MUSCULOSKELETAL SYSTEM PART-2

ARTHRITE

Osteoarthritis (Degenerative joint disease) is the most common joint disorder. It is a frequent consequence of aging and is an important cause of physical disability in individuals over the age of 65. The fundamental feature of osteoarthritis is degeneration of the articular cartilage.

In most cases, osteoarthritis appears insidiously with age and without apparent initiating cause (primary osteoarthritis). When osteoarthritis manifests in youth, there is typically some predisposing condition, such as previous traumatic injury, developmental deformity, or marked obesity. In these settings the disease is called secondary osteoarthritis.

Pathological features
- Early changes include proliferation with disorganization of the chondrocytes in the superficial part of the articular cartilage with subsequent reduction of elasticity.
- As the superficial part of the cartilage are degraded vertical and horizontal fibrillation and cracking of the matrix occur.
- Eventually, full-thickness portions of the cartilage are lost, and the subchondral bone plate is exposed. Friction smooths and polishes the exposed bone (eburnation).
- Small fractures displace pieces of cartilage and subchondral bone into the joint, forming loose bodies (joint mice). The fracture gaps are filled with synovial fluid to form eventually fibrous walled cysts.
- Mushroom-shaped osteophytes (bony outgrowths) develop at the margins of the articular surface that may have mechanical effect on adjacent structures e.g., nerves.
- In severe disease, a fibrous synovial pannus covers the peripheral portions of the articular surface.

Pathogenesis
- Regardless of the inciting stimulus (wear & tear of aging, estrogens in females, and genetic susceptibility), early osteoarthritis is marked by degenerating cartilage containing more water and less proteoglycan. The collagen network is also diminished, presumably as a result of decreased local synthesis and increased breakdown; chondrocyte apoptosis is increased.
- Overall, cartilage tensile strength and resilience are reduced. In response to these degenerative changes, chondrocytes in the deeper layers proliferate and attempt to "repair" the damage by synthesizing new collagen and proteoglycans. Although these reparative changes are initially able to keep pace, matrix changes and chondrocyte loss eventually predominate.

Gout
This is a disorder caused by the tissue accumulation of excessive amounts of uric acid, an end product of purine metabolism. It is marked by recurrent episodes of acute arthritis, sometimes accompanied by the formation of large crystalline aggregates called tophi & chronic joint deformity. All of these are the result of precipitation of monosodium urate crystals from supersaturated body fluids. Not all individuals with hyperuricemia develop gout; this indicates that influences besides hyperuricemia contribute to the pathogenesis. Gout is traditionally divided into primary (90%) and secondary forms (10%). Primary gout designates cases in whom the basic cause is
unknown or when it is due to an inborn metabolic defect that causes hyperuricemia. In secondary gout the cause of the hyperuricemia is known.

Pathologic features

The major morphologic manifestations of gout are

1. Acute arthritis
2. Chronic tophaceous arthritis
3. Tophi in various sites, and
4. Gouty nephropathy

In gouty Acute arthritis in addition to features of acute inflammation needle shape monosodium urate crystals are frequently found in the cytoplasm of the neutrophils as well as in small clusters in the synovium.

In Chronic tophaceous arthritis: visible deposits seen in the synovium that becomes hyperplastic, fibrotic, and thickened by inflammatory cells, forming a pannus that destroys the underlying cartilage, and may erode subjacent bone. In severe cases, fibrous or bony ankylosis occurs, resulting in loss of joint function.

Tophi are the pathognomonic hallmarks of gout.

- Tophi can appear in the articular cartilage, periarticular ligaments, tendons, and soft tissues, including the ear lobes. Superficial tophi can lead to large ulcerations of the overlying skin.
- Microscopically, they are formed by large aggregations of urate crystals surrounded by an intense inflammatory reaction of lymphocytes, macrophages, and foreign-body giant cells, attempting to engulf the masses of crystals.

Gouty nephropathy

- This refers to the renal complications associated with urate deposition including medullary tophi, intratubular precipitations and renal calculi. Secondary complications such as pyelonephritis can occur, especially when there is urinary obstruction.

Pathogenesis

- Although the cause of excessive uric acid biosynthesis in primary gout is unknown in most cases, rare patients have identifiable enzymatic defects or deficiencies that are associated with excess production of uric acid.
- In secondary gout, hyperuricemia can be caused by increased urate production (e.g., rapid cell lysis during chemotherapy for lymphoma or leukemia) or decreased excretion (chronic renal failure), or both. Reduced renal excretion may also be caused by drugs such as thiazide diuretics, because of their effects on uric acid tubular transport.
- Whatever the cause, increased levels of uric acid in the blood and other body fluids (e.g., synovium) lead to the precipitation of monosodium urate crystals. The precipitated crystals are chemotactic to neutrophils & macrophages through activation of complement components C3a and C5a fragments. This leads to a local accumulation of neutrophils and macrophages in the joints and synovial membranes to phagocytize the crystals. The activated neutrophils liberate destructive lysosomal enzymes. Macrophages participate in joint injury by secreting a variety of proinflammatory mediators such as IL-1, IL-6, and TNF. While intensifying the inflammatory response, these cytokines can also directly activate synovial cells and cartilage cells to release proteases (e.g., collagenases) that cause tissue injury.
- Repeated bouts of acute arthritis, however, can lead to the permanent damage seen in chronic tophaceous arthritis.
**Pseudogout (chondrocalcinosis) (Calcium pyrophosphate crystal deposition disease).** Pseudogout typically first occurs in the age 50 years or older. It involves enzymes that lead to accumulation and eventual crystallization of pyrophosphate with calcium. The pathology in pseudogout involves the recruitment and activation of inflammatory cells, and is reminiscent of gout. The knees, followed by the wrists, elbows, shoulders, and ankles, are most commonly affected. Approximately 50% of patients experience significant joint damage.

**Infectious Arthritis:**
Can cause rapid joint destruction and permanent deformities. Microorganisms can lodge in joints during hematogenous dissemination, by direct inoculation or by contiguous spread from osteomyelitis or a soft tissue abscess.

**Suppurative Arthritis** is a subtype of infectious arthritis in which the bacteria seed the joint during episodes of bacteremia. *Haemophilus influenzae* predominates in children under age 2 years, *S. aureus* is the main causative agent in older children and adults, and *gonococcus* is prevalent during late adolescence and young adulthood. There is sudden onset of pain, redness, and swelling of the joint with fever, leukocytosis, and elevated ESR. In 90% of nongonococcal suppurative arthritis, the infection involves only a single joint-usually the knee. Joint aspiration is typically purulent, and allows identification of the causal agent.

**JOINT TUMORS AND TUMOR-LIKE LESIONS**

**Ganglion and Synovial Cysts**
A *ganglion* is a small (<1.5 cm) cyst located near a joint capsule or tendon sheath; the *wrist* is an especially common site. It is firm to fluctuant pea-sized nodules. Because they arise by cystic degeneration of connective tissue they are grossly translucent and microscopically lack a true cell lining. They are usually asymptomatic.

A *Synovial cyst* occurs due to herniation of synovium through a joint capsule or massive enlargement of a bursa. A good example is the *Baker cyst* that occurs in the popliteal fossa.

**Pigmented Villonodular Tenosynovitis (PVNS) & Giant-Cell Tumor (GCT) of Tendon Sheath**
These are closely related benign neoplasms of synovium. PVNS tends to involve joints diffusely, whereas GCT usually occurs as a single tendon sheath nodule.

**Grossly,** both lesions are red-brown to orange-yellow. In PVNS the joint synovium is diffusely converted into red-brown finger-like projections, and nodules. In contrast, GCT is well circumscribed and contained. **Microscopically,** Tumor cells in both lesions resemble synoviocytes. In PVNS they spread along the surface and infiltrate the subsynovial compartment. In GCT the cells grow in a solid nodular aggregate. Other typical findings include hemosiderin deposits, foamy macrophages, & multinucleated giant cells. **PVNS usually affects the knee** (80% of cases). Patients typically complain of pain, locking, and recurrent swelling. In contrast, GCT manifests as a solitary, slowly growing mass frequently involving wrist and finger tendon sheaths. **GCT is the most common soft tissue tumor of the hand.**

**SKELETAL MUSCLES**
Diseases that affect skeletal muscle can involve any portion of the motor unit; these include
1. Disorders of the motor neuron or axon (neurogenic atrophy)
2. Abnormalities of the neuromuscular junction (e.g. myasthenia gravis)
2. Disorders of the skeletal muscle itself (myopathies)

**Muscle Atrophy** is a non-specific response in a variety of muscle disorders. It is characterized by abnormally small myofibers; the type of fibers affected by the atrophy, their distribution in the muscle, and their specific morphology help identify the etiology of the atrophic changes.

**Neurogenic Atrophy** is due to lack of normal enervation. The loss of a single neuron will affect all muscle fibers in a motor unit, so that the atrophy tends to be scattered over the field. It is characterized by involvement of both fiber types, and by clustering of myofibers into small groups.

**Muscular Dystrophy**
The muscular dystrophies are “a heterogeneous group of inherited disorders, often presenting in childhood, characterized by progressive degeneration of muscle fibers leading to muscle weakness and wasting.” In advanced cases muscle fibers are replaced by fibrofatty tissue. This histologic feature distinguishes dystrophies from myopathies, which also present with muscle weakness.

**Example on this group are:**
1. **X-Linked Muscular Dystrophy: Duchenne Muscular Dystrophy (DMD):**
   This X-linked inherited disease is the most common & the most severe form of muscular dystrophy. It becomes clinically evident by age 5, with progressive weakness leading to wheelchair dependence by age 10 to 12 years, and death by the early 20s. The same gene is involved in a related but milder form designated Becker muscular dystrophy. DMD is caused by abnormalities in the dystrophin gene located on the short arm of the X chromosome. In affected families, females are carriers; they are clinically asymptomatic. Boys with DMD show delayed walking.

2. **Myotonic Dystrophy:** The cardinal neuromuscular symptom in myotonic dystrophy is myotonia, which is a sustained involuntary contraction of a group of muscles. Patients often complain of "stiffness" and have difficulty in releasing their grip, for instance, after a handshake. Myotonic dystrophy is inherited as an autosomal dominant trait that is associated with a CTG trinucleotide repeat expansion on chromosome 19 that affects the mRNA for the myotonia-protein kinase. The disease often presents in late childhood with gait abnormalities.

**Diseases of the Neuromuscular Junction**
**Myasthenia Gravis** is “an autoimmune disorder of the neuromuscular junction characterized by muscle weakness.” The disease can present at any age and has a predilection for women. Thymic hyperplasia is found in 65% and a thymoma in 15% of patients. Circulating antibodies to the skeletal muscle acetylcholine receptors (AChRs) are present in nearly all patients, associated with a decrease in the number of AChRs.

**Pathogenesis**
In most cases, the autoantibodies against the AChR lead to loss of functional AChRs at the neuromuscular junction either by (1) increasing degradation of the receptors, and/or (2) blocking the binding of acetylcholine (ACh) to its receptor.

The link between autoimmunity to AChRs and the thymic abnormalities is unclear. Nevertheless, most patients show improvement after thymectomy. Typically, weakness is first noticed in the extraocular muscles as evidenced by drooping eyelids (ptosis) and double vision (diplopia). The generalized muscle weakness can fluctuate dramatically, with alterations occurring over the course of days, hours, or even minutes. Sensory and autonomic functions are not affected. Respiratory impairment was a major cause of mortality in the past.

**Lambert-Eaton Myasthenic Syndrome** characteristically develops as a paraneoplastic process, most commonly in the setting of small-cell carcinoma of the lung; it can also occur in the absence of malignancy. Although individuals with this syndrome also present with muscle weakness.

**Skeletal Muscle Tumors**

**Rhabdomyosarcoma**

Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood and adolescence, usually appearing before age 20. They occur most commonly in the head and neck or genitourinary tract.

*Chromosomal translocations are found in most cases; the more common t(2;13) translocation (gene that controls skeletal muscle differentiation & development)*

**Gross features**

- Tumors arising near the mucosal surfaces of the bladder or vagina, can present as soft, gelatinous, grapelike masses, designated *sarcoma botryoides*.
- In other cases they are deceptively demarcated or infiltrative grayish-white to brownish masses.

**Microscopic features**

- Rhabdomyosarcoma is histologically subclassified into the *embryonal, alveolar, and pleomorphic variants*.
- *The rhabdomyoblast is the diagnostic cell* in all types; it exhibits granular eosinophilic cytoplasm, and may be round or elongated; the latter are known as *tadpole or strap cells* and may contain cross-striations visible by light microscopy. Skeletal muscle differentiation can be demonstrated by immunohistochemistry and electron microscopy.

Rhabdomyosarcomas are aggressive neoplasms. Location and the histologic variant of the tumor influence survival; embryonal, pleomorphic, and alveolar variants have progressively worsening prognoses. The malignancy is curable in almost two-thirds of children, but adults do much more poorly.

**SOFT TISSUE TUMORS**

**Fatty Tumors**

1. **Lipomas** are benign tumors of fat, and are the most common soft tissue tumors of adulthood. Most lipomas are solitary lesions. Lipomas can be subclassified based on their histologic features (e.g., conventional, myolipoma, spindle cell, myelolipoma,
pleomorphic, angiolipoma). Most lipomas are mobile, slowly enlarging, painless masses. They are usually seen in adults age 40+; associated with obesity; there are no gender differences. They are rare in children. Multiple lipomas are more common in women. **Pathological features: Conventional lipomas** (the most common subtype) are soft, yellow, well-encapsulated masses. They can vary considerably in size. Microscopically, they consist of mature fat cells with no pleomorphism.

2. **Liposarcoma** is a malignant neoplasm of adipocytes. These tumors occur most commonly in the 40 to 60 years of age & mostly in the deep soft tissues or in visceral sites. The prognosis of liposarcomas is greatly influenced by the histologic subtype; well-differentiated and myxoid variants tend to grow in a fairly indolent fashion and have a more favorable outlook than do the more aggressive round cell and pleomorphic variants, which tend to recur after excision and metastasize to lungs. A **t(12;16)** chromosomal translocation is associated with myxoid liposarcomas.

**Pathological features:**
- Usually they are relatively well-circumscribed large masses.
- Several different histologic subtypes are recognized, including two low-grade variants, the **well-differentiated liposarcoma** and the **myxoid liposarcoma**, the latter characterized by abundant, mucoid extracellular matrix.
- Some well-differentiated lesions can be difficult to distinguish histologically from lipomas, whereas very poorly differentiated tumors can resemble various other high-grade malignancies.
- In most cases, cells indicative of fatty differentiation are present. Such cells are known as **lipoblasts**; they recapitulate fetal fat cells with cytoplasmic lipid vacuoles that scallop the nucleus.

**Fibrous Tumors and Tumor-Like Lesions**

**Reactive Proliferations**

1. **Nodular Fasciitis** is a self-limited, reactive fibroblastic proliferation that typically occurs in adults on the volar aspect of the forearm. Patients characteristically present with a several-week history of a solitary, rapidly growing mass. Preceding trauma is noted in up to 15% of cases.

2. **Myositis Ossifican** is distinguished from other fibroblastic proliferations by the presence of metaplastic bone. It usually develops in the proximal muscles of the extremities in athletic adolescents and young adults after trauma. The involved area is initially swollen and painful, eventually evolving into a painless, hard, well-demarcated mass. It is vital to distinguish the lesion from extra-skeletal osteosarcoma.

3. **Fibromatoses** are a group of fibroblastic proliferations distinguished by their tendency to grow in an infiltrative fashion and, in many cases, to recur after surgical removal. Although some lesions are locally aggressive, they do not metastasize. The fibromatoses are divided into two major clinicopathologic groups: superficial (**palmar fibromatosis** (Dupuytren contracture) and penile fibromatosis (Peyronie disease)) and deep (include the so-called **desmoid tumors** that arise in the abdominal wall & muscles of the trunk and extremities)

**Fibrosarcoma:**

is a malignant neoplasm composed of fibroblasts. Most occur in adults, typically in the deep tissues of the thigh and retroperitoneal area. As with other sarcomas, fibrosarcomas often recur locally after excision (>50% of cases) and can metastasize hematogenously (>25% of cases), usually to the lungs.

**Pathological features:**
These unencapsulated, infiltrative sarcomas show frequently areas of hemorrhage and necrosis. Microscopically, the low-grade tumors may closely resemble fibromatosis; less differentiated examples show densely packed spindled cells growing in a herringbone fashion, there are frequent mitoses, and necrosis.

**Fibrohistiocytic Tumors**

These are composed of a mixture of fibroblasts and phagocytic, lipid-laden cells resembling activated macrophages. The neoplastic cells are most likely fibroblasts. Nevertheless, a significant number of such tumors actually derive from other mesenchymal cell types. Thus, the term fibrohistiocytic, especially in regard to the malignant variants, should be considered descriptive and not necessarily referring to a specific cellular origin. These tumors are divided into benign, of intermediate malignant potential, frankly malignant.

1. **Benign Fibrous Histiocytoma (Dermatofibroma)** are relatively common benign lesions in adults presenting as small (<1 cm) mobile nodules in the dermis or subcutaneous tissue. Microscopically, the lesion consists of bland, interlacing spindle cells admixed with foamy, lipid-rich histiocyte-like cells.

2. **Malignant Fibrous Histiocytoma (MFH)** is a term rather loosely applied to a variety of soft tissue sarcomas characterized by considerable cytologic pleomorphism, the presence of bizarre multinucleate cells, and storiform architecture. Despite the name, the phenotype of many such tumors is fibroblastic and not histiocytic. MFH exhibiting fibroblastic differentiation are usually large (5-20 cm), gray-white unencapsulated masses that often appear deceptively circumscribed. They usually arise in the musculature of the proximal extremities or in the retroperitoneum. Most of these tumors are extremely aggressive, recur unless widely excised, and have a metastatic rate of 30% to 50%.

**Smooth Muscle Tumors**

1. **Leiomyomas** are common, well-circumscribed neoplasms that can arise from smooth muscle cells anywhere in the body, but are encountered most commonly in the uterus.

2. **Leiomyosarcomas** (15% of soft tissue sarcomas). They occur in adults, more commonly females. Deep soft tissues of the extremities and retroperitoneum are common sites. Microscopically, they show spindle cells with cigar-shaped nuclei arranged in interweaving fascicles. Superficial leiomyosarcomas are usually small and have a good prognosis, whereas retroperitoneal tumors are large, cannot be entirely excised, and cause death by both local extension and metastatic spread.

**Synovial Sarcoma** (10% of all soft tissue sarcomas)
The cell of origin is unclear and is most certainly not a synoviocyte. Reflecting a non-joint origin, 90% of synovial sarcomas are not intra-articular but rather paraarticular. They are typically seen in the 20-40 years of age. Most develop in deep soft tissues around the large joints of the extremities, especially around the knee. Most synovial sarcomas show a characteristic t(X;18) translocation, which relates to prognosis. Microscopically, synovial sarcomas may be biphasic or monophasic. Classic biphasic synovial sarcoma exhibits differentiation of tumor cells into both epithelial-like cells and spindle cells. Common metastatic sites are lung, bone, and regional lymph nodes. Only 10% to 30% live for more than 10 years.