the propensity of neurofibromas to undergo malignant degeneration is increased

NEUROFIBROMATOSIS TYPE 2

- Autosomal dominant disorder, frequency: 1 in 40000 to 50000
- Gene: merlin (chr. 22)
- Bilateral acustic schwannomas, multiple menigiomas, ependymomas of the spinal cord, neurofibromas, nodular ingrowth of Schwann cells into the spinal cord (schwannosis), microscopic nodular collections of glial cells at abnormal locations like superficial and deep cortex (glial hamartias)

TUBEROUS SCLEROSIS

- Autosomal dominant disorder
- Genes: hamartin (chr.9) and tuberin (chr.16) – clinical and pathologic features of disease caused by mutations in these two genes are indistinguishable
- CNS: cortical tubers, subependymal nodules, subependymal giant cell astrocytoma
- Skin: angiofibromas, leathery thickening in localized patches (shagreen patches), hypopigmented areas (ash-leaf patches)
- Elsewhere in the body: renal angiomyolipomas, cardiac and pulmonary myomas, retinal glial hamartomas, cysts in the liver, kidney, pancreas