Skull Tumors

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PATHOLOGY

1. BONE forming tumors:
   1) OSTEOMA (most common primary tumors of calvaria) - growths of mature dense lamellar cortical bone (outer or inner table); typical appearance - nodule of osteoid tissue in background of osteoblastic connective tissue, which is enclosed completely by reactive bone.
   2) OSTEOID-OSTEOMA
   3) COMPTETING FIBROMAS - fibrous spindle cells with varying amounts of woven bone; tumor periphery is composed of mature lamellar bone.
   4) OSTEOLASTICUM - fibrous stroma with irregular osteoid deposition.
   5) OSTEOXARCOMA (second most frequent malignant skull tumor after multiple myeloma) - malignant spindle cell stroma, which directly produces osteoid or immature bone (osteoblastic, chondroplastic, or fibroplastic form); association with prior radiation exposure, Paget disease, fibrosing dysplasia, chronic osteomyelitis.

2. CARTILAGE forming tumors:
   1) CHONDROMA (enchondroma, juxtacortical chondroma, osteochondroma) - mature hyaline cartilage; arises from cartilaginous portion of bone formed by enchondral ossification (skull base and parasymal sinuses).
   2) CHONDROMYXOID-FIBROMA - chondroid and myxoid differentiation with lobular growth.
   3) CHONDROBLASTOMA - immature cartilage cells.
   4) CHONDROXARCOMA (third most common malignant skull tumor); often associated with abnormalities of chromosomes 10 and 22; low-grade type (neurochondrosarcoma) - chondroid and immature cartilage deposition in areas of myxomatous change and cystic degeneration; high-grade type (mesenchynl chondrosarcoma) - absence of cartilage lobules and presence of fibrouschonomatous areas (groups of chondromes cells lose their usual lobulation and begin to spread out); both types are vimentin positive.

3. CONNECTIVE TISSUE tumors:
   1) DERMATOPUNCTATE FIBROMA (very rare) - fibrous connective tissue origin marked by collagen formation.
   2) FIBROBLASTOMA - varying amounts of collagen production and absence of bone, osteoid, or cartilage; medullary subtype has better prognosis than perivascular subtype.

4. HISTIOCYTIC TUMORS (very rare!):
   1) GIANT CELL GRANULOMA - giant cells around hemorrhagic foci, numerous spindle-shaped fibroblastic cells, and new bone formation; tumor cells are smaller than those of giant cell tumor of bone, whereas stromal cells and giant cells resemble each other.
   2) NONCOMPTETING FIBROMA - fibrolast proliferation with multinucleated giant cells.
   3) XANTHOMA - foamy xanthomatous cells.
   4) ERGIC SARCOMA - uniform, densely packed small cells with indistinct cytoplasmic borders.

5. Tumors of BLOOD or BLOOD VESSEL origin:
   1) EOSINOPHILIC GRANULOUCOSIS (common) - mononuclear histocytes* mixed with eosinophiles; giant cells and areas of hemorrhage or necrosis may be observed.
   *Histocytes stain positive for protein S-100; on electron microscopy, Birbeck granules (that characterize Langerhans or X cells) are noted.

6. Tumors of NEUROEPITHELIAL origin:
   1) AGNET DISEASE
   2) SQUAMOUS CELL CARCINOMA

7. Tumors of SQUAMOUS CELL origin:
   1) SQUAMOUS CELL CARCINOMA (nasal sinuses and temporal bone)

8. Tumors of APocrine GLAND origin (salivary, lacrimal glands); propensity for perineural spread.

9. METASTASES (skull is common site!); data in effective barrier - brain invasion is rare!

10. OTHER types:
   1) FIBROUS DISPLASIA - see below.
   2) PAGET DISEASE - increased osteoclastic activity (bone resorption) - increased osteoblastic activity (bone formation).
   3) EPIENDYMOM AND ERMID TUMORS (one of most common benign skull lesions in children)

   a) Anirratural bone cysts - large vascular spaces with thin endocardiet lining separated by trabecular of connective tissue and bone; locally aggressive progression - continue to expand until treated.
   b) INTRACRANIAL MENINGIOMAS - multiple meningiomas - widespread osteodytic bone destruction by dense tumor cells that look like plasma cells clustered in close aggregates.

- 19% are benign and 81% - malignant.
- Features of benign tumor
  1) single, small, gronduly round / oval lesion
  2) peripheral sclerosis
  3) intradlesional calcifications
  4) peripheral bone vacuolaty
  5) malignant transformation (to osteosarcoma, chondrosarcoma, or fibrosarcoma) - in 2% PAGET DISEASE and 0.5% FIBROUS DISPLASIA cases.

- Lesion Location is of little differential diagnostic value, but certain tendencies exist:
  1) lesions of Developmental origin - strong midline propensity; OSTEOMA - paramanal sinuses, frontal bone.
  2) OSTEOLASTICUM - frontoparietal region;
  3) OSSIFYING Meningioma - frontoparietal area, PAGET DISEASE - skull base, usually multicentric.

GENERAL FEATURES OF BONE, CARTILAGE, SOFT TISSUE TUMORS -> see p. 1197-1198>
carotid tumors - skull base; 
**GIANT CELL GRANULOMA** - sphenoïd, temporal, and ethmoid areas; 
**HEMANGIOMAS** (more common in vertebral column): globular variety - skull base; sessile variety - frontotemporal region; 
**EPIDERMOLYSIS and DERMOMAS** - cerebellopontine angle, parasellar region, calvaria (dermolomas prefer midline).

**Hyperostoses** - local overgrowth of skull bones: 
- **intracranial meningiomas** 
- **nonneoplastic** (hyperostoses may involve either outer or inner tables; outer table involvement is insignifcant except for possible disfigurament; hyperostoses of inner table rarely grow enough to compress intracranial contents).

Hyperostosis frontalis interna - asymptomatic symmetric hyperostosis of inner table of frontal bone - common incidental finding in women > 40 yrs; diploe and external table are not affected; differentiate from en plaque meningiomas.

**Epidemiology** 
- account for ≈ 1% of all bone tumors. 
- most manifest in young adults! (except INTRAOSSEOUS MENINGIOMA, PAGET DISEASE, MULTIPLE MYELOMA, SQUAMOUS CELL CARCINOMA - affect older adults).

**Clinical Features**

1. *Enlarging skull mass ± pain / tenderness* (due to periosteal involvement). 
   - **OSTEOID OSTEOMA** - nocturnal local tenderness relieved by NSAIDs. 
   - rapidly growing mass - **ANEURYSMAL BONE CYST**, **CHONDROBLASTOMA**, **CHONDROMYXOID FIBROMA**, **DESMOPLASTIC FIBROMA**, **GIANT CELL GRANULOMA** or malignant tumor. 
   - malignant tumors without pain - **MULTIPLE MYELOMA**, **OSTEOSARCOMA**.

2. Cranial nerve deficits (if tumor involves skull base), e.g. visual and hearing loss.

3. Dural erosion, direct brain compression.

4. Recurrent sinusitis, CSF rhinorrhea
   - if tumor obstructs sinus ostium → mucocele (encapsulated, thick fluid collection); mucocele may erode through base of skull to compress intracranial structures.

5. Subdural collections - associated with malignant tumors invading dura (esp. metastatic).

** Syndromes**

**Gardner syndrome**
1) multiple osteomas of skull, sinus, mandible 
2) soft tissue fibromas of skin 
3) colon polyps

**McCune-Albright syndrome** - postzygotic mutation (spontaneous mutation) of GNAS1 gene - involved in G-protein signaling - mutation prevents downregulation of cAMP signaling
1) polyostotic fibrous dysplasia 
2) “autonomous production” of hormones - precocious puberty, hyperthyroidism, Cushing syndrome 
3) unilateral hyperpigmented skin macules (“café-au-lait”) - jagged “coast of Maine” borders, and tendency to respect midline and follow developmental lines of Blaschko

**Hand-Schüller-Christian disease:**
1) diabetes insipidus 
2) exophthalmos 
3) bone lesions

**Ollier syndrome** - multiple enchondromas.

**Maffucci syndrome**
1) enchondromas 
2) dyschondroplasia 
3) cavernous hemangiomas of soft tissues / viscera

**Diagnosis**

Plain skull radiography with special projections, CT (extent of intracranial extension): 
- a) *radiolucent (osteolytic)* - most tumors (benign and malignant) 
- b) *radiopaque (osteoblastic)* - OSTEOMA, OSSIFYING FIBROMA, INTRAOSSEOUS MENINGIOMA, sclerotic form of FIBROUS DYSPLASIA, later stages of PAGET DISEASE, some METASTASES (e.g. prostate, breast, bladder, hypernephroma).
• Malignant tumors - irregular poorly defined borders, no peristomial reaction.

OSTEOMA - condensation of cortical bone (circumscribed homogenous bone density) which may project external to skull (exostosis) or towards cranial cavity (enostosis); arises from outer table without involvement of diploe (SPONT. OSTEOMA may be radiolucent; OSTEOID OSTEOMA - radiolucent nidus with surrounding dense sclerosis). Osteoma of skull vault (named as K-ony) - circumscribed nature of lesion is suggested by its very well defined border (translucent sun-burst shadow but inner and outer table was affected).

OSTEOID FIBROMA - initial lesion is radiolucent, but progressively becomes radiopaque, with sharp margins and dilated vascular channels.

INTRAMEDULLARY MENINGIOMA - irregular bone deposition on inner and outer tables, usually in vicinity of coronal suture.

OSTEOBLASTOMA - well-demarcated nonenhancing lytic lesion with smooth calcified margins.

CHONDROMA - well circumscribed lytic lesion eroding surrounding bone; stippled calcification helps to distinguish from metastasis or chordoma.

CHONDROMYOID FIBROMA - radiolucent with tissue calcification.

DENSE OSTEOID FIBROMA - well-defined lytic and expansile lesions with typical soap bubble appearance; causes thinning of overlying cortex without peristomial reaction.

GIANT CELL GRANULOMA - radio-opaque, well demarcated, multiloculated, with expansion and thinning of bone cortex; CT - isodense lesion, which may erode overlying cortical bone.

NONOSSEOUS FIBROMA, XANTHOMA - radiolucent with sclerotic margins and bony trabecular with soap bubble appearance.

XENOSINUSOID GRANULOMATOSIS - radio-opaque, oval, well-delineated lesion without sclerosis; appearance of punched-out defect or doughnut-shaped lesion that involves both inner and outer table; CT - soft tissue mass within area of bony destruction (cortical density may also be present).

Hemangiomas - well defined nonenhancing lytic lesion with characteristic honeycomb or trabecular appearance; 35% show peripheral sclerosis; 10-15% show classic “sunburst” or “spoke wheel” pattern (spicules radiate from central point); intralesional calcifications are common, prominent vascular groove may be seen in vicinity (external carotid arteriography sometimes shows blush); diploë is expanded, but inner table is preserved!

Hemangiomas of skull vault (A - lateral radiograph; B - CT, bone window) - well defined lucrecy; or parietal bone has typical “spoke wheel” appearance (due to prominent vascular impressions).

LEIOMYXOID - cystic bone defect.

ANEURISMAL BONE CYST - well-demarcated lesion that arises from diploe; expands both inner and outer table; CT - multiloculated expansile lesion with characteristic fluid level.

OSTEOID/CHONDROID - round lytic lesion arising within diploe; may expand inner and outer tables away from each other; sharp dense sclerotic borders that involve all three layers of bone; CT - hypodense nonenhancing lesion with irregular borders.

FIBROUS DWELLER - see below.

PAGET DISEASE - expansion of skull base by thickened abnormal bone: sharply demarcated lytic lesions (osteoporosis circumscripta) - enlarged, coarsened trabeculae; thickening of cortex, and nonhomogeneous patchy densities (resemble cotton wool) with varying degrees of bone formation and no clear edges - lytic-sclerotic type (can be confused with fibrous dysplasia, but occurs in older age).

OSTEOBLASTOMA - osteolytic soft-tissue extension; may have calcification; typical (but not frequent) appearance in sun-ray picture.

A. Noncontrast CT - calcified mass within medial right parietal-occipital lobes with massive extracranial soft tissue swelling.

B. CT bone window - thinning and erosive changes of calvarium with several large areas of calcification and ossification within extracranial soft tissue in right parietal-occipital region

OSTEOIDOYD FIBROMA - no reliable radiological features (lytic and sclerotic changes within poorly defined margins).

FIBROUSABMMA - lytic lesion with thinning and widening of cortex.
ERIDG SKULL TUMORS

Ewing Sarcoma - typical onion skin appearance (laminated peristome changes); CT - isodense mass surrounded by hypodense area and hyperostosis, contrast enhancing.

Angeiosarcoma - destructive lesion with cortical erosion and reactive ossification; CT - heterogeneous enhancement with focal necrosis.

PLASMOCYTOID/MULTIPLE MYELOMA - multiple lytic lesions that involve both inner and outer tables, as well as diple from which they arise; CT - hypodense, homogeneous enhancing lesions.

GIANT CELL TUMORS - involve sphenoid bone and commonly erode sellar region; CT - hypodense, contrast-enhancing masses.

METASTATIC NEPHEMATOMAS

a) osteoblastic - sclerosis and thickening (e.g. prostate, breast, bladder, hypernephroma).
b) osteoclastic - bone destruction and lucency (e.g. lung, uterus, GI tract, thyroid, melanoma, neuroblastoma).
c) combined (sclerotic and lytic) lesions - prostate, breast.

Metastases from breast carcinoma (lateral plain skull film) - numerous irregular lytic defects in cranial vault associated with large vascular grooves.

MRI - hypointense on T1, hyperintense on T2.

• some degree of contrast enhancement is common.

Brain and skull mts image review protocol:
 parenchymal - gadolinium MRAGE, FLAIR (not all mts enhance so FLAIR is even more sensitive; esp. for small mts calvarial - DWI (bright areas in the skull; vs. bone marrow abnormalities - will be diffuse signal along entire skull)

Bone scanning with Tc-99m – “hot” area of increased radioisotope uptake (OSTEOSARCOMA, OSTEOSARCOMA, MULTIPLE MYELOMA).

Arteriography - high vascularity (tumors of vascular origin, MULTIPLE MYELOMA); not helpful in diagnosis of other tumors.

Biopsy - paramount importance!

DIFFERENTIAL DIAGNOSIS

1. Encephalohcele, meningoencephalohcele

2. Venous lakes of skull, pacchionian depression

3. Fractures, surgical defects

4. Osteomyelitis, tuberculosis, sarcoidosis, syphilis

5. Hyperparathyroidism, osteoporosis, congenital hemolytic anemia

TREATMENT

No treatment is required for asymptomatic benign lesions unless diagnostic concerns exist!

1. Pain control (aspirin or NSAIDS for OSTEOSARCO)

2. Surgical excision:

a) benign tumors – for symptomatic relief, cosmetic reasons, or cranial nerve decompression.
b) malignant tumors – treatment of choice for cure (except MULTIPLE MYELOMA); if other means cannot control tumor expansion, surgery is still option in metastatic disease.

• complete en bloc resection is preferred (with extensive margins for malignant tumors).

• preoperative embolization is recommended for ANGIOSARCOMA (to reduce intraoperative blood loss).

• unresectable lesions → curettage, Gamma Knife and CyberKnife.

3. Radiotherapy - for some partially resected benign lesions with high recurrence rates (OSTEOSARCOMA, MULTIPLE MYELOMA, OSTEOSARCOMA, MULTIPLE MYELOMA).

Radiotherapy is primary treatment for secondary OSSIFYING FIBROMA (esp. in elderly patients), MULTIPLE MYELOMA (if chemotherapy fails).

• not indicated for OSSIFYING FIBROMA and ANGIOSARCOMA; use in CHONDROSARCOMA controversal.

4. Chemotherapy (combinations including EPIPLATIN, CYCLOPHOSPHAMIDE, CARMUSTINE, LOMUSTINE) – for OSSIFYING FIBROMA, OSSIFYING FIBROMA, MULTIPLE MYELOMA (first choice of treatment); efficacy in CHONDROSARCOMA unknown.

PROGNOSIS

Recurrence rates:

ASSYMETRICAL BONE CYST - 40-50%
ASSYMETRICAL BONE CYST - 20-30%
ASSYMETRICAL BONE CYST - 12-16%

5 yrs survival (cure): OSSIFYING FIBROMA 20-50%
CHONDROSARCOMA 10-year survival 30-80%
FIBROSARCOMA 10-year survival 40%
ERIDG SARCOMA 40-65%
ANGIOSARCOMA 50%
**Fibrous Dysplasia**

Benign FIBROUS LESIONS of bone:
1) fibrous dysplasia
2) osteofibrous dysplasia (ossifying fibroma)
3) nonossifying fibroma

**PATHOLOGY**

- Skeletal dysplasia - developmental anomaly (not true neoplasm) - normal bone formation arrested at woven stage → lamellar bone is not formed → typical overgrowth of fibrous tissue among woven bone; portions of the bone are replaced by fibrous connective tissue and poorly formed trabecular bone.
- Process originates in the medullary cavity.
- May occur in single (70-80%) or multiple (20-30%) bones (monostotic and polyostotic fibrous dysplasia).
- Polyostotic form is part of McCune-Albright syndrome see above.
- Any bone but is most common in proximal femur, tibia, ribs, and skull.

Characteristic thin, irregular (Chinese character-like) bony trabeculae and fibrotic marrow space:

**ETIOLOGY**

- Postzygotic (nonhereditary) mutation in guanine nucleotide stimulatory protein (GNAS1) gene.

**CLINICAL FEATURES**

- Most commonly presents in the teens or 20s.
- Most are asymptomatic.
- May cause painful swelling, repeated pathologic fractures or severe bone deformity (e.g. "shepherd’s crook" varus deformity of the proximal femur).

Mauricio Saravia, a Uruguayan artist:
**MAGING**

Plain radiographs - lytic lesion with a "ground glass" appearance, bone expansion, endosteal erosion, periostal reaction usually is absent (unless there is a pathologic fracture).

CT - "ground glass" - skull lucency with patches of increased density; multilobulated intradiploic lesion (can be confused with Paget disease, but occurs in younger age group); 3 different forms:

- **cystic form** - involves mainly outer table;
- **sclerotic form** - characterized by bone thickening;
- **mixed form** - manifests after third decade.

Fibrous dysplasia of orbit and ethmoid sinus (CT with bone windows).

**DIFFERENTIAL DIAGNOSIS**

1. Nonossifying fibroma
2. Unicameral bone cyst
3. Aneurysmal bone cyst
4. Chondromyxoid fibroma

**TREATMENT**

Symptomatic patients:
1) bisphosphonate therapy
2) curettage, bone grafting, and stabilization.

- autograft should not be used because it will be resorbed.

**PROGNOSIS**

- deformity of fibrous dysplasia progresses with skeletal growth → static after growth ceases (may be reactivated with pregnancy)
- often recurs after curettage and bone grafting.
• 0.5% fibrous dysplasia cases undergo malignant transformation (to osteosarcoma, chondrosarcoma, or fibrosarcoma).

SOLITARY PLASMACYTOMA / MULTIPLE MYELOMA

Plasmacytoma
- solitary benign neoplasm of monoclonal plasma cells.

Multiple Myeloma
- disseminated malignant form of plasmacytoma, potentially fatal.

• more often found in the vertebral column, thoracic cage, and long bones; involvement of the cranial vault is not infrequent.
  ▪ involvement of the skull base is a strong positive predictor for progression from solitary plasmacytoma to multiple myeloma.
  ▪ plasmacytoma affects patients in the late 5th decade; vs. MM occurs in the late 6th decade.

Pathology
• smooth and lobulated but can cause irregular destruction of the involved bone
• made up of abnormal plasma cells that produce monoclonal immunoglobulins.
• widespread osteolytic bone destruction by dense tumor cells that look like plasma cells clustered in close aggregates
• plasmacytomas may be of low (plasmacytic), intermediate, or high (plasmablastic) grade based on histologic findings.

Clinical Features
• cranial neuropathies may be caused by mass effect or direct infiltration with myelomatous cells.
• involvement of the orbit may result in exophthalmos or ophthalmoparesis.
• headaches of increased intracranial pressure.
• intradural extension may give rise to seizures.

Diagnosis
It is essential to perform both CT and MRI.
• thorough evaluation to exclude multiple myeloma (particularly if the lesion is at the skull base) - bone marrow evaluation, a skeletal survey, a bone scan, and serum and urine protein electrophoresis.

Plain radiography and CT
• multiple myeloma - well-defined lytic lesions involving the diploe and cortical bone, without a sclerotic border.
• isodense to hyperdense on CT
MRI
- Isointense to hyperintense on T1, markedly hypointense on T2.
- DWI: Plasmacytomas - restriction, whereas multiple myeloma - increased diffusion.
- Avid contrast enhancement.

Radioisotope bone scanning
- "Cold" lesion.
- Relatively high false-negative rate.

Angiography - tumor blush from ECA branch feeders.

TREATMENT
Solitary plasmacytomas → surgical resection → irradiation (plasmacytoma is a radiosensitive lesion).
- Tumors are often quite vascular - significant blood loss should be anticipated (preoperative embolization may be helpful).
- Indications for radiotherapy alone (after biopsy):
  a) Prohibitive medical comorbid conditions
  b) Lesions of the skull base

Multiple myeloma - not treated by surgical resection
- Chemotherapy with C-VAD (cyclophosphamide, vincristine, Adriamycin, and dexamethasone), along with stem cell transplantation and palliative irradiation, forms the mainstay of treatment.
- Median survival - 3 years (several months to 10 years).

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