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BASIC SCIENCE

# Extra-skeletal calcifications An overview of soft tissue calcifications and ossifications

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## ABSTRACT

Extraskeletal calcifications is a common radiographic finding. The classification of the deposition of calcium and phosphorous salts in the soft tissues includes metastatic calcification, dystrophic calcification and calcinosis. **Metastatic calcification** develops when the calcium-phosphorous levels are elevated and implicate normal tissues. Conditions associated with metastatic calcifications are hyperparathyroidism, malignancies, hypervitaminosis D and milk-alkali syndrome. **Dystrophic calcification** is the calcification occurring in degenerated or necrotic tissues without imbalance in the metabolism of calcium and phosphorous. It is associated with multiple clinical conditions such as venous insufficiency, granulomatous infection, cysticercosis, neoplasms (primary bone forming tumors: osteosarcoma, other sarcomas especially synovial sarcoma), tumor necrosis, scleroderma, dermatomyositis and CREST syndrome, as well as with trauma (heterotopic ossification and injection granuloma). Calcinosis, also known as dystrophic calcification, is a distinct type of extra-skeletal calcification and it is usually not associated with calcium and phosphorus abnormalities. **Calcinosis** reveals most often in subcutaneous tissues, skin, and related connective tissues. It has been described in inflammatory connective-tissue diseases, including SLE, scleroderma and dermatomyositis. Other associated disorders include: calcinosis universalis, calcinosis circumscripta and tumoral calcinosis.

**KEY WORDS: soft tissue; calcium deposition; calcification; ossification**

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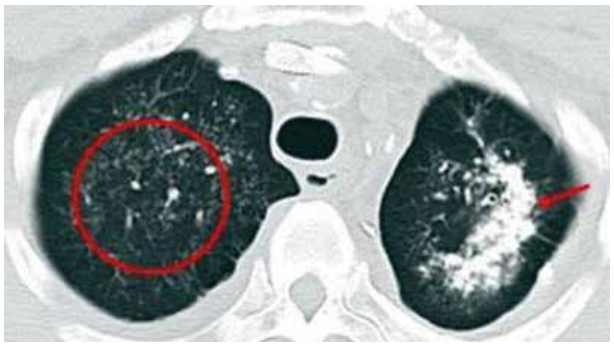

***Fig.1*** *Metastatic callcification of the lung secondary to chronic renal disease and hyperparathyroidism*

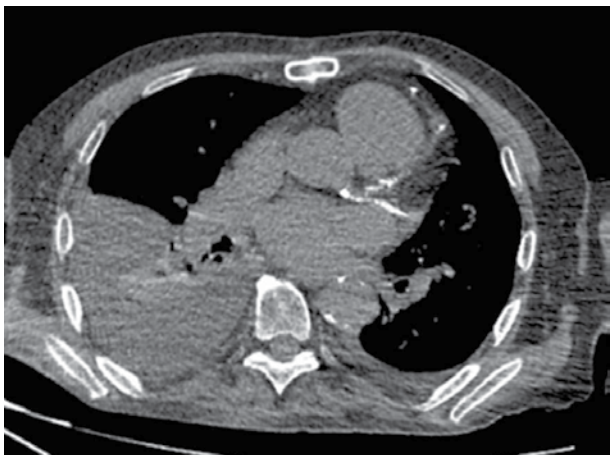

***Fig.2*** *Coronary artery calcifications and calcifications of the descending thoracic aorta in a patient with chronic kidney disease*

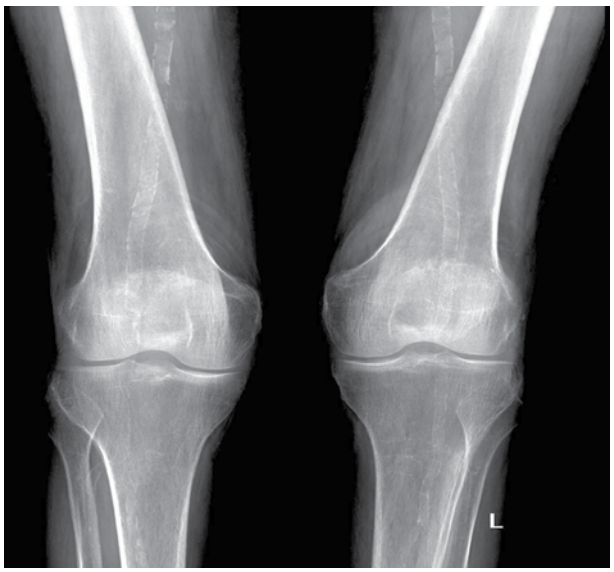


***Fig.3*** *Patient with end stage renal failure (ESRF). There is extensive metastatic calcification involving the femoral, popliteal and tibial arteries*

**Introduction**

Extra-skeletal deposition of calcium and phosphate has been associated with a considerable number and variety of disorders. This extra-skeletal deposition sometimes takes the form of amorphous calcium phosphate or hydroxyapatite crystals and sometimes bone tissue formation is noted. The classification of the deposition of calcium and phosphorous salts in the soft tissues includes metastatic calcification, dystrophic calcification and calcinosis [1-3].

There are three underlying mechanisms in relation to the pathogenesis of the ectopic mineralization on these disorders [4]. One mechanism that can cause metastatic calcification is a supra-normal "calcium/phosphate solubility product" in extracellular fluid. The second mechanism, in spite of normal serum levels of calcium and phosphate, mineral may be deposited as dystrophic calcification into metabolically damaged or dead tissue. Third, heterotopic ossification develops in a few disorders, for which the pathophysiology is unknown. Probably, according to some theories, a local tissue injury causes a cellular response which releases chemical mediators that stimulate excessive bone proliferation. This is most frequently seen in musculoskeletal trauma. This review describes the different categories of extra-skeletal calcification with reference to the pathogenesis, the clinical presentation, the laboratory and radiographic findings as well as the treatment the prognosis.

*Distinction between Ossification and Calcification*

**Ossification** is the process of bone tissue formation. In any region where there are fibroblasts, superfluity of calcium and sufficient blood-supply bone may form. Ossification forms a new bone. There is a surrounding shell of dense cortical bone, which surrounds a central medullary space [5].

**Calcification** is the deposition of calcium salts in a body tissue. The term pathological calcification refers to the abnormal deposits of calcium salts in any tissue except teeth and bones. Soft tissue calcification arise in the appendicular skeleton in different compartments which are the subcutaneous, neurovascular, fascial, muscular, and periarticular compartment. In the axial skeleton (calcification is found at spine) the soft tissue compartments such as the anterior longitudinal ligament, posterior longitudinal ligament, intervertebral disk, in-

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terspinous and supraspinous ligaments, and paravertebral soft tissues [2]. There are two distinct types of pathological calcification: Metastatic calcification and dystrophic calcification.

**A. Metastastic calcification**

Metastatic calcification (MC) refers to deposition of amorphous calcium phosphate and calcium hydroxyapatite crystals in tissues and it is often associated with metabolic disorders, secondary to an increased serum calcium-phosphorous product. MC usually occurs with a calcium phosphorus product greater than 70 mg/dL [6]. Microscopic calcification is common in lungs, kidneys, stomach and calcium salts and may also be deposited diffusely in the soft tissues, blood vessels, or in intra or para-articular locations.

*Epidemiology-Etiology*

MC is a frequent complication encountered in patients undergoing maintenance dialysis [7]. Entities that lead to MC due to hypercalcemia are primary hyperparathyroidism, Milk alkali syndrome, Vitamin D intoxication. There are other causes of hypercalcemia including sarcoidosis, Paget's disease, widespread malignancy and multiple myeloma which may cause similar soft tissue calcification, but the hypercalcemia usually is corrected or the cause proves fatal prior to radiographic detection of calcification. Also, secondary hyperparathyroidism and tumoral calcinosis are causes that lead to metastatic calcification due to hyperphosphatemia.

*Radiologic Findings*

MC from any cause may be "tumoral" or "diffuse" as well as intra- or para-articular. The location and morphologic appearance of MC represent nonspecific responses to the increased serum calcium-phosphorus product [8]. In patients with primary hyperparathyroidism intra-articular deposition of calcium pyrophosphate is not uncommon and crystals may be deposited in hyaline or fibrocartilage. In Milk Alkali Syndrome deposits of calcium salts can be diffuse, amorphous and may be seen particularly in the subcutaneous and para-articular areas. The calcium deposits may have variable size and can cause erosion in normal bone. Calcification may involve the kidneys, lungs, and blood vessels (**Fig.1, 2, 3**). Calcification in the extremities is commonly seen in patients with secondary hyperparathyroidism with renal osteodystrophy than in those with primary hyperparathyroidism. Particularly among dialysed patients diffuse tumor-like masses in the soft tissues, especially in para-articular locations, are frequently seen. With the correction of the metabolic abnormality these diffuse metastatic soft tissue calcifications may recede.

*Treatment*

Early recognition and prompt initiation of treatment is vital. The best treatment of MC is prevention with maintaining normal levels of calcium and phosphate. The decrease dietary calcium intake may be also helpful. In case of acute renal failure reported therapeutic strategies for the treatment and prevention of MC include: increasing dialysis dose, lowering serum calcium phosphorous and Ca×P solubility products, and avoiding calcium-based Pi binders and vitamin D analogs. Also intravenously administered sodium thiosulfate raises the solubility of calcium deposits [9]. In the treatment of both nephrolithiasis and tumoral calcinosis sodium thiosulfate is shown to be successful. It has antioxidant effects on endothelial cells, but its exact mechanism of effect is unclear.

**B. Dystrophic Calcification**

The term dystrophic soft tissue calcification enclose a broad spectrum of pathologies that cause soft tissue calcification. Essentially is the deposition of calcium salts in necrotic or degenerated tissues and generally is irreversible. The amorphous calcification that results may be small or large. In some cases, ossification may occur - this is characterized by cortical formation and a central medullary cavity. Almost every calcification that one sees in the soft tissues in actual radiographic practice is due to dystrophic calcification. They have a high prevalence of 95%-98% of all soft tissue calcification [6]. Usually the calcium metabolism and the calcium serum levels are normal.

For the differential diagnosis of dystrofic calcifications it is useful to memorize the VINDATE (Vascular, Infectious, Neoplasmatic, drud, Autoimmune, traumatic, and Extraneous etiologies diseases) classification: [2].

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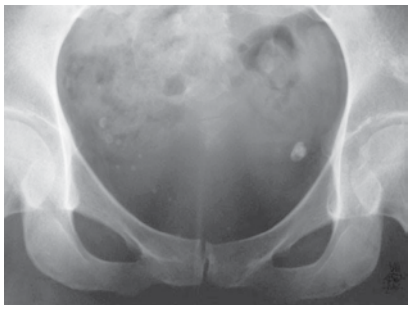

***Fig.4*** *Dystrophic Calcification – Vascular. Patient with multiple bilateral phleboliths in the pelvic veins with characteristic central lucency*

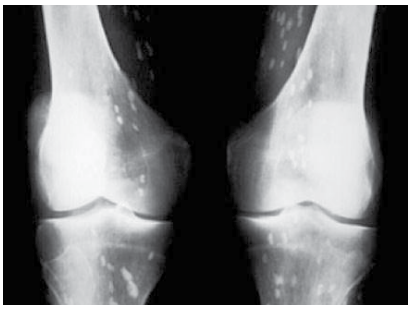

***Fig.5*** *Dystrophic Calcification – Infection. Patient with multiple «rice-grain» calcifications in muscles about knees due to cysticercosis. The calcifications are oriented along the direction of the muscle fibers*

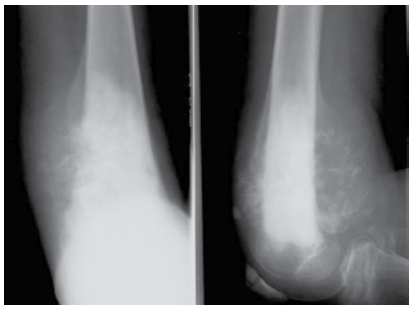

***Fig.6*** *Dystrophic calcifications – Neoplasm. Osteosarcoma may occasionally metastasize to soft tissue. This is uncommon, and can mimic heterotopic ossification*

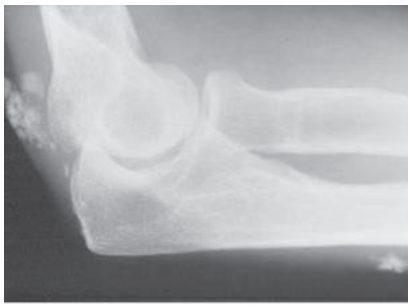

***Fig.7*** *Dystrophic Calcification – Drugs. Hypervitaminosis D - Calcification over the elbow*

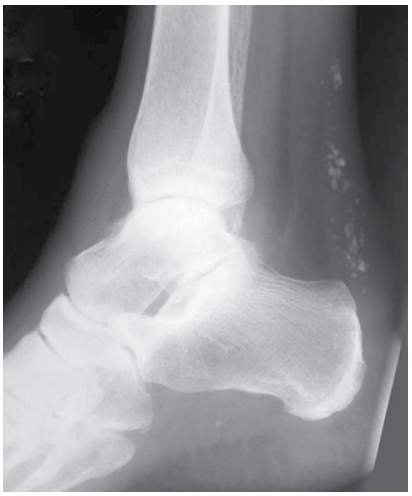

***Fig.8*** *Dystrophic Calcification-Trauma. Patient with Achilles tendon calcification due to recurrent trauma and tendinitis*

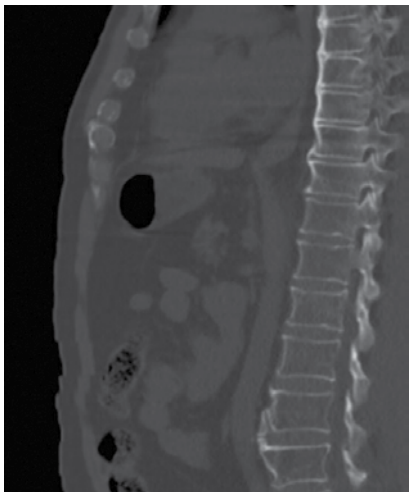

***Fig.9*** *DISH. Ossification of the anterior longitudinal ligament in thoracic spine*

**Vascular**

- Venous insufficiency as in phleboliths. Phleboliths are focal calcifications, often with radiolucent centers which is a helpful sign to distinguish them from urolithiasis. This appearance is attributed to calcification peripherally within the vessel, and is frequently seen on abdominal radiographs (66% of phleboliths) (**Fig.4**).

**Infection**

- Granulomatous infection
- Parasitic infestation
- Cysticercosis (the classic findings are multiple elongated foci of calcification just about the shape and size of grains of rice. These "rice grain" calcifications are usually oriented along the direction of the muscle fibers.) (**Fig.5**).
- Dracunuliasis (forms small crescentic calcifications)
- Armillifer armillatus tropical disease

**Neoplasm**

- Primary bone-forming tumors: osteosarcoma (**Fig. 6**)

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- Other sarcomas: specially synovial sarcoma
- Osteoma
- Tumor necrosis

**Drugs**
- Vitamin D hypervitaminosis (**Fig. 7**)
- Milk-alkali Syndrome

**Autoimmune**
- Dermatomyositis
- Scleroderma
- Crest Syndrome: calcinosis cutis (usually under the skin of the hands or wrists), Raynaud's phenomenon, esophageal disorders, sclerodactyly, telangiectasia.)

**Trauma**
- Heterotopic ossification (**Fig. 8**)
- Injection granuloma

**Extra**
- DISH (**Fig. 9**)
- Ankylosing spondylitis

**Dermatomyositis**

Dermatomyositis is an autoimmune inflammatory myopathy with characteristic cutaneous findings caused by small-vessel vasculitis. It involves striated muscles and skin. Often the formation of dystrophic calcifications is the result of the inflammatory episodes [10]. Soft-tissue calcification occurs most commonly in chronic Dermatomyositis, especially with onset in childhood, being uncommon in adult-onset disease [3].

*Epidemiology -Clinical Presentation*

There is a female predilection. There are two types of dermatomyositis: Juvenile dermatomyositis (JDM) which affects children and tends to be more severe and adult dermatomyositis (ADM) which typically affects adults around the age of 50. There are two peak ages of incidence: Childhood (5-15 years) and adulthood (50-60 years). When the disorder manifests before age 16, it is called juvenile or childhood dermatomyositis [11]. In juvenile dermatomyositis, the severity of calcinosis is irrelevant to the patient's sex and the beginning of symptoms, although increased delay to diagnosis and treatment impair this complication [12]. Generally, calcification is noted 1 to 3 years after the onset of the disease and occurs in 25% to 50% of patient. Calcinosis may precede the myopathy [13]. Mineral deposits develop over a period of 1 to 3 years. In calcinosis universalis, calcification occurs in subcutaneous tissues, but firstly in periarticular regions or in areas that are subject to trauma. In calcinosis circumscripta, the calcifications are more localized and typically appear around joints. Symptoms such as pain and skin ulceration may limit mobility and result in skin contractures. Additonally, abscess formation is not rare. Usually the dystrophic calcification remains stable but rarely some spontaneous resolution is reported [11,14]. Dystrophic calcification is rare in adults with dermatomyositis [15].

*Etiology and pathogenesis*

Juvenile dermatomyositis appears to be a form of complement-mediated micro-angiopathy [16]. There seems to be an association with the HLA-DQA1*051 allele [17]. The precise cause of the dystrophic calcification, however, is unknown and it consists of hydroxyapatite crystals according to electron microscope [18]. Immune deficiencies may predispose the patient to this complication. Calcinosis seems to occur in the majority of long-term survivors and it is possible to reflect a scarring process, which is supported by the observation that mineral deposition seems to appear initially in the muscles that were most severely affected during the acute phase of the disease. There is a variety of mechanisms for the formation of dystrophic calcification, such as the release of alkaline phosphatase or discharge of free fatty acids from affected muscles that, successively, directly precipitate calcium or bind acid mucopolysaccarides. Calcium-binding proteins may be responsible for the mineral deposition, which is speculated from the creased urinary levels of gamma-carboxylated peptides. More specifically, regarding to the immunopathology of dermatomyositis, an early event in the disease is the damage to the endothelial cells of endomysial capillaries mediated by complement activation and formation of membranolytic attack complexes (MAC), which causes lysis of the endothelial cells, destruction of capillaries, and muscle ischemia. As a re-

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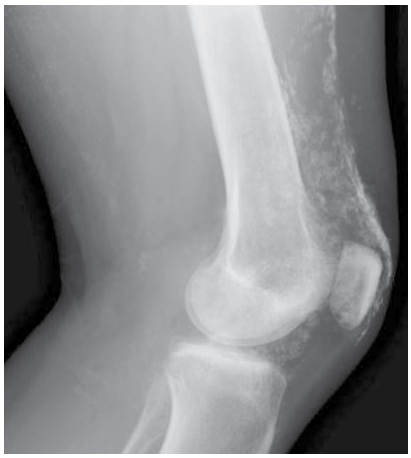


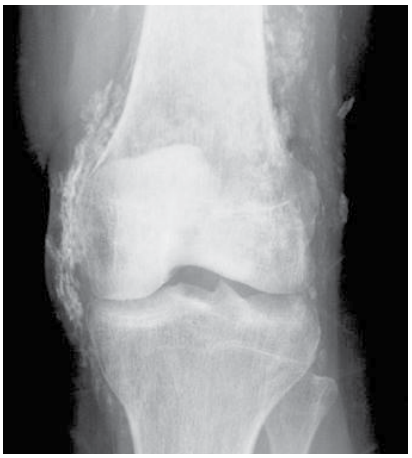
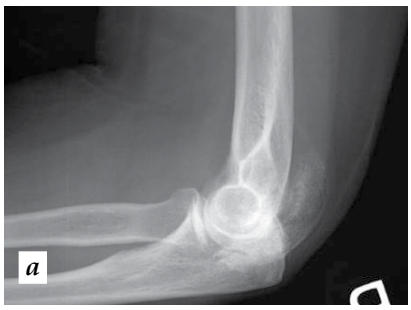
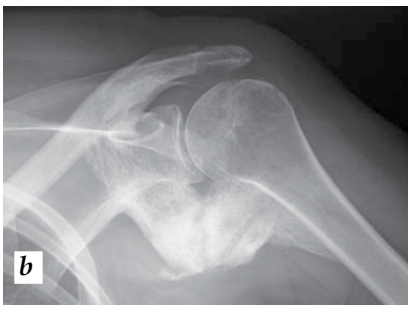


***Fig.10*** *46 year old female with dermatomyositis and extensive soft tissue calcifications about the knee*



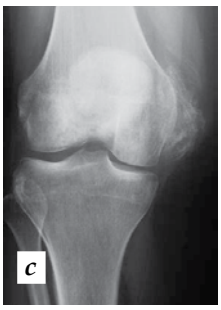




***Fig.11 a,b,c*** *33 year old female with limited range of motion about shoulder, elbow and knee after closed head injury. Heterotopic ossification is noted at all three sites.*

sult, the number of capillaries is reduced throughout the muscle, while the lumen of the remaining ones is dilated to compensate for the ischemic process. The pathology is more pronounced in the outer layers of the fascicles probably due to hypo-perfusion resulting in 'perifascicular atrophy' [19].

*Laboratory Findings*

Mineral metabolism in juvenile dermatomyositis has been studied. Hypercalcemia with hypercalciuria and hyperphosphaturia may occur, although these values are usually normal. Elevated levels of gamma- carboxyglutamic acid have been found in the urine of children with dermatomyositis, especially if there is calcinosis [10]. Several laboratory findings are characteristic of dermatomyositis (DM) and polymyositis (PM). These include: elevated levels of muscle enzymes [20, 21]. Autoantibodies, including antinuclear antibodies, in up to 80 percent of patients with Dermatomyositis and Polymiositis [20-23], myositis-specific autoantibodies, in at least 30 to 40 percent of patients [24-26] and myositis-associated autoantibodies, especially in patients with overlap syndromes, elevated levels of serum and urine myoglobin [27-28]. The erythrocyte sedimentation rate (ESR) is often normal or is only mildly elevated, even in patients with active muscle disease [29].

*Radiographic Findings*

In juvenile dermatomyositis, four types of dystrophic calcification occur [3]:

**1.** Superficial masses (small circumscribed nodules or plaques) within the skin.

**2.** Deep discrete subcutaneous nodular conglomerations near joints that can reduce mobility (calcinosis circumscripta) **(Fig. 9)**

**3.** Sheet-like, linear deposits within intramuscular fascial planes (calcinosis universalis) (**Fig. 10**).

**4.** Reticular subcutaneous deposits that enclose the torso forming a generalized "exoskeleton".

Magnetic resonance imaging (MRI) of skeletal mus-

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cles is a noninvasive sensitive but nonspecific modality for detecting areas of muscle inflammation and edema with active myositis, fibrosis and calcification [30].

*Treatment*

Important for minimizing the risk of calcinosis and for reserving good functional recovery is the use of high dose prednisone immediately after the onset of symptoms. If the response is incomplete, consideration is given to additional immunosuppressive agents, but their efficacy remains unclear. New agents such as monoclonal antibodies or fusion proteins that target cytokines, adhesion molecules, T-cell transduction or transmigration molecules, and B cells or their activation factors are promising immunotherapeutic agents [31]. Rituximab, a B cell-depleting agent, is currently tested in a controlled study. Combination therapy with intravenous corticosteroids and IVI may be required for the treatment of aggressive Dermatomyositis. In contrast to Polymyositis and Dermatomyositis, there is currently no effective treatment for sporadic inclusion body myositis (sIBM). The use of prednisone, cyclosporine, azathioprine, methotrexate, total body irradiation, and IFN-b didn't work as well as the use of oxandrolone. Treatment with IVIg, in some patients, caused transient improvement of muscle strength and swallowing [31]. Alemtuzumab (Campath), a T-cell-depleting monoclonal antibody, in a small and uncontrolled study, significantly slowed down disease progression for a 6-month period. Most importantly, this proof-of-principle study showed that depletion of T-cells from the periphery caused reduction of T-cells in the muscle and suppression of some degeneration-associated molecules, based on repeated muscle biopsies [32]. Phosphate-binding antacid therapy may reverse the mineral deposition [33]. In a small clinical trial, warfarin sodium treatment to decrease gamma-carboxylation was not associated with changes in calcium or phosphorus excretion or a reduction in calcinosis. Remarkable resolution of calcinosis universalis occurred in a young man treated with probenecid to improve renal handling of phosphate [34], and positive response to alendronate [35] and diltiazem has been described [36]. Surgical removal is also a solution for calcium deposits which affects patient's life.

*Prognosis*

The clinical course of dermatomyositis in children vary and more specifically some have long-term relapsing persistent disease, whereas others recover. Severe residual weakness, joint contractures, and calcinosis which can cause long term disability are clinical manifestations when recovery is incomplete [34]. The use of cytostatics had no visible impact on the survival of the patients. The association between dermatomyositis and malignancy has been reported in many recent studies. Studies suggest that the patient's age, the association with cancer, the delay of diagnosis and the initial dose of corticosteroids predict the prognosis of polymyositis/ dermatomyositis. However, neither the baseline levels of creatine kinase and ESR nor the use of cytotoxic drugs appeared to have any impact on the survival of these patients [37].

**Heterotopic Ossification**

The extraskeletal formation of bone (heterotopic ossification -HO) is noticed in patients following traumatic injuries or invasive surgeries while it is related to many congenital disorders. HO can occur almost anywhere in the human body and it can be locally or systematically appeared. Locally it is commonly seen after an injury to an area. Systematically extraskeletal calcification is a complication of paraplegia, quadriplegia or consequence after closed head injury. In these cases, ossification usually is noticed about the shoulders, elbows and hips and implies immovability and certainly reduced quality of life for the affected individuals [38]. Although several systems have been used, the Brooker classification is widely used (especially at the hip) for the classification for the severity of HO. According to Brooker classification there are five grades: **Grade 0:** no ossification present. **Grade 1:** Small bone islands are identified in the tissues around the bone. **Grade 2:** Bone spurs are identified at the pelvis and/or proximal femur. There is more than 1 cm of space between the opposing bones. **Grade 3:** Bone spurs identified at the pelvis and/or proximal femur. There is less than 1 cm of space between the opposing bones. **Grade 4:** Ankylosis present at the hip [39].

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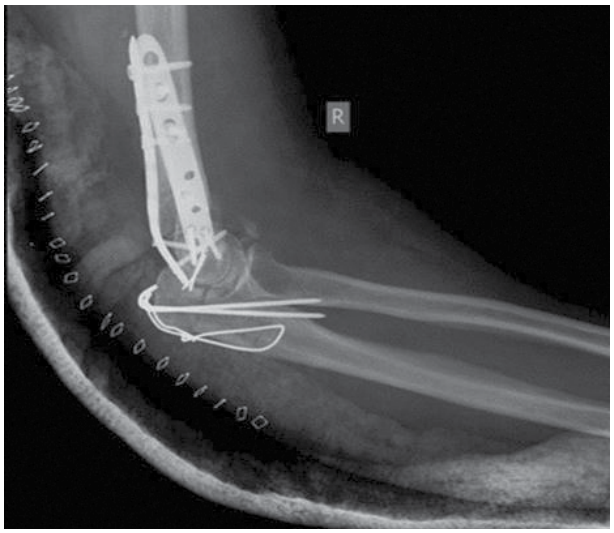


***Fig.12*** *Post traumatic heterotopic ossification*

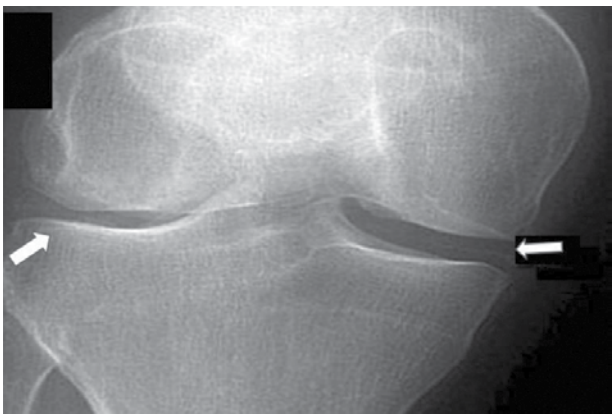

***Fig.13*** *Chondrocalcinosis of the articular hyaline cartilage and meniscal fibrocartilage of the knee in patients with calcium pyrophosphate dehydrate deposit*

*Pathophysiology*

The pathogenesis of HO is not fully understood but there is a genetic predisposition. Several factors, such as prostaglandin E2, bone morphogenetic protein (BMP), and the inflammatory process, establish a major role to the development of HO [40].

*Clinical presentation*

The presentation of the clinical symptoms of HO may varies from 3 weeks to 12 weeks after the triggering event. The most common symptom is pain around the site of HO (common affected side is the hip). Associated features can include fever, soft tissue swelling, and poor mobility of the affected joint [38].

*Laboratory findings*

Alkaline phosphatase (ALP) is used as a useful screening tool. ALP serum levels increase approximately two weeks after injury. Recently the measurement of the 24-h PGE2 urinary excretion has been recommended as a valuable indicator of early HO [38]. Also Creatine Kinase (CK) elevated serum levels correlates with the muscle involvement and it is an indicator for HO. Elevated C-reactive protein (CRP) correlates with inflammatory activity of HO.

*Radiographic findings*

Plain radiograph is the primary imaging method (**Fig. 11**). The typical radiologic appearance of HO is circumferential ossification with a lucent center [41] (**Fig.12)**. CT is able to identify lesion mineralization earlier and has good overall specificity. There is no specific role for MRI once the diagnosis of HO has already been made. MRI is usually used in the evaluation of a soft tissue mass and for other possible causes such as neoplasms (i.e. osteosarcoma) or subjacent osteomyelitis [42].

The use of SPECT/CT is superior to other imaging methods, such as radiography and computed tomography. It is able to determine the osteoblastic activity and the maturation of HO, evaluating if resection would be safe. It is a helpful diagnostic tool for the preoperative evaluation because it helps to define which patients shall present higher risk of recrudescence after surgical resection [43].

*Treatment*

Prophylaxis or early treatment of heterotopic ossification is very important due to the possible complications of HO (peripheral nerve entrapment, pressure ulcers, and functional impairment) if joint ankylosis develops [44-45]. For the treatment or prophylaxis for HO, non-steroidal anti-inflammatory drugs (NSAIDS) such as indomethacin, bisphosphonate (such as ethane-1-hydroxy-1,1-diphosphate), or local radiation therapy is used [38]. Indications for surgical resection are severe loss of motion and decreased function.

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**Chondrocalcinosis**

Calcium Pyrophosphate dehydrate deposition disease (CPPD). The names used for the calcium pyrophosphate crystal-related disorders include: (a) pseudo-gout, for the acute attacks of inflammatory arthritis caused by calcium pyrophosphate crystal (CPP) deposition; (b) chondrocalcinosis, for the radiographic calcification in hyaline and/or fibrocartilage tissues; and pyrophosphate arthropathy, for the radiographic or joint abnormalities accompanying calcium (c) pyrophosphate dehydrate crystal deposition (CPPD) disease. It is a type of arthritis that, as the old name of pseudo-gout suggests, can cause symptoms similar to gout. Yet in CPPD a different type of crystals triggers the reaction. CPPD can cause bouts of severe pain and swelling in one or more joints, which can limit activity for days or weeks. The condition most often involves the knees, but can affect wrists, shoulders, ankles, elbows, hands or other joints.

The range of presentations, named as proposed by a European League Against Rheumatism (EULAR) [46] includes:

- Asymptomatic CPPD disease
- Acute CPPD crystal arthritis (pseudo-gout)
- Chronic CPPD crystal inflammatory arthritis
- Osteoarthritis with CPPD, with or without superimposed acute attacks
- Severe joint degeneration (pseudo-neuropathic joint disease)
- Spinal involvement

*Epidemiology*

It is either hereditary (Autosomal dominant), idiopathic or associated with various metabolic disorders. The estimation of affection of CPPD 4 -7 % of the adult populations of Europe and the United States [47,48], especially in the elderly. According to one study, the average age at diagnosis of CPPD disease was 72 years [49]. There is an age-related increase in the prevalence of cartilage calcification according to radiographic surveys [50, 51]. According to age, the predominance of radiographic calcium pyrophosphate deposition, in a survey carried out in a geriatric clinic was:

- 65 to 74 years – 15 %
- 75 to 84 years – 36 %
- >84 years – Almost 50 %

The gender distribution of CPPD disease has differed among large series [49, 52, 53]. No major gender predominance appears. In men, attacks of acute arthritis are more common, while in women, atypical patterns of osteoarthritis with calcium pyrophosphate crystal deposition is usually seen.

*Pathophysiology*

CPP crystal formation is initiated in cartilage located near the surface of chondrocytes. There is an association with excessive cartilage pyrophosphate production, leading to local calcium pyrophosphate supersaturation and CPP crystal formation or deposition. Aberrance in both mineral and organic phase metabolism have involvement in CPPD disease [54, 55]. A definitive causative role of CPPD in all of the clinical manifestations with which deposition is associated, particularly the non-inflammatory changes, has not been established but there is compelling evidence for a role of the CPP crystal in acute and subacute joint inflammation [56-60]. There is a self-limited nature of acute attacks of CPP arthritis, which is not well understood [61, 62]. Most cases of CPPD disease are idiopathic. Joint trauma, including prior joint surgery, familial chondrocalcinosis, metabolic and endocrine disorders, including hemochromatosis are also associated with or may cause the illness, especially among the young [63]. The only disorder associated with the full spectrum of CPPD diseases is hemochromatosis [63]. Hypomagnesemia, hyperparathyroidism and hypophosphatasia have association with chondrocalcinosis as well as with acute CPP crystal arthritis but are not clearly associated with chronic CPPD arthropathy [63].

*Arthroscopic-Laboratory findings*

For the establishment of the diagnosis arthrocentesis of an affected joint with synovial fluid analysis for CPP crystals should be undertaken if possible. The presence of positively birefringent CPP crystals by compensated polarized light microscopy is the most prominent finding. Phagocytosed crystals within polymorphonuclear leukocytes are virtually always present in inflamed joints during an attack of acute CPP crystal arthritis. Total synovial fluid leukocyte concentration in an acute

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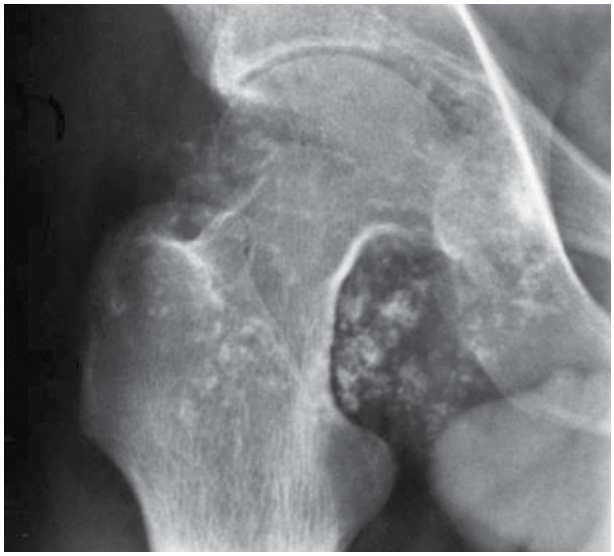

***Fig.14*** *Synovial osteochondromatosis in a 24-year-old man with hip pain. Multiple small, dense, punctate calcifications*

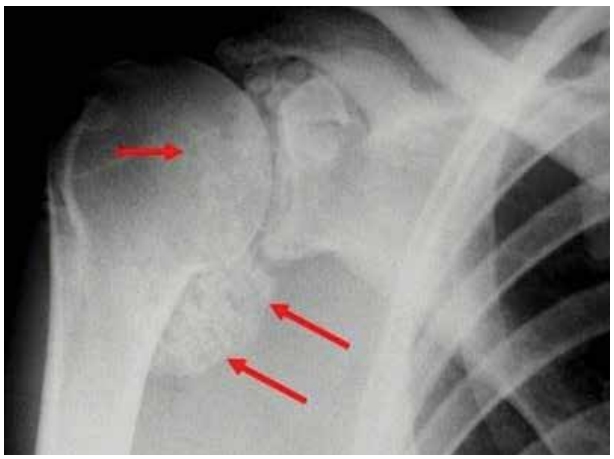

***Fig.15*** *Synovial osteochondromatosis in a 30-year-old man with shoulder pain. Multiple small, dense, punctate calcifications and loose bodies*

attack is typically 15,000 to 30,000 per $mm^3$, 90 percent of which are neutrophils. In chronically symptomatic joints, cell counts are typically lower and also crystals are often found extracellularly. The number of CPP crystals in the synovial fluid is related to the degree of clinically apparent inflammation [64] and the proportion of intracellular crystals correlates roughly with the level of inflammation (as reflected clinically and by the synovial fluid neutrophil concentration). In some cases, CPP crystals are too small to be visualized [65]. The coexistence of urate and CPP crystals in a single inflammatory effusion is neither uncommon nor unexpected, given the observed frequencies of hyperuricemia and gout among patients with CPPD disease [64].

*Radiographic findings*

Plain film radiography, which depicts findings of cartilage calcification, is the imaging evidence for CPPD. Among affected fibrocartilages in CPPD disease are the menisci of the knee (usually bilaterally) (**Fig.13**), the symphysis pubis, the triangular discs of the wrist joints, and the glenoid and acetabular labra. CPP crystal deposits in hyaline cartilage usually appears as a radiopaque line paralleling the surface of the underlying bone. Degenerative changes in the joint are also frequently present. Larger joints, such as the knee, wrist, elbow, shoulder, and hip, are most frequently involved in CPPD disease, but almost any diarthrodial joint may be affected radiographically. Articular capsule or synovial calcification is often fainter and more diffuse than cartilage calcification. Linear calcifications involving the Achilles tendon or plantar fascia are often seen in CPPD disease [66]. Ultrasonography findings that correlate with radiographic features of CPPD disease have also been described. Magnetic resonance imaging (MRI) is a less sensitive imaging modality for documenting CPP crystal deposition than plain film radiography, ultrasonography, or computed tomography (CT).

*Treatment*

No treatment is available to dissolve the crystal deposits. Treatment strategies are supported from the aforementioned European League Against Rheumatism (EULAR) panel based on a careful analysis of the literature [46, 47]. In patients with acute CPP crystal arthritis with no more than two acutely inflamed joints as initial treatment is suggested joint aspiration and intraarticular glucocorticoid injection rather than oral agents. In patients with features suggesting joint infection, glucocorticoid injection is postponed until infection is excluded by synovial fluid Gram stain and culture, and treat as in patients who are unable to undergo arthrocente-

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sis. In patients with acute CPP crystal arthritis who are not treated with arthrocentesis and injection, oral anti-inflammatory therapy is suggested with: A non-steroidal anti-inflammatory drug or oral colchicine in a low-dose regimen or an oral glucocorticoid, such as prednisone. Parenteral glucocorticoids may be used when oral glucocorticoid therapy is ineffective or not obtainable. In patients with acute CPP crystal arthritis in whom oral anti-inflammatory treatment is initiated within 24 hours of flare onset, low-dose oral colchicine is prescribed rather than an NSAID or an oral glucocorticoid [67]. For patients with three or more attacks of acute CPP crystal arthritis annually prophylaxis with colchicine is suggested rather than limiting treatment to the period of each acute attack. Appropriate dose adjustment for renal and hepatic dysfunction, drug intolerance, and potential drug interactions is necessary [68]. In chronic CPP crystal inflammatory arthritis, NSAIDs and/or colchicine are used. If needed hydroxychloroquine (HCQ), low-dose glucocorticoids, and methotrexate (MTX) can be used also. Surgery to repair and replace damaged joints is an option in severe cases [69-71].

**Synovial chondromatosis**

Synovial chondromatosis is a relatively common disorder characterized by loose cartilaginous bodies. It is caused by a metaplasia of the synovium and results in deposition of cartilaginous foci in the joint which may or may not be calcified. Up to 30% of the time, the cartilaginous deposits do not calcify [72]. It is classified under two main types:

**1.** Primary synovial chondromatosis: principally mono – articular disorder of unknown aetiology

**2.** Secondary synovial chondromatosis: resulting in intra – articular loose bodies after trauma or from causes such as osteoarthrosis and neuropathic arthropathy.

*Epidemiology*

Primary synovial chondromatosis typically affects adults, predominantly men, in the third to fifth decades of life. Any synovium-lined joint may be affected. Most commonly affects knee, hip and shoulder joint. It tends to be mono-articular. Knee is the most commonly affected site [73].

*Histopathology*

Primary synovial chondromatosis histopathologically is characterized by hyperplastic synovium covering bluish white, multilobulated, nodular projections of hyaline cartilage diffusely which involves the entire joint surface [74-75]. These nodules may be multiple and give a "cobblestone" appearance to the synovium. The extension of sub-synovial lobular nodules of hyaline into adjacent soft tissues and bursae is possible. Also they may extrinsically erode bone. The pathologic appearance of extra-articular (tenosynovial or bursal) chondromatosis is similar to that of intraarticular disease, but extra-articular disease involves the subsynovium that extends about bursae or along tendon sheaths [76]. The subsynovial nodules of hyaline cartilage may distract from the synovium to lie within the joint, bursa, or tendon sheath. They may reconnect to the synovium and be reabsorbed or be loose within the affected space.

*Clinical Presentation*

Patients present with pain, swelling and limited range of motion of the affected joint. Physical examination depicts diffuse joint swelling and enlargement, articular tenderness, articular crepitus, locking and palpable nodules or a mass. Associated muscle atrophy has been reported. At the onset of the disease symptoms are often insidious and gradually they progress. Rare spontaneous regression is also reported [77]. The duration of clinical symptoms before diagnosis is often long, with an average of 5 years.

*Imaging findings*

Radiologic findings are frequently pathognomonic. Radiographs reveal multiple intraarticular calcifications (70%-95% of cases) of similar size and shape, distributed throughout the joint, with typical "ring-and-arc" chondroid mineralization (**Fig.14, 15**). Extrinsic erosion of bone is seen in 20%–50% of cases [78]. Computed tomography (CT) optimally depicts the calcified intraarticular fragments and extrinsic bone erosion. Magnetic resonance (MR) imaging findings are more variable, depending on the degree of mineralization, although the most common pattern (77% of cases) reveals low to intermediate signal intensity with T1-weighting and very high signal intensity with T2-weighting with hy-

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po-intense calcifications. These signal intensity characteristics on MR images and low attenuation of the non-mineralized regions on CT scans reflect the high water content of the cartilaginous lesions. CT and MR imaging depict the extent of the synovial disease (particularly surrounding soft-tissue involvement) and lobular growth [78]. Secondary synovial chondromatosis can be distinguished from primary disease both radiologically (underlying articular disease and fewer chondral bodies of variable size and shape) and pathologically (concentric rings of growth).

*Treatment*

Treatment of choice for primary synovial chondromatosis is surgical synovectomy with removal of chondral fragments [78]. Recurrence is not unusual and may be related to incomplete resection. Arthroscopic treatment has been used successfully in the knee, hip, elbow, shoulder and the subacromial bursa with very low recurrence rates. Arthroscopic techniques can not treat extra-articular disease which has been noted in 21%-80% of cases [79, 80]. Local recurrences can be treated effectively with additional surgical intervention. Malignant transformation of primary synovial chondromatosis to chondrosarcoma is unusual and can be difficult to distinguish from benign disease, both pathologically and radiologically. Multiple recurrences with development of marrow invasion should be viewed as representing malignant transformation [78].

**Fibrodysplasia (Myositis) Ossificans Progressiva**

Fibrodysplasia ossificans progressiva (FOP), also called myositis progressive, is a rare heritable connective tissue disease characterized by (a) congenital malformation of the great toes, and (b) recurrent episodes of painful soft tissue swelling that lead to heterotopic ossification [81]. Posttraumatic myositis ossificans, a different disorder, also features bone and cartilage formation within soft tissues. In this sporadic condition, injured sites may initially be painful, warm, and feel "doughy", but 4 to 6weeks later, they contain mineralization that is apparent radiographically. Heterotopic ossification also may follow hip and spinal cord injury.

*Epidemiology*

FOP is very rare with a worldwide prevalence of approximately 1 case in 2 million individuals. No ethnic, racial, or geographic predisposition has been described [82].

*Clinical Presentation*

If the typical congenital skeletal malformations are recognized, FOP should be suspected at birth before soft-tissue lesions occur. The characteristic feature is short big toes caused by malformation (hallux valgus) of the cartilaginous anlage of the first metatarsal and proximal phalanx. In some patients, the thumbs are also strikingly short. Synostosis and hypoplasia of the phalanges is typical. Nevertheless, the digital anomalies are not pathognomic. FOP is usually diagnosed when soft-tissue swellings and radiographic evidence of heterotopic ossification are first noted. The severity of FOP differs significantly among patients, although most become immobilized and confined to a wheelchair by the third decade of life [83]. Typically, episodes of soft-tissue swelling begin during the first decade. Occasionally, the onset is as late as early adulthood. There are also reports of in utero involvement. Painful, tender, and rubbery soft-tissue lesions appear spontaneously or may seem to be precipitated by minor trauma including intramuscular injections. Swellings develop rapidly during the course of the several days. Fever may occur during periods of induration and can erroneously suggest an infectious process. Typically, lesions affect the paraspinal muscles in the back or in the limb girdles and may persist for several months. Aponeuroses, fascia, tendons, ligaments, and connective tissue of voluntary muscles may be affected. Although some swellings may regress spontaneously, most mature through an endochondral pathway, engendering true heterotopic bone.

Gradually, bone masses immobilize joints and cause contractures and deformity, particularly in the neck and shoulders. Ossification around the hips, typically present by the third decade of life, often prevents ambulation. Ankylosis of the spine and rib cage further restricts mobility and may imperil cardiopulmonary function. Scoliosis is common and

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associated with heterotopic bone that asymmetrically connects the rib cage to the pelvis. Hypokyphosis results from ossification of the paravertebral musculature. Restrictive lung disease with predisposition to pneumonia may follow. However, the vocal muscles, diaphragm, extraocular muscles, heart, and smooth muscles are characteristically spared. Although secondary amenorrhea may develop, reproduction reproduction may occur. Hearing impairment (beginning in late childhood or adolescent) and alopecia also manifest with increased frequency.

*Radiologic features*

Skeletal adnormalities instead of anomalies and soft-tissue ossification are the characteristic radiographic features of FOP. The principal malformations involve the great toe, although other toes are frequent. A remarkable feature of FOP is progressive fusion of cervical vertebrae that may be confused with Klippel-Feil syndrome or Still's disease. The femoral necks may be broad yet short. However, the remainder of the skeleton is unremarkable. Ectopic ossification in FOP progresses in several regular patterns or gradients (proximally before distally, axially before appendicularly, cranially before caudally, and dorsally before ventrally). Paraspinal muscles are involved early in life, with subsequent spread to the shoulders and hips. The ankles, wrists and jaw may be affected later. Radiographic and bone scan findings suggest normal modeling and remodeling of heterotopic bone. Fractures are not increased but respond similarly in either the heterotopic or normotopic skeleton. Bone scans are abnormal before ossification and can be demonstrated before conventional radiography findings. Computerized tomography and magnetic resonance imaging of early lesions has been described.

*Laboratory Findings*

Routine biochemical studies of mineral metabolism are usually normal, although alkaline phosphatase activity in serum may be increased, especially during disease "flare-ups". Urinary basic fibroblast growth factor levels may be elevated during disease flare-ups coinciding with the pre-osseous angiogenic phase of fibro-proliferative lesions [84].

*Histopathology*

The earliest FOP consists of significant aggregation of B and T lymphocytes in perivascular spaces of otherwise normal-appearing skeletal muscle. Subsequently, a nearly pure T-cell infiltrate is seen between edematous muscle fibers at the leading edge of an angiogenic fibro-proliferative lesion, which is indistinguishable from aggressive juvenile fibromatosis. Misdiagnosis is common, but can be avoided by examining the patient's toes [83].

*Etiology and Pathogenesis*

The genetic defect causing FOP has not been mapped. Dysregulation of BMP4 gene expression has been reported, but mutational screening and linkage-exclusion analysis indicate that the molecular defect lies elsewhere [84].

*Treatment*

There is no established medical treatment for FOP. The disorder's rarity, variable severity and fluctuating clinical course pose substantial uncertainties when evaluating experimental therapies. Adrenocorticotropic hormone (ACTH), corticosteroids, binders of dietary calcium, intravenous infusion of ethylene-diamine-tetra-acetic acid (EDTA), nonsteroidal anti-inflammatory agents, radiotherapy, disodium etidronate, and warfarin are ineffective. Limited benefits have been reported using corticosteroids and disodium etidronate together during flare ups and by using isotretinoin to prevent disease activation. However, these impressions represent uncontrolled studies. Accordingly, medical intervention is currently supportive. Nevertheless, physical therapy to maintain joint mobility may be harmful by provoking or exacerbating lesions. Surgical release of joint contractures is unsuccessful and risks new, trauma-induced heterotopic ossification. Removal of FOP lesions is often followed by significant recurrence. Osteotomy of ectopic bone to mobilize a joint is uniformly counterproductive because additional heterotopic ossification develops at the operative site. Spinal bracing is ineffective, and surgical intervention is associated with numerous complications [83]. Measures against recurrent pulmonary in-

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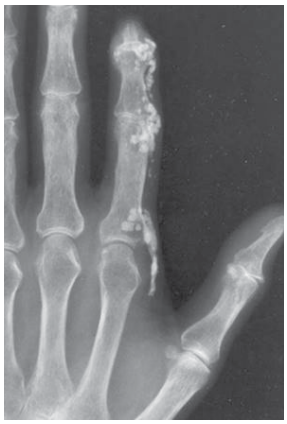

***Fig.16*** *Calcinosis circumscripta. Radiograph of the hand show multiple, punctate calcifications in the soft tissue characteristic of calcinosis circumscripta. The patient had a 10 year history of scleroderma*

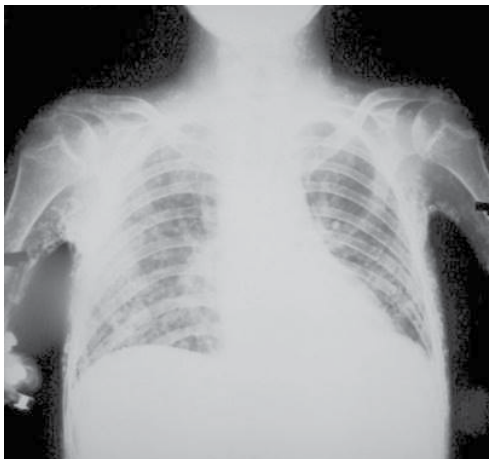

***Fig.17*** *Calcinosis universalis. Diffuse cutaneous, subcutaneous and muscular calcification*

fections and the onset of cardiopulmonary complications of restrictive lung disease are important.

**C. Calcinosis**

Calcinosis is the calcification of cutaneous, subcutaneous or deep connective tissue and it is not associated with metabolic disturbance while it may be associated with collagen-vascular disease. It is divided in three types:

1. Calcinosis Circumscripta
2. Calcinosis Universalis
3. Tumoral calcinosis

**1. Calcinosis circumscripta**

Calcinosis circumscripta (CC) is a local form of calcinosis and it is characterized by the deposition of calcium in the subcutaneous tissues, muscles and fascia.

*Clinical presentation*

Usually skin and subcutaneous tissues are affected, mainly the upper limbs and especially the fingers [85]. It occurs in the periarticular area as a painful mass with surrounding erythema and edema. Patients present with firm white dermal papules, plaques or subcutaneous nodules.

Ulceration is possible as well as extrusion of a chalky white material. It is visible in x-rays as localized, scattered calcification.

*Epidemiology*

There is a predilection in women (male to female ratio of 1:6) and occurs mainly in adult, rarely in children [86].

*Aetiology*

The etiology is unknown. It is a condition usually associated with scleroderma, Raynaud's disease, and telangiectasia [85].

*Radiographic Finding*

The most common finding is fine clustered calcifications, usually around the finger and toe tips (**Fig.16**). In case of an associated underlying disease soft tissue swelling and joint arthropathy may be present. Features that distinguish CC from tumoral calcinosis include the extent of calcification, which is generally less in CC, and the distribution of calcification in the subcutaneous tissues rather than in bursal regions. Otherwise, the radiographic appearances are similar [85].

*Treatment*

There is no specific treatment described for calcinosis. Some attempts have aimed at preventing further deposition of calcium and reabsorbing existing deposits. Restricted calcium diets have shown little success. Drugs such as calcium disodium edentate, acetylcholine, parathyroid extract, insulin and pilocarpine have also proven to be ineffective. Locally, the lesions can be removed,

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particularly when occurring over a joint and restricting function; however, as the condition resolves spontaneously it is difficult to advocate this. Some researchers have reported local removal of calcium deposits to be ineffective [85]

.

**2. Calcinosis universalis**

Calcinosis universalis (CU) is a rare disease characterized by the deposit of calcium in the skin, in the subcutaneous cellular tissue, and also in the tendinous and muscle tissues.

*Epidemiology*

Most cases become apparent during the first decade of life.

*Clinical presentation*

Clinical aspects may vary from arthralgia to movement limitation, with calcification of soft tissues. Fatigue, muscle pain and stiffness could be present. Palpable calcific plaques in subcutaneous or deeper tissue are usual findings. One third of cases are associated with scleroderma, dermatomyositis, - polymyositis, and systemic lupus erythematosus. Differential diagnosis should exclude fibrodysplasia ossificans progressive, progressive osseous heterodysplasia, myositis ossificans and dermatopolymyositis.

*Laboratory findings*

The diagnosis is difficult and usually made by exclusion. Laboratory results show normal serum and urinary calcium and phosphorus concentrations, normal hepatic and renal function, and normal complement values. The results for lupus erythematosus cells, anti-nuclear and anti-DNA antibodies are negative [2]. High rates of hemosedimentation and microcytic and hypochromic anemia may be found [87].

*Radiographic findings*

The radiographs showed calcifications of various sizes, linear or nodular, usually bilateral (87). The characteristic sheet like distribution of CU and its involvement of muscle and fascial planes usually makes this condition distinct from tumoral calcinosis at imaging [88] (**Fig.17**).

*Treatment*

There is no specific treatment, but the use of calcium chelates (EDTA), bisphosphonates (disodium etidronate) and steroids [87].

*Prognosis*

CU is a chronic disease characterized by a poor prognosis [87].

**3. Tumoral calcinosis**

Tumoral calcinosis (TC) is a rare entity characterized by calcium salt deposition in different peri-articular soft tissue regions. The classic TC masses are densely lobular calcified lesions confined to the soft tissue, commonly at the extensor surface of the joint in the anatomic distribution of a bursa. In descending order, the most common locations are the hip, elbow, shoulder, foot, and wrist. Visceral calcification does not occur, but segments of vasculature may contain mineral deposits. There are two types of TC, according to the presence or absence of an underlying calcifying disease process. TC has been divided into primary (idiopathic) and secondary. Two subtypes of the primary variety exist; a hyper-phosphatemic type and a normo-phosphatemic type. The secondary variety is mainly associated with chronic renal failure and the resulting secondary or tertiary hyperparathyroidism [89].

*Epidemiology*

There is familial tendency and no sex predominance. Also there is a significantly higher incidence in patients of African descent. Lesions primarily proliferate during the first 2 decades of life. In many patients hyperphosphatemia is a pathogenic factor [88].

*Clinical Presentation*

The soft tissue tumors of ectopic calcification are typically painless and grow at variable rates. The major clinical complications of TC are due to metastatic calcification that occurs around joints and in skin, marrow, teeth and blood vessels. Frequently they are lobulated, and firmly attached to deep fascia. Occasionally the swellings infiltrate into muscles and tendons [5]. Because the deposits are extracapsular, joint range of motion is not impaired unless the tumors are particularly large. There can, however, be compression of ad-

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jacent neural structures. The lesions also can ulcerate the skin and form a sinus tract that drains a chalky fluid; this may lead to infection. Other potential secondary problems include anemia, low-grade fever, regional lymphadenopathy, splenomegaly, and amyloidosis. Some patients have features of pseudoxanthoma elasticum (i.e. skin and vascular calcifications and angeoid streaks in the retina). A dental abnormality, featuring short bulbous roots and calcific deposits that often obliterate pulp chambers, is a characteristic finding [2, 8].

*Diagnosis*

TC appears in radiographs as an amorphous, cystic, and multi-lobulated calcification located in a periarticular distribution. CT findings are similar to that of plain radiography, but with more clarity to the lesion. Cystic components may show a layer of calcium within them, which is known as the "sedimentation sign"[88]. Erosion or osseous destruction by adjacent soft-tissue masses is absent. Despite the calcification magnetic resonance imaging, T2-weighted sequences show inhomogeneous high-signal-intensity and T1-weighted sequences show inhomogeneous low-signal intensity lesions. Two patterns are generally observed: (a) a diffuse, lower-signal-intensity pattern or (b) a bright, nodular pattern with alternating areas of high signal intensity and signal void. Martinez, et al. [90] discovered additional radiologic features, primarily bone marrow involvement, which demonstrates a periosteal reaction on radiographs and increased radionuclide uptake at bone scintigraphy. Cerebral and peripheral aneurysms have been also identified in patients with TC. TC has extensive variation in appearance and can be confused with other soft-tissue calcifications. The differential diagnosis of TC includes calcific tendonitis, calcinosis of chronic renal failure, calcinosis universalis, calcinosis circumscripta, synovial osteochondromatosis, synovial sarcoma, osteosarcoma, myositis ossificans, tophaceous out as well as calcific myonecrosis.

*Laboratory Findings*

Serum Calcium levels and alkaline phosphatase activity are usually normal. Hyperphosphatemia and increased serum calcitriol levels occur in some patients. The phosphate transport maximum/ glomerular filtration rate (TmP/FGR) may be supranormal but renal function is otherwise unremarkable. Patients are in positive calcium/phosphate balance. Renal studies reflect both the ongoing calcium and phosphate retention, and some patients are frankly hypo-calciuric. The chalky fluid found in lesions is predominantly hydroxyapatite.

*Treatment*

The treatment of TC should be according to the type of the lesion, stage of the pathology as well as with the site, size, relations of the lesion and the symptoms of the patient [89]. Surgical resection of the calcified mass is the main treatment for the primary type, but should be avoided in hemodialysis-related types, which are instead often treated with parathyroidectomy [91]. Surgical removal of subcutaneous calcified masses may be helpful if they are painful, interfere with function, or are cosmetically unacceptable. Administration of steroids, diphosphonates, or calcitonin and radiation therapy have not proven to be effective. Treatment of secondary TC is mainly medical and includes calcium and phosphorus restricted diets, dialysates, and phosphate binders (except aluminum containing binders). Several other medical treatments including Vinpocetine, Sodium thiosulfate, intravenous Pamidronate, have been used in treatment of the secondary TC. Subtotal or total parathyroidectomy in case of underlying secondary or tertiary hyperparathyroidism and kidney transplantation in case of end stage renal disease-related or hemodialysis-related TC may also be considered [89].

*Prognosis*

Despite widespread heterotopic ossification and severe disability, some patients live up to their seventh decade of life the seventh decade. Most, however, die earlier because of pulmonary complications, including pneumonia, secondary to restricted ventilation from chest-wall involvement.

***Conflict of interest:***

*The authors declared no conflicts of interest.*

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# ΠΕΡΙΛΗΨΗ

Οι εξωσκελετικές ασβεστώσεις αποτελούν συχνό απεικονιστικό εύρημα. Η αναγνώρισή τους και η συσχέτισή τους με νοσολογικές οντότητες και μεταβολικά νοσήματα του μυοσκελετικού συστήματος είναι σημαντική. Η ταξινόμηση των παθήσεων με εξωσκελετική εναπόθεση ασβεστίου και φωσφόρου περιλαμβάνει τρείς κύριες κατηγορίες: (1) την μεταστατική ασβεστοποίηση, (2) τη δυστροφική ασβεστοποίηση, και (3) την ασβέστωση. Η μεταστατική ασβεστοποίηση αναπτύσσεται στις περιπτώσεις παθολογικής αύξησης των επιπέδων ασβεστίου και φωσφόρου στο αίμα με αποτέλεσμα την εναπόθεσή τους σε διάφορους ιστούς. Στις παθήσεις που προκαλούν μεταστατική ασβεστοποίηση περιλαμβάνονται ο υπερπαραθυρεοειδισμός, οι νεοπλασίες, η υπερβιταμίνωση D και το σύνδρομο γάλατος-αλκάλεως. Η δυστροφική ασβεστοποίηση εμφανίζεται σε εκφυλιστικούς ή νεκρωτικούς ιστούς χωρίς να υπάρχει διαταραχή της ομοιοστασίας ασβεστίου – φωσφόρου. Σχετίζεται με μεγάλο αριθμό παθήσεων όπως αγγειακή ανεπάρκεια, κοκιωματώδη νοσήματα, κυστικέρκωση, νεοπλασίες των οστών, σκληρόδερμα, δερματομυοσίτιδα, σύνδρομο CREST, αλλά αναπτύσσεται και μετά από τραυματισμό ενός ιστού (έκτοπη οστεοποίηση).

Η ασβέστωση αποτελεί μια ξεχωριστή μορφή εξωσκελετικής ασβεστοποίησης που συνήθως συμβαίνει στο δέρμα και σε υποδόριους ιστούς, συνήθως δεν παρουσιάζεται διαταραχή της ομοιόστασης του ασβεστίου και φωσφόρου ενώ σχετίζεται με φλεγμονώδη νοσήματα του συνδετικού ιστού και των αγγείων.

**ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: ασβεστοποίηση, ασβέστωση, εξωσκελετικές εναποθέσεις ασβεστίου και φωσφόρου**