Familial Tumoral Calcinosis

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Familial tumoral calcinosis (FTC), first described in the US literature by Inclan and colleagues[1] in 1943, is a rare autosomal recessive disease characterized by progressive deposition of massive ectopic calcifications in periarticular cutaneous and subcutaneous tissues. There are 2 main types: hyperphosphatemic FTC (HFTC) and normophosphatemic FTC (NFTC).[2] Autosomal recessive mutations of the GALNT3 gene, which codes for a glycosyltransferase, and of the FGF23 gene, which codes for a phosphaturic protein, have been identified as the cause of phosphate dysregulation in HFTC.[2] The less common NFTC results from dysregulation of endothelial cell and fibroblast function caused by SAMD9 gene mutation.[2]

The disease usually becomes apparent in the first 2 decades of life and is more common in African Americans. There is a positive family history in 30% to 40% of cases, with the remainder occurring sporadically (nonfamilial form).[3,4]

Patients with FTC have normal or elevated phosphate and 1,25-dihydroxy-vitamin D levels, with normally functioning kidneys, as well as normal serum calcium, alkaline phosphatase, and parathyroid hormone levels.[3,4] Serum chemistry levels help distinguish FTC from other types of ectopic soft-tissue calcifications, which can result from inflammation (dystrophic) or hypercalcemia (chronic renal failure, hypervitaminosis D, milk alkali syndrome, hyperparathyroidism, sarcoidosis, malignancy).[3,4] Distinguishing FTC from other causes of dystrophic and metabolic periarticular calcifications is critical, as they may have different treatments. Differentiation is challenging, as other mimicking entities have similar radiographic and histologic features.[5]

The term *tumoral calcinosis* should be used only in reference to a hereditary metabolic dysfunction of phosphate regulation resulting in massive periarticular calcinosis.[6] An inconsistency arose when authors began using the term descriptively, without regard to the biochemical derangement characteristic of FTC. Calcifications associated with chronic renal failure—the most common cause of periarticular calcifications mimicking FTC—have been designated *uremic tumoral calcinosis, secondary tumoral calcinosis, pseudotumor calcinosis,* and *nonfamilial tumoral calcinosis* (Figure 1).[5]

A distinguishing feature of FTC is the lack of adjacent osseous destruction or erosion. Periosteal reaction, cortical sclerosis, and intramedullary sclerosis are seen in hyperostosis-hyperphosphatemia syndrome (HHS). FTC and HHS have similar biochemical abnormalities and both are caused by mutation of the GALNT3 gene. FTC and HHS are, therefore, considered different manifestations (allelic variants) of the same disease.[3] Clinically, HHS can be confused with osteomyelitis, osteoid osteoma, and osteoblastoma, as it presents with recurrent pain and swelling of the involved extremity, most commonly the tibia.[2]

FTC is clinically characterized by massive amorphous, cystic, and multilobulated periarticular calcifications, predominantly about the extensor surfaces of large joints, such as the hip, elbow, and shoulder.[1] These calcified masses, single or multiple, often are painless at presentation. They grow silently for many years until large enough to cause mechanical symptoms about the affected joints, including decreased range of motion, pain, and nerve compression.[3] Although often located deep within soft-tissue structures, including skeletal muscle, these lesions also may develop in very superficial or bursal locations, most commonly in the greater trochanteric bursa. Large masses abutting the skin may externalize spontaneously, leading to ulcer-

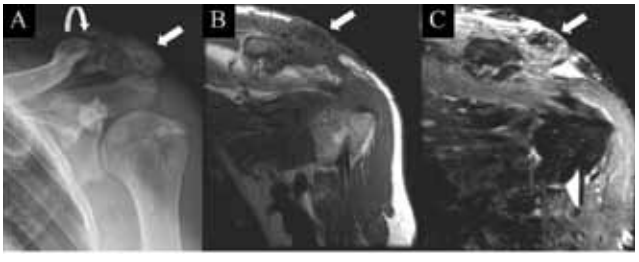

Figure 1. Anteroposterior radiograph (A), coronal oblique T_1-weighted magnetic resonance imaging (MRI) scan (B), and short tau inversion recovery MRI scan (C) show large, periarticular calcified masses in left shoulder of patient with history of chronic renal failure. Largest periarticular mass extends to skin surface, where ulceration extruding chalky, milk-like substance was seen clinically (arrow). Distal clavicular osteolysis resulted from secondary hyperparathyroidism (curved arrow).

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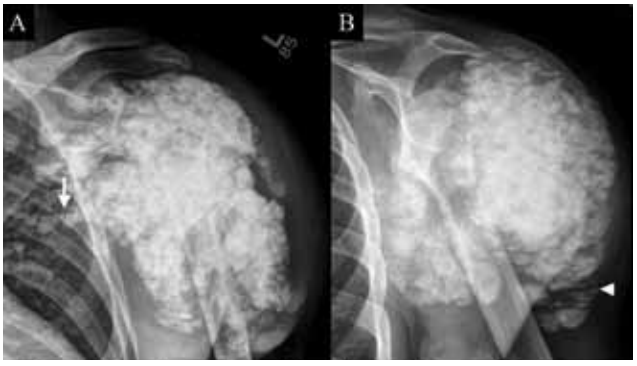

Figure 2. Anteroposterior and scapular Y radiographs of 50-year-old patient with tumoral calcinosis, and amorphous, multilobulated periarticular calcifications about left shoulder. Findings about right shoulder were similar. Note fluid-fluid levels and sedimentation sign (arrows).

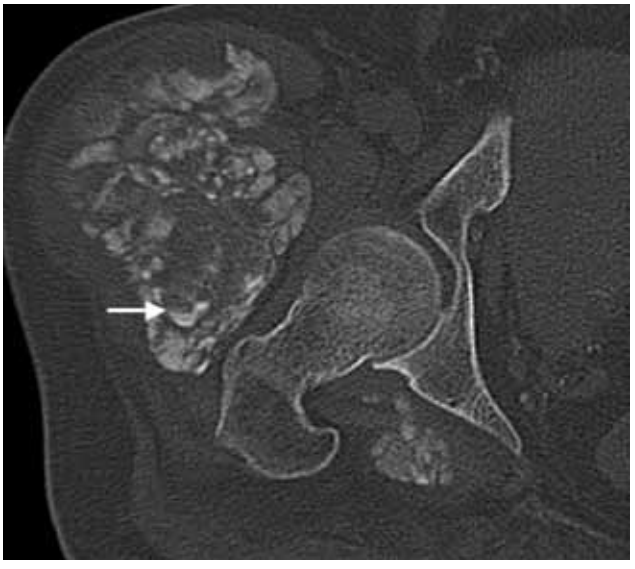

Figure 3. Axial computed tomography scan of right hip shows amorphous, multilobulated calcifications with fluid-fluid levels (sedimentation sign) about right hip (arrow).

ation and sinus tract formation, from which, chalky, milk-like hydroxyapatite crystals and noncrystalline calcific deposits may drain.[4] In addition, there can be superimposed severe skin and bone infections as well as pulmonary restriction.

Dental and ocular abnormalities (angioid streaks, corneal calcifications), and cerebral and peripheral aneurysms also have been described, presumably related to degeneration of elastic fibers, similar to pseudoxanthoma elasticum.[3]

FTC lesions consist of epithelioid elements and multinucleated giant cells surrounding calcium granules and cysts, containing calcium hydroxyapatite, amorphous calcium carbonate, and calcium phosphate.[2,3]

The characteristic radiographic finding of FTC is that of amorphous, cystic, multilobulated periarticular calcifications along the extensor surfaces

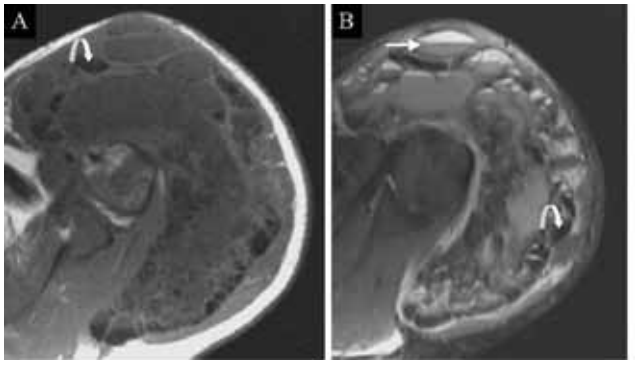

Figure 4. (A) T_1-weighted axial magnetic resonance imaging (MRI) scan of left shoulder shows heterogeneous intermediate and low–signal-intensity masses, the latter related to calcium deposition. (B) T_2-weighted axial MRI scan shows heterogeneous nodular pattern of alternating areas of high signal-intensity and signal void (or low signal) caused by calcification (curved arrows). Note fluid-fluid level (arrow).

of joints (Figure 2).[5,6] Computed tomography more clearly defines the masses and shows patchy increased attenuation of involved areas (Figure 3).[4,5] Fluid-fluid levels caused by calcium layering within cysts (sedimentation sign) is best appreciated on cross-sectional imaging, but may be seen on plain radiographs (Figures 2, 3). A homogenous rather than layered cystic appearance indicates lower metabolic activity and decreased rate of growth.[4-6] The HHS variant presents with cortical hyperostosis and intramedullary sclerosis that can mimic osteomyelitis and sclerosing bone dysplasias.[2]

On magnetic resonance imaging (MRI), FTC has a variegated appearance.[6,7] T_1-weighted images typically show heterogeneous low signal-intensity (Figure 4A). T_2-weighted images show a nodular pattern of heterogeneous, predominantly high signal-intensity alternating with focal areas of signal void caused by calcification and fluid-fluid levels (Figure 4B). Martinez and colleagues[6] described an intense bone marrow edema pattern and periosteal reaction associated with the disease (particularly the HHS variant), with increased radionuclide uptake at bone scintigraphy, and high–signal-intensity rings within periosseous subcutaneous tissues on MRI.[5-7]

Treatment of FTC is difficult and does not offer reliable results.[8,9] Surgical excision of the lesions, though reportedly more successful in infants, is associated with high recurrence rates and complications in adults. Phosphate depletion (using aluminum hydroxide and acetazolamide) and low-phosphate, low-calcium diets have a varied effect on FTC, with only marginal benefits reported.[9] Extremity pain and swelling associated with HHS (allelic form of FTC) usually respond to nonsteroidal anti-inflammatory drugs.[3] Recently identified mutations of the GALNT3, FGF23, and SAMD9 genes hold promise for novel future treatments.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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