Bone pathology, soft tissue tumors

Zoltán Sápi MD, PhD
1st Department of Pathology and Experimental Cancer Research
Non-neoplastic or metabolic disease

**Hyperparathyroidism:** parathyroid glands produce excess parathyroid hormone, resulting in elevated levels of calcium associated with "leaching" calcium from the bones.
Only 25% have bone disease, usually bone pain
Presents in young to middle-aged adults with recurring kidney stones, peptic ulcer, vomiting, weakness, headaches
Affects entire skeleton, cortical bone more than medullary bone
Usually detected early, so osteitis fibrosa cystica (severe changes, also called Recklinghausen’s disease) are rare
Skeletal abnormalities with secondary hyperparathyroidism are typically mild

**Causes:** parathyroid adenoma; rarely carcinoma or hyperplasia

**Laboratory:** marked hypercalcemia and hypophosphatemia

**Gross:** thin bone cortices, rarely associated with brown tumor of hyperparathyroidism

**Micro:** increased osteoclastic activity with tunneling of osteoclasts into bone matrix (dissecting resorption)
Achondroplasia

An inherited disorder in which there is reduced proliferation of the chondrocytes in the epiphyseal plate of long bones. The result is a form of dwarfism in which the trunk is of normal length, but the extremities are short.

Normal mental ability.

Fibroblast growth factor receptor 3 (FGFR3) has a negative regulatory effect on bone growth. **Activating point mutation of FGFR3.** 4 out of 5 are new spontaneous mutations.
Osteogenesis imperfecta
One of the most common congenital connective tissue matrix diseases
Disease of type I collagen due to mutations in genes coding for alpha 1-2 collagen chains, usually autosomal dominant
A type of osteoporosis with marked cortical thinning and attenuation of trabeculae
Skeletal abnormalities may be mild or severe associated with short stature and increased fractures
Blue sclera: due to translucent sclera and visualization of choroid
Hearing loss: due to abnormalities of middle ear bones
Dental imperfections: small, misshapen, blue-yellow teeth, due to dentin deficiency
Paget’s disease
Also called osteitis deformans
Late-onset disorder (90% are over age 55) characterised by focal areas of increased bone turnover containing enlarged hyperactive osteoclasts.
“Collage of matrix madness”, with furious osteoclastic bone resorption (osteolytic phase), hectic bone formation (mixed osteoclastic/osteoblastic phase), burnt-out osteosclerotic stage (gain in bone mass, but bone is disordered)
Symptoms: often mild; localized pain due to microfractures and nerve compression
Associated neoplasms: sarcoma (5% with severe polyostotic disease), giant cell tumor
Micro: diagnostic features are increased osteoclastic and osteoblastic activity; primarily woven bone; focal mosaic pattern of lamellar bone, osteoclasts may have up to 100 nuclei
# Bone Tumors

## WHO classification

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Osteoid osteoma
Rare; benign tumor, nidus measures 1.5-2.0 cm or less
75% under age 25; 2/3 male; 50% in femur/tibia;
Intense localized pain, particularly at night, due to production of prostaglandin E2 or nerve fibers in reactive zone; pain relieved dramatically by aspirin
Xray: small, round lucency with variable mineralization surrounded by extensive sclerosis
Micro: central nidus is sharply circumscribed, anastomosing bony trabeculae with variable mineralization, plump osteoblasts, vascularized connective tissue
Treatment: CT localization of nidus and excision or radiofrequency ablation; recurrence is unusual
Osteosarcoma
Most common primary bone tumor after myeloma

**Definition:** malignant bone tumor that **produces osteoid directly from tumor cells and unconnected with cartilage**

60% male; usually ages 10-25 years, associated with Paget’s disease after age 40
Not associated with trauma, although trauma may lead to discovery of tumor

**Sites:** metaphysis of long bones

**Xray:** large, destructive, lytic or blastic mass with permeative margins

**Codman's triangle:** shadow between cortex and raised ends of periosteum (due to reactive bone formation), non-specific

**Sites of metastasis:** lung (98%, 20-80% at diagnosis)

**Note:** excision of metastatic lung nodules may prolong survival

**5 year survival:** 70%

**Treatment:** preoperative chemotherapy is helpful to spare limbs

**Micro:** high grade spindle cell tumor that produces osteoid matrix
Chondroma
Benign cartilaginous tumor
Either enchondroma (arise from diaphyseal medullary cavity), subperiosteal/juxtacortical chondroma or soft tissue chondroma
Usually asymptomatic or pain due to pathologic fracture
Age 20-49 years, no gender preference; may be due to displaced growth plate
**Sites:** small bones of hands and feet; 70% solitary; 30% multiple
**Molecular:** 12q13-15 (HMGA2 / HMGI-C)
**Maffuci’s syndrome:** multiple enchondromas and soft tissue hemangiomas;
**Ollier’s disease:** nonhereditary disease of multiple enchondromas of long bones and flat bones
**Treatment:** excision, may recur if incompletely excised; often leave alone
Chondrosarcoma
Malignant cartilage forming tumor that does not produce osteoid
May arise from osteochondroma
Third most common bone malignancy after myeloma and osteosarcoma
Usually ages 30-60 years, 75% males
Often large painful tumors of long bones or ribs that grow rapidly
**Grading:** based on cellularity and nuclear changes in chondrocytes; well, moderate or poorly differentiated correspond to grades 1-3
**Prognostic features:** grading important for 5 year survival: well differentiated-78%, moderate-53%, poorly differentiated-22%
**Gross:** pearly white or light blue, often with focal calcification
**Micro:** tumor cells produce cartilaginous matrix, may have only minor or focal atypia, but consider malignant if malignant radiologic features
Giant cell tumour of bone

**Definition**
Giant cell tumour of bone is a benign, locally aggressive neoplasm which is composed of sheets of neoplastic ovoid mononuclear cells interspersed with uniformly distributed, large osteoclast-like giant cells.

**Clinical feature**
- 4-5% primary bone tumors
- peak: 20-45 years
- very rare below 10 years
- female predominance (slight)
- end of long bones – typical
- 5% flat bones
- pain, swelling, lim. joint movement
- path. fracture: 5-10%
Imaging/macro

expanding, eccentric, lytic area

epiphysis and adjacent metaphysis

well-defined margin with sclerosis
well-defined margin without sclerosis
ill defined margin with cort. destr.

soft and reddish brown

blood filled spaces
GCTB with benign histological appearance: sheets of mononuclear cells admixed with numerous osteoclastic giant cells

Metastasizing GCTB: the same as above, but distant metastasis

Malignancy in GCTB: a sarcoma appears at the site of previously documented GCTB; progression in the same tumor

Malignant GCTB/giant-cell rich MFH: a high grade sarcoma arises within the GCTB
Ewing’s sarcoma / primitive neuroectodermal tumor (PNET)

Terms usually used interchangeably; some suggest to call PNET if neural morphologically or a soft tissue tumor and Ewing’s if undifferentiated or a bone tumor

#2 bone sarcoma in children
May present with pain, fever, weight loss, leukocytosis and increased erythrocyte sedimentation rate mimicking osteomyelitis

Sites: marrow of femur, tibia, humerus, fibula, pelvis, ribs, vertebra

Xray: destructive, lytic tumor with reactive periosteal bone resembling onion skin

Treatment: preoperative chemotherapy, surgery, radiation therapy

5 year survival: 75%; 50% are cured; metastases to lung, skull, pleura

Poor prognostic factors: high stage, direct extension into soft tissue, aneuploidy

Molecular: t(11,22)(q24;q12)
22q12 is EWS, a transcription factor;
11q24 is FL-1;
EWS-FL1 is a transactivator of the c-myc promoter
Micro: sheets of small, round, uniform cells 10-15 microns with scant clear cytoplasm, divided into irregular lobules by fibrous strands; indistinct cell membranes; round nuclei with indentations, small nucleoli
SOFT TISSUE TUMORS (GENERAL)

* LARGE AND HETEROGENEOUS GROUP (MORE THAN 200 ENTITY)
* CLASSIFIED ACCORDING TO A HISTOGENETIC CONCEPT (E.G. FIBROSARCOMA FROM FIBROBLAST)
* PRIMITIVE MULTIPOTENTIAL MESENCHYMAL CELLS --> DIFFERENTIATION ALONG ONE OR MORE LINES
* INCISIONAL BIOPSY OR FNA (INITIAL DIAGNOSIS)
* LIGHT MICROSCOPIC EVALUATION (H&E), ANCILLARY TECHNIQUES
SOFT TISSUE TUMORS

BENIGN: WELL CIRCUMSCRIBED (PUSHING BORDER), UNIFORM CELL MORPHOLOGY, RARE MITOSES, NO RECURRENCE AFTER REMOVAL, METASTASIZING POTENTIAL

INTERMEDIATE MALIGNANCY: INFILTRATIVE GROWTH PATTERN, MONOMORPH CELL MORPHOLOGY, RARE MITOSES FREQUENT RECURRENCE AFTER REMOVAL, NO METASTASIZING POTENTIAL
MALIGNANT: INFILTRATIVE GROWTH PATTERN, ATYPICAL-POLYMORPHIC TUMOR CELLS, FREQUENT MITOSES, FREQUENT RECURRENCE, METASTASIZING POTENTIAL

BORDERLINE: UNABLE TO DETERMINE WHETHER THE TUMOR IS BENIGN OR MALIGNANT BY MORPHOLOGY AND/OR PROGNOSTIC FACTORS
SOFT TISSUE TUMORS, ANCILLARY TECHNIQUES

* ELECTRON MICROSCOPY
* IMMUNOHISTO- OR CYTOCHEMISTRY
* CYTOGENETICS
* DNA PLOIDY
* PROGNOSTIC FACTORS (P-53, MDM-2, CDK4, Her2, etc.)
SOFT TISSUE TUMORS; THERAPY

* Small clearly benign STT (on clinical grounds) can be removed directly with a rim of uninvolved normal tissue
* If the tumor is benign by FNA, can be safely enucleated („shelling out” the tumor)
* If the tumor is intermediate and/or low grade malignant by FNA, a wide excision is recommended (often myectomy!), because of the existance of microsatellite tumor tissue
* If the tumor is high grade malignant by FNA, a combination of surgery, radiation therapy and multidrug chemotherapy is necessary
TUMORS AND TUMORLIKE LESIONS OF FIBROUS TISSUE

BENIGN: FIBROMA
  NODULAR FASCIITIS
  ELASTOFIBROMA
  NASOPHARINGEAL FIBROMA
  KELOID
  FIBROMATOSIS COLLI
  INFANTILE DIGITAL FIBROMATOSIS
  FIBROMATOSESES, SUPERFICIAL AND DEEP

MALIGNANT: FIBROSARCOMA

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ELASTOFIBROMA

* POORLY CIRCUMSCRIBED TUMOR OF SUBSCAPULAR REGION

* MAINLY SPORADIC BUT FAMILIAL CASES HAVE BEEN DESCRIBED

* COLLAGEN BUNDLES ALTERNATE WITH DEGENERATED ELASTIC FIBERS

* NOT TRUE NEOPLASM BUT RATHER REACTIVE HYPERPLASIA INVOLVING ABNORMAL ELASTOGENESIS

* ORCEIN STAIN
NODULAR FASCIITIS

- SUBCUTANEOUS PSEUDOSARCOMATOUS TUMOR

* YOUNG ADULTS

* UPPER EXTREMITIES, TRUNK AND NECK

* HISTORY OF RAPID GROWTH (USUALLY A FEW WEEKS)

* SMALL SIZE

* CELLULAR SPINDLE-CELL GROWTH SET IN A LOOSELY TEXTURED MUCOID MATRIX
FIBROMATOSSES

* PROLIFERATION OF WELL-DIFFERENTIATED FIBROBLASTS, MYFIBROBLASTS

* INFILTRATIV GROWTH PATTERN

* LACK OF CYTOLOGIC FEATURES OF MALIGNANCY, SCANTY MITOSIS

* OFTEN ARISE IN MUSCULAR FASCIA

* FREQUENT LOCAL RECURRENCE BUT NO METASTASIZING POTENTIAL

* PROMPT RADICAL EXCISION WITH A WIDE MARGIN OF INVOLVED TISSUE
FIBROSARCOMA

* CELLULAR, FIBROBLASTIC SPINDLE CELL PROLIFERATION WITH A LOT OF MITOSES

* DIAGNOSIS OF EXCLUSION (NO SPECIAL IMMUNOSTAINING)

* MAY BE CONGENITAL; ARISE FROM SUPERFICIAL AND DEEP CONNECTIVE TISSUES
FIBROHISTIOCYTIC TUMORS

BENIGN: FIBROUS HISTIOCYTOMA (DERMATOFIBROMA)
JUVENILE XANTHOGRANULOMA

INTERMEDIATE:
DERMATOFIBROSARCOMA PROTUBERANS

MALIGNANT:
MALIGNANT FIBROUS HISTIOCYTOMA (MFH)
- myxoid
- giant cell
- inflammatory
- storiform-pleomorphic

2013.04.25.
**FIBROUS HISTIOCYTOMA (DERMATOFIBROMA)**

* VERY COMMON
* VARIABLE MIXTURE OF FIBROBLASTIC AND HISTIOCYTE-LIKE CELLS (FOAMY, MULTINUCLEATED CELLS)
* MAINLY SUBCUTANEUS
**DEMATOFIBROSARCOMA PROTUBERANS**

* TYPICAL STORIFORM PATTERN, HIGH CELLULARITY

* LOCAL AGGRESSIVENESS (HIGH TENDENCY FOR LOCAL RECURRENCE)

* VERY RARELY TURNS TO FIBROSARCOMA DURING RECURRENCE

hard bumps over the skin; flesh-colored
MALIGNANT FIBROUS HISTIOCYTOMA

* MOST COMMON TYPE OF SOFT TISSUE SARCOMA

* HIGHLY PLEOMORPHIC TUMOR CELLS, STORIFORM GROWTH PATTERN

* VIMENTIN AND CD-68 POSITIVITY OF TUMOR CELLS

* LOCAL RECURRENCE AND CAPACITY TO METASTASIZE TO DISTANT SITES
vimentin
TUMORS OF ADIPOSE TISSUE

BENIGN: LIPOMA
   ANGIOMYOLIPOMA
   MYELOLIPOPM
   HIBERNOMA

MALIGNANT: LIPOSARCOMA
   - Well-differentiated
   - Myxoid
   - Round-cell
   - Pleomorphic
LIPOMA

* BENIGN FATTY TUMOR WHICH CAN ARISE IN ANY LOCATION, VERY COMMON

* MAINLY SUPERFICIAL RARELY DEEP-SEATED

* OFTEN GROW TO A LARGE SIZE AND ARE USUALLY ENCAPSULATED

* MAY BE SINGLE OF MULTIPLE

* MATURE FATTY TISSUE; OFTEN MIXED WITH VESSELS, SMOOTH MUSCLE (ANGIOMYOLIPOMA IN KIDNEY)

* CHROMOSOMAL ABBERATION OF 12q, 6p BUT NOT RING OR GIANT CHROMOSOMES
LIPOSARCOMA

* SECOND MOST FREQUENT SOFT TISSUE SARCOMA IN ADULTS
* USUALLY LARGE AND OCCUR MOST FREQUENTLY IN THE LOWER EXTREMITIES
* DIFFERENT SUBTYPES BUT THE CLUE IS THE LIPOBLAST
* MYXOID LIPOSARCOMA: $t(12;16)(q13;p11)$
Different lipoblasts
RHABDOMYOMA

* ADULT TYPE (IN THE ORAL CAVITY), FETAL FORM (HEAD AND NECK AREA AND HEART) AND GENITAL TYPE (VULVOVAGINAL REGION); VERY RARE

* WELL DIFFERENTIATED LARGE, ROUNDED OR POLYGONAL TUMOR CELLS WITH ABUNDANT ACIDOPHILIC CYTOPLASM; CROSS STRIATION

Rhabdomyoma in a 3-month-old boy with tachycardia.
RHABDOMYOSARCOMA

* MOST FREQUENT SOFT TISSUE SARCOMA OF CHILDHOOD
* HEAD AND NECK REGION, RETROPERITONEUM, UROGENITAL TRACKT
* SPINDLE OR PLEOMORPHIC TUMOR CELLS WITH EOSINOPHILIC CYTOPLASM AND WITH CROSS STRIATION
* ALVEOLAR TYPE: t(2;13)(q35;q14) VERY POOR PROGNOSIS
* OTHER TYPES: GOOD RESPONSE FOR THERAPY
**Synovial sarcoma**

Usually a deep seated mass present for years around large joints (80% in knee and ankle) in young adults (age 20-40); only 10% actually involve the joint.

Represent 10% of adult soft-tissue tumors.

5 year survival is 50-70%; 10 year survival 40%; recurs locally, 10-15% metastasize to lung and pleura, bone, regional nodes.

**Treatment:** wide local excision plus radiation.

**Gross:** well circumscribed, firm, gray-pink; focal calcifications on X-ray.

**Micro:** biphasic or monophasic or undifferentiated;

Spindle cells are arranged in plump fascicles; biphasic have spindle cells and plump epithelial cells forming glands/cords.
**Genetic findings**

- **t(X;18)(p11.2;q11.2)**
- SYT on chromosome 18
- SSX1, SSX2, and SSX4 on chromosome X
- SYT-SSX chimeric protein

**Oncogenic effect**

[Images of genetic findings and cytology]
Prognostic factors

**Low risk for metastasis**
- Patient age < 25 years
- Tumor size < 5cm
- Absence of poorly diff. areas

**High risk for metastasis**
- Patient age > 25 years
- Tumor size > 5cm
- Poorly diff. areas

Heavily calcified sc.
Mono-biphasic type
Extensive tu. necrosis
High MI (> 10 m/10 HPF)
Aneuploidy
Increased apoptotic index
p53 mutation
SYT/SSX2 fusion transcript
YB-1 protein (P-glycopr.)
p27 low expression

Her-2 over-expression → better pr.
A doctor is likely to call for a muscle biopsy after looking at preliminary blood tests, performing an electromyogram (EMG) and physical examination, and determining that the patient’s symptoms indicate an underlying neuromuscular disorder. The muscle biopsy can help distinguish between muscular and neurological problems and can help pinpoint the exact neuromuscular disorder present.

A muscle biopsy is a surgical procedure in which one or more small pieces of muscle tissue are removed for further microscopic or biochemical examination. The procedure, often used in the diagnosis of a neuromuscular disorder, is considered „minor” surgery and is usually performed under local anesthetic.
SPINAL MUSCULAR ATROPHY

H&E stain

ATPase pH 9.4 stain

Grouped atrophy
Small muscle fibers are often rounded
Pyknotic nuclear clumps are not present.
Large muscle fibers are hypertrophied.

Large fibers are hypertrophied and type 1.
Small fibers are type 1 and 2.
Dermatomyositis (DM): DM is an auto immune muscle disease which occurs in children and adults. The cardinal sign of this disorder is the presence of a rash commonly over the upper chest and back or shoulders. Occasionally, a purplish (heliotrope) discoloration is present over the eyelids. Along with the rash, muscle weakness in the hips and shoulders is noted. The disease develops over weeks to months. The cause is unknown but involves inflammation of the blood vessels in the skin and muscle. Diagnosis is clinical with supportive evidence from blood levels of muscle enzymes (creatine kinase), and EMG findings. Many people undergo muscle biopsy for a definitive diagnosis. The disease responds well to oral steroids but is sometimes resistant.
Perivascular inflammation

Perivascular & Perimysial

Endomysial inflammation

**Inflammation**
Vessel wall is infiltrated by cells.
**Polymyositis (PM):** PM is similar to DM but doesn’t have the rash. Symptoms develop over weeks to months in most cases. The cause is usually unknown but occasionally, PM and DM are associated with cancer or rheumatoid conditions. Treatment is similar to that of DM.

**Drug-induced myositis:** Several medications may lead to muscle damage. These include certain cholesterol lowering agents, colchicine, and some other drugs.
Duchenne’s muscular dystrophy (DMD): DMD is a progressive hereditary disease that presents in boys during infancy or early childhood. Affected children will be slow to walk and may fail to master certain motor activities by the appropriate age. Initially, patients have weakness in shoulder and hip girdle muscles but, over years, weakness appear in hand and foot muscles as well as respiratory and cardiac muscles. The disease progresses to death often by the age of 20 due to heart failure or respiratory compromise. A severe deficiency or absence of the protein dystrophin underlies this disease but the exact mechanism is unknown. Diagnosis is clinical with supportive evidence from EMG and CK elevation.

Duchenne Muscular Dystrophy: Biopsy from 2 year old boy

Degenerating muscle fibers undergoing phagocytosis.

Acid phosphatase positive cells in a focus of muscle fiber necrosis.

“Myopathic group”: Small cluster of regenerating muscle fibers.
Definite diagnosis is now possible by muscle biopsy or by genetic testing of blood. The disease partially responds to high doses of oral steroids but there is no cure. A milder form of DMD is known as Becker dystrophy and results from a partial loss of dystrophin. In some cases, women who carry the abnormal gene have some mild symptoms of muscle disease (cramps, slight weakness, mildly elevated CK) and are known as manifesting carriers.
Myotonic dystrophy:

Unlike most muscular dystrophies, MD usually shows severe distal weakness prior to the development of proximal weakness. It is inherited in a dominant fashion. Symptoms can be evident at birth or not be noticeable until adulthood. Drooping of the eyelids (ptosis) and cataracts are other frequent features of the disease. No cure or effective treatment is available.
Myasthenia gravis (MG): *Auto immune* disease where the target of inflammation are the *acetylcholine receptors* on the muscle membrane. MG may occur at any age and common early symptoms are *double vision*, *droopy eyelids*, *difficulty swallowing*, or *generalized weakness*. The onset may be gradual over months or develop rapidly over several days or weeks. Diagnosis is clinical with supportive evidence including presence of acetylcholine receptor antibodies, positive tensilon test, or abnormal electrodiagnostic testing. A number of therapeutic agents are available and include *steroids*, *plasmapheresis*, azathiorpine, pyridostigmine and surgical removal of the thymus gland.
**Fatigue (Ptosis) in a patient with MG**

**Repetitive nerve stimulation: Decrement**

**MYASTHENIA GRAVIS**

**Small neuromuscular junctions** from patients with acquired (left) and congenital (right) myasthenia.

**Normal neuromuscular junctions.**

**Lymphorrhage** from a patient with myasthenia gravis and thymoma.