Hemangioma, Aneurysmal Bone Cyst, Unicameral Bone Cyst, Giant Cell Tumor, & Langerhan’s Cell Histiocytosis

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Introduction

• Hemangioma, Aneurysmal Bone Cyst, Unicameral Bone Cyst, Giant Cell Tumor, Langerhan’s Cell Histiocytosis:
• What do they have in common?
  – They are at the end of the pathology books
  – Most are of undefined nature
• Impossible to treat in 15 minutes....

So what’s new ????
Hemangioma

- Hemangioma of bone
  - Benign, extremely common, seldom symptomatic, found in 10% of subjects on spine autopsy
  - Any age, peak in the 50, slightly more female
  - Vertebra > skull > long bones > Others
  - Capillary, venous, cavernous, sclerotic hemangioma, or angiomatosis
  - Made from well formed mature vessels of different calibers
  - Positive for vascular markers (CD31, CD34, ERG & FLI-1)
  - Usually not to be biopsied or resected

_Vascular bone tumors: a proposal of a classification based on clinicopathological, radiographic and genetic features._
Hemangioma

- Hemangioma of bone
  - Some are painful
    - To distinguish from usual back pain
    - Embolization
    - Cementoplasty
  - Some look not like hemangiomas
    - Biopsy
    - Embolization
    - Cementoplasty
- Surgery exceptionally
  - Decompression
  - Osteosynthesis (Fracture)
Hemangioma

- Epithelioid hemangioma
  - Occasional bone destruction with soft tissue involvement
  - Locally aggressive, 10% local recurrence rate, 3% lymph node involvement. No distant metastases.
  - Male slightly > female, young adult
  - Capillary or venous sized vessels lined by epithelioid endothelial cells.
  - Positive for vascular markers (CD31, CD34, ERG, FLI-1) ± Keratin, EMA.
  - To be differentiated from epithelioid hemangioendothelioma (malignant with a specific translocation WWTR1/CAMTA1 in FISH)
  - Surgical treatment is endolesional excision after embolization or resection

Epithelioid hemangioma of bone and soft tissue: a reappraisal of a controversial entity
Unicameral Bone Cyst

• WHO 2013 :
  – Simple bone cyst or unicameral bone cyst (UBC) are lytic benign bone lesions, of undetermined nature.
  – Intramedullary cavity filled with serous or sero-sanguineous fluid, usually unilocular
  – UBC can involve all skeleton but usually the long bone metaphysis and primarily proximal humerus and femur
  – Unique

• Pathogenesis
  – More a dysplastic lesion than a real tumor
  – Impairment of venous blood circulation in cancellous bone
  – Bone resorption by increased blood pressure and high concentration of inflammatory proteins

• Epidemiology
  – Very frequent, male predominance
  – 85% of patients are aged 10 to 20
Unicameral Bone Cyst

- Clinical presentation
  - Often asymptomatic
    - X-ray for other reason (Trauma, spine)
  - Pathological fracture
    - The most frequent
  - Pain, limping
    - Fissuring of the cyst
Unicameral Bone Cyst

• Imaging:
  – Nothing new....
  – Usually characteristic
  – The fallen fragment sign
  – The rising bubble sign
  – Cystography

  – But some look like ABC
Unicameral Bone Cyst

• Diagnosis:
  – Macroscopy
    • Usually characteristic
    • More difficult if fractured

  – Histology
    • Characteristic if a whitish membrane is found on curettage
    • Difficult in fractured UBC, showing aneurysmal changes
Unicameral Bone Cyst

• Prognosis
  – Spontaneous involution in adult
  – No malignant degeneration
  – Growth disturbance is rare
  – Fractures
    • Femoral neck (risk of necrosis)
    • In young children
    • If close to the physis, multi-locular
    • CT : evaluation of cortex thickness
Unicameral Bone Cyst

• Surveillance
  – In asymptomatic cases with no risk of fracture

• Treatment:
  – Nothing will be effective in 100% of cases
  – Choose the less aggressive and less expensive methods
  – Corticosteroid injections: “an old trick that still works”

Unicameral Bone Cyst

• Methyl prednisolone injection
Unicameral Bone Cyst

- Surgery: when there is a risk of fracture......
Unicameral Bone Cyst

• Surgery:
  - Curetage, perforation, filling with bone substitute
  - Osteosynthesis according to localization and age
Aneurysmal Bone Cyst

• WHO 2013 : Benign bone lesion of undetermined neoplastic nature, locally aggressive

• There are several types of ABC :
  – The primitive ABC, or classic ABC :
    • Expansive and hemorrhagic tumor
    • Formerly considered as a reactive lesion
    • It is a true neoplastic lesion with a characteristic translocation (USP6 rearrangement in chromosome 17)
    • The diagnosis must be assessed by a biopsy because a telangiectatic sarcoma can mimic an ABC (no USP6 rearrangement)
Aneurysmal Bone Cyst

– The secondary ABC
  • Represents 30% of ABC and has no translocation.
  • It is developed in reaction to another lesion, usually benign to be looked for on imaging for biopsy
  • GCT, chondroblastoma, osteoblastoma, fibrous dysplasia....
  • It should be called with the name of the lesion (for example GCT with aneurysmal changes)

– The solid ABC or giant cell reparative granuloma
  • Perhaps a healing classic ABC

– Soft tissue ABC
  • Rare, characteristic USP6 translocation


Aneurysmal Bone Cyst

• Epidemiology
  – Quite rare (1.4 /1 000 000 per year)
  – Most patients are 10 to 20 year old
  – Rare after 30 and exceptional after 50
  – Usually unique

• Localization
  – Long bones (67%), distal femur > tibia > humerus > fibula
  – Spine (15%): posterior arch, lumbar > cervical > thoracic
  – Pelvis (9%).
  – Others bones...
Aneurysmal Bone Cyst

— Clinical presentation
  • Pain
  • Swelling
  • Rarely pathologic fracture
  • Spine
    — Wry neck
    — Stiff and painful scoliosis
    — Neurologic symptoms
Aneurysmal Bone Cyst

- Imaging: X-ray
  - ABC are metaphysal, excentrated, bulging, containing liquid
  - May develop in all bones of the skeleton
  - Apparent multiple septa
  - ABC could be aggressive lesions with a risk of bone destruction.
Aneurysmal Bone Cyst

• Imaging
  – In MRI, the liquid level image is usual on axial in T2 sequence after rest of the patient
  – Septa appear enhanced by gadolinium injection
  – Characteristic in case of multiple fluid levels filling completely the lesion
Aneurysmal Bone Cyst

- Solid component in the tumor?
- MRI, cystography
Aneurysmal Bone Cyst

• Biopsy
  – Mandatory to eliminate a telangiectatic sarcoma or an associated tumor (oriented by imaging)
  – Percutaneous (Core biopsy) or preferably surgical
  – « curopsy »
  – Supposed to formally differentiate ABC and UBC ...
    • Blood on aspiration could be a bleeding UBC
    • Histology is very difficult in case of fractured UBC (showing aneurysmal changes)
  – In spine could be very hemorrhagic (embolization ?)
Aneurysmal Bone Cyst

• Histopathology
  – Blood filled spaces with no endothelium, no muscular or elastic fibers
  – Connective tissue septa with osteoclast-like giant cells and reactive woven bone
  – Characteristic fibrochondroid matrix, deeply calcified and blue

Aneurysmal Bone Cyst

- Differential diagnosis: unicameral bone cyst
  - Same population, same localization, same X ray....
  - Curopsy could be useful
Aneurysmal Bone Cyst

- **Telangiectatic osteosarcoma**
  - Biopsy is mandatory
  - Very confusing
  - Atypical cells and mitoses
  - Irregular osteoid matrix
  - No USP6 mutation
Aneurysmal Bone Cyst

• Differential diagnosis: giant cell tumor
  – Exceptional in children
  – More epiphyso metaphysyal
  – High expression of P63 and H3F3 A mutation
  – Possibly associated

7 y ≠ GCT

ABC or GCT ?
Aneurysmal Bone Cyst

• Evolution
  – 3 groups of variable evolution:
    • Quiet, active and aggressive
  – No malignant transformation (excepted after radiotherapy)
  – Some will heal spontaneously
  – Possible growth disturbance or severe bone destruction
  – Need for quick diagnosis and therapy
Aneurysmal Bone Cyst

• Treatment
  – Observation
    • After biopsy (4 to 8 weeks)
    • If the diagnosis is certain
    • Not potentially complicated lesions (spine, or fracture)
    • Spontaneous healing is possible....
  – Other treatments
    • 15 to 44 % local recurrence
    • Less aggressive techniques if possible
Aneurysmal Bone Cyst

• Treatment
  – Methyl prednisolone injection
    • Contra indicated = possible stimulation of the lesion
  – Radiotherapy
    • It works....
    • Risk of malignant transformation
    • Contra indicated (excepted in some inoperable spine tumors)


– Selective embolization
  • In spine & sacral lesions curative (alone) or preoperatively


Aneurysmal Bone Cyst

- **Treatment**
  - Intra lesional injections
    - Demineralized bone matrix, calcitonin, bone substitutes, bone marrow etc.....
    - Nothing widely accepted and proven
  - Doxycyclin
    - Many injection (up to 10) could be necessary
    - Useful in ABC close to physis, spinal cord, nerves

_Percutaneous Doxycycline Treatment of Juxtaphyseal Aneurysmal Bone Cyst._
Aneurysmal Bone Cyst

- Treatment
  - Intralesional sclerotherapy
    - Ethibloc®
      - 70 à 94% healing but no more available
    - Polidocanol (Aetoxysclérol®)
      - 3 injections in average
      - Same efficiency than intralesional surgery with adjuvants
      - Less complications than Ethibloc®
    - Sclerotherapy with alcohol
      - Few complications, efficient, simple and cheap
      - Possible in sacrum
      - 1 to 4 injections, 10% failures


Aneurysmal Bone Cyst

- Alcohol sclerotherapy
Aneurysmal Bone Cyst

• Alcohol sclerotherapy
  
  – Pr Brunelle. Necker hospital, Paris
Aneurysmal Bone Cyst

• Treatment
  – Cryoablation
    • Per cutaneous, interventional radiology
    • Spine lesions
    • Cementoplasty after cryoablation
    • Or cryoablation after selective embolization


Aneurysmal Bone Cyst

• Medical treatment
  – Zolendronic acid
  – Denosumab

– In spine and sacral lesions: can avoid dangerous surgery
– In case of recurrence after treatment
– Still in evaluation but definitive healing published (≠ GCT)
Aneurysmal Bone Cyst

- Treatment: Is there still a place for surgery?
  - Large resection
    • Few local recurrence
    • Complications not justified in a benign condition
  - Marginal or subperiosteal resection
    • In very aggressive lesions?
    • Less recurrences than curettage...
    • After failure of sclerotherapy
  - Curettage ???
    • If curopsy
    • Otherwise better to do sclerotherapy (Polidocanol or alcohol)
  - Large spinal and sacral lesions: Denosumab or surgery in case of fracture after pre operative embolization.

Aneurysmal Bone Cyst
Aneurysmal Bone Cyst

• Acute paraplegia in a pregnant woman:
  – Ceasarean section
  – Decompression + fixation in emergency
  – Denosumab post operatively
Giant Cell Tumor

- WHO 2013: Benign bone tumor, locally aggressive
  - Less than 2% become malignant and some gives lung mets
- Relatively frequent
  - 5% of all bone tumor and 20% of all benign bone tumors (but 20% of all bone tumors in India and China)
- Arises in patient with closed physis
  - Very rare in children
  - Developed from the metaphyseal side of the growth cartilage then comes to the epiphysis
  - Distal femur, proximal tibia, pelvis, proximal humerus, sacrum, distal radius (very rare in skull scapula & diaphysis)
Giant Cell Tumor

- Pathogenesis remains unclear
  - Reactive response to vascular insufficiency: deep hypoxia and acute hemorrhage
  - Stimulation of osteoblast-like cells, monocytes recruitment and osteoclast differentiation then inducing tumor formation.
  - High percentage of GCT cells have chromosomal changes (without loss of genetic material)
  - GCT with complex clonal karyotypes have highest risk for aggressive behavior
Giant Cell Tumor

• Clinical features
  – Pain, pathological fracture, swelling
  – Young adult

• Radiology
  – Lytic bone lesion, usually characteristic
  – Growing to the epiphysis
  – To differentiate from other epiphyseal lesions
    • Chondroblastoma
    • Clear cell chondrosarcoma
    • Subchondral degenerative cysts

• Biopsy is mandatory
Giant Cell Tumor

• Histology:
  – Mononuclear cell proliferation of primitive mesenchymal stromal cells
  – RANKL expression in tumor cells
  – Macrophages and osteoclastic giant cells
  – P63 expression
Giant Cell Tumor

• New diagnostic tool
  – Molecular biology: Histone 3.3 mutation
  – H3F3 A gene in osteoblastic tumors
    • GCT (49/53 = 92 %) => Mutations G34W/L
  – H3F3 B gene in cartilaginous tumors
    • Chondroblastoma (73/77 = 95 %) => Mutations K36M
  – No H3F3 mutation in Chondromyxoid fibroma and chordoma

Giant Cell Tumor

• Prognosis
  – Local recurrence in 10 to 30%
  – Lung metastases or implants
    • In 2%, 3-4 years after diagnosis
    • Mainly with distal radius
    • CGT with intravascular growth or emboli
    • Some will disappear, some will kill the patient
  – Malignant transformation
    • After radiotherapy
    • Role of denosumab?
    • Or misdiagnosis (giant cell osteosarcoma, malignant GCT)?
Giant Cell Tumor

• Local treatment
  – Surgery
    • Aggressive curettage, high speed burr, pulsed lavage
    • Adjuvant therapy have no proven efficiency (phenol, liquid nitrogen, argon laser)
    • Thermic effect of PMMA cement used in filling
    • Osteosynthesis only if needed
    • En bloc resection in recurrent lesions or expendable bones such as rib, fibula, iliac wing)
  – Radiation therapy
    • In some spinal recurrent lesions ?

• Resection of lungs mets
Giant Cell Tumor

- **Medical therapy**
  - Based on the TCG biology (RANKL activation of osteoclasts)
  - Osteoclasts Inhibition
    - Diphosphonates (Zometa)
    - Anti RANKL antibody = Denosumab
  - Indication for Denozumab to be discussed in MDT
    - When surgical treatment is not possible
    - When surgical treatment would be mutilating
    - In metastatic GC tumor
    - Locally aggressive and recurrent tumors (very effective)
    - With Ca and D Vitamin supplementation, Phosphorus and Ca Monitoring, and dental panoramic radiograph

Giant cell tumors of the spine: has denosumab changed the treatment paradigm?

GSF-Geto Groupos recommandations (Chevreau C, Dumaine V, Brouchet A, Missenard G) 2016
Giant Cell Tumor

- Many concerns with Denosumab
  - Recurrence after end of treatment
  - When to stop?
  - General complications
  - Difficult to perform a curettage after Denosumab
  - Could help to perform en bloc resection?
  - Induction of malignant transformation?
  - Some teams are already using it less

Langerhan’s Cell Histiocytosis

• It is known that:
  – Letterer-Siwe disease (multi organ involvement)
  – Hand-Schüller-Christian (rash, bone lysis, diabetes insipidus)
  – Eosinophilic granuloma
  – Have the same histology: histiocytosis X (Lichtenstein 1953)
  – Have common features with the epidermal Langerhans cells as the Birbeck granules in electron microscopy: Langerhan’s cell histiocytosis

• Histiocytosis X or Langerhans Cell Histiocytosis (LCH) is characterized by a proliferation in various tissues of dendritic cells of Langerhans type expressing several phenotypic markers including CD1a and protein S100.
Langerhan’s Cell Histiocytosis

• Formerly considered as a reactive process

• Now considered as a neoplastic proliferation
  – Recurrent BRAF (V600E) mutations are found in 60% of LCH (also found in melanoma)
  – The LCH is due to a mutation in a myeloid precursor cell. The more immature the cell at time of the mutation, the greater chance for a more extensive disease: « Misguided myeloid differentiation hypothesis »

BRAF and MAP2K1 mutations in Langerhans cell histiocytosis: a study of 50 cases.
Langerhan’s Cell Histiocytosis

• Epidemiology
  – LCH affects 4 to 8 children per million and 1 to 2 adults per million each year
  – Less cases in black, more in Hispanic population
  – Higher risk of LCH in poor socio-economic circumstances and in crowded conditions
  – Most are diagnosed between September and February (Sweden)
Langerhan’s Cell Histiocytosis

• Clinical presentation
  – Highly variable from a self-healing bone lesion to a severe life-threatening multi-organ disease with 10 to 20% mortality.
  – In children the organs that are frequently involved are: firstly bone (75%), then skin (34%), lymph nodes, mastoids and ears, bone marrow, spleen and liver, lung, post-pituitary (diabetes insipidus) and lastly the gastro-intestinal tract.
  – In adults bone and lung (mainly in smokers)

• Different risk groups:
  – Low risk: Skin and bone (and lung)
  – High risk: Risk organs (spleen, liver, bone marrow)
  – Central nervous system: LCH neurodegenerative disease
Langerhan’s Cell Histiocytosis

• Orthopedic lesions
  – Pain, soft tissue mass, pathologic fracture (Vertebra plana)
  – Lytic bone lesions (Skull, femur, maxillary, pelvis, ribs...)
  – May mimic malignant bone tumors
  – Biopsy is mandatory (at the first onset)

Ewing sarcoma
Langerhan’s Cell Histiocytosis

• Initial Staging: patient referral
  – Pediatric oncology team
  – Specialized adult department (national experts)
  – Physical examination
    • Skin, mucosae, lung, spleen and liver
  – Laboratory
    • Complete blood cell count, liver function tests
    • Bone marrow biopsy and aspiration in young patients
  – Imaging
    • Skeletal survey or PET
    • CT of the head
    • MRI of the brain in case of neurologic involvement
Langerhan’s Cell Histiocytosis

• Treatment
  – Stratified on the extent of the disease.
  – MDT discussion (national experts)
  – Single system diseases in which the prognostic is usually excellent, require a minimal treatment (either no treatment or only local therapy)
  – The multi-organ diseases are usually treated with chemotherapy (weekly Vinblastine and steroids)
  – Mutation-specific targeted therapy is in development (BRAF inhibitors in tumors with mutation)
Langerhan’s Cell Histiocytosis

• Local treatment
  – Sometimes biopsy is sufficient
  – No surgical treatment in mechanically solid lesions (with chemotherapy) or vertebra plana
Langerhan’s Cell Histiocytosis

• Local treatment
  – Steroids injection
  – Curettage with or without grafting
  – Osteosynthesis
  – No radiation therapy
Conclusion

• In many of these lesions why do surgery?
  – Medical treatments and interventional radiology have so much progressed that surgery could be avoided in many of the above conditions....
  – Surgical complications could be devastating for the patient (and the surgeon...)

• Even in benign condition the approach becomes multidisciplinary
Conclusion

• What would you prefer for your child?