Imaging findings of arterial calcification due to deficiency of CD73: A case study

Aniruddh Mandalapu[1]*, Kathryn J Stevens[2]

[1]*Department of Radiology, University of Rochester School of Medicine, Rochester, USA*
[2]*Department of Radiology, Stanford University School of Medicine, Palo Alto, USA*

***Correspondence:** Aniruddh Mandalapu, University of Rochester School of Medicine; 1399 Mt. Hope Ave., Rochester, NY
aniruddh_mandalapu@urmc.rochester.edu

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ABSTRACT

A 52-year-old male developed right knee pain after hiking in Guatemala. On his return he underwent a knee MRI for an indication of medial knee pain, which demonstrated a medial meniscal tear. However, the MRI demonstrated marked tortuosity and dense calcification of the popliteal artery, confirmed on subsequent radiographs. Review of previous CT studies of the abdomen and lower extremities showed severe ectasia and arterial calcification in the femoral and popliteal arteries bilaterally, but no calcifications in the aorta and common iliac arteries. Dual energy CT studies of the extremities demonstrated extensive periarticular soft tissue calcification throughout the wrists, hands, ankle and feet without evidence of uric acid. Review of the electronic medical records revealed a diagnosis of Arterial Calcification due to Deficiency of CD73 (ACDC), a rare genetic disorder presenting with debilitating pain in the wrists and hands, claudication of the calves, thighs and buttocks, progressing to chronic ischemia of the feet which may be limb-threatening. The patient was enrolled in an NIH trial of bisphosphonates and dual-antiplatelet therapy with stabilization of symptoms. This case discusses the imaging findings of this rare condition, differential diagnosis to consider, and current management.

CASE REPORT

CASE REPORT

A 52-year-old male presented as a new patient with right knee pain that developed while hiking in Guatemala with concern for meniscal tear. The patient underwent an MRI examination of his right knee. Subsequent review of the electronic medical records revealed that the patient had previously been seen with a 6-to-7-year history of cramping in his calves bilaterally. There was no family history of dyslipidemia or premature coronary disease. The patient's mother had a history of obesity and hypertension. Clinical work-up at this time demonstrated an Ankle-Brachial Index (ABI) of 0.4 (normal value is over 0.9) in his legs bilaterally. In addition, the patient had a 20-year history of recurrent episodes of synovitis in his elbows, wrists, hands, ankles, and feet, previously diagnosed as pseudogout post-joint aspiration. Previous rheumatological work-up demonstrated normal erythrocyte sedimentation rate and C-reactive protein, normal uric acid and parathyroid hormone levels, and negative results for rheumatoid factor and anti-CCP. However, he was found to have a fasting blood glucose of 108 and an HgbA1c of 6.1, suggesting impaired glucose tolerance. Genetic testing at this time had found an R463X variant mutation in the ecto-5'-nucleotidase (NT5E) gene characteristic of Arterial Calcification due to Deficiency of CD73 (ACDC).

IMAGING FINDINGS

The knee MRI demonstrated a tear of the medial meniscus. However, there was striking tortuosity and dense calcification of the popliteal artery (Figure 1). Subsequent knee radiographs showed severe ectasia and extensive atherosclerotic calcification of the popliteal arteries (Figure 2). Review of previously obtained Computed Tomography Angiography (CTA) study of the chest, and a non-contrast CT examination of the abdomen and lower extremities demonstrated severe tortuosity and arterial calcifications in the femoral and popliteal arteries bilaterally (Figure 3). There were minimal scattered calcifications within the left anterior descending coronary artery but no calcifications in the aorta, external iliac, or internal iliac arteries (Figure 3). A dual energy CT examination of the left wrist demonstrated scattered periarticular soft tissue calcifications, most marked at the metacarpophalangeal and proximal interphalangeal joints. There was no evidence of monosodium urate deposition on fused overlay images, so the calcifications were most likely calcium pyrophosphate crystals (Figure 4).

Management

The patient's current medications included atorvastatin 10mg daily, amlodipine 10mg daily, clopidogrel 75mg daily, and ibuprofen 200mg as needed. Bisphosphonates have been found to be a potentially effective management option for patients with ACDC, and the patient was enrolled in an NIH trial of bisphosphonates and had been put on Etidronate to try and mitigate symptoms.

Follow-up

On follow-up, the patient's peripheral artery disease remains stable with a right-sided ABI of 0.66 and a left-sided ABI of 0.74 and no increase in claudication symptoms. He still experiences intermittent arthralgias which respond to nonsteroidal anti-inflammatory medication or prednisone and is being followed by endocrinology for his impaired fasting glucose. The patient is no longer on Etidronate but is now regularly taking amlodipine, clopidogrel, and a statin to manage his peripheral artery disease.

DISCUSSION

Etiology and demographics: ACDC is an extremely rare autosomal recessive disease that causes calcifications in the intima media of peripheral arteries, caused by a mutation in NT5E rendering the cell-surface protein CD73 non-functional [1]. The deficiency of CD73 causes increased activity of tissue non-specific alkaline phosphatase (TNAP), a key mediator of pathological ectopic tissue calcification [1], thereby affecting inorganic pyrophosphate and phosphate metabolism [2]. Per Orphanet, there are less than 20 described patients to date of this adult-onset disease [3].

Clinical and Imaging Findings

ACDC leads to progressive arterial calcifications of the lower extremities and periarticular calcifications affecting the peripheral extremities. Patients may experience debilitating lower extremity claudication, and recurrent painful synovitis and swelling of the peripheral joints similar to pseudogout-type flares [4]. Imaging findings include tortuosity and calcification of the superficial femoral and popliteal arteries bilaterally on radiographs and CT. Periarticular calcifications are seen in the hands and feet, typically manifesting as bilateral, asymmetric, bulky calcifications at the metacarpophalangeal and metatarsophalangeal joints, and smaller curvilinear pericapsular calcifications at the proximal and distal interphalangeal joints. There are usually no erosive changes or intra-articular mineralization [4].

Treatment and Prognosis

The current investigational treatment of this disease is Etidronate, a bisphosphonate used in other disease of abnormal mineralization including Paget's disease [4]. This can be combined with dual anti-platelet therapy of clopidogrel and low-dose aspirin to combat the arterial claudication. Current prognosis remains unclear due to the rarity of the disease.

Differential Diagnosis

The periarticular calcifications of the hand and foot in ACDC present similarities to other diseases (Table 2). Differential diagnosis includes pseudoxanthoma elasticum and generalized arterial calcification of infancy, which present with ectopic mineralization while in homeostasis [5]. However, these disorders usually have cardiovascular effects and generalized arterial calcification of infancy does not match the timeline of this adult-onset disease [6]. Other possibilities include chronic renal failure which may cause periarticular calcifications and soft tissue calcifications secondary to hyperparathyroidism. These patients present differently with renal issues and abnormal labs of increased calcium, parathyroid hormone, creatinine, and blood urea nitrogen (BUN). Tophaceous gout can also result in periarticular calcifications, but there are also periarticular erosions and there is no vascular calcification unless the patient also has renal disease [7]. Similarly, scleroderma may present with calcinosis of the small joints in the extremities but is usually associated with a plethora of other findings such as esophageal dysfunction and sclerodactyly [4,8]. Wilson's disease may also present with periarticular calcifications but often presents with hepatic, neurologic, and endocrine symptoms [9]. Finally, calcium pyrophosphate disease could also present with periarticular and intra-articular calcifications but there is no associated vascular calcification [10].

TEACHING POINT

ACDC is a homozygous recessive disease that presents with periarticular calcifications of the small joints of the extremities and tortuosity and dense arterial calcification in the lower extremity including the popliteal and superficial femoral arteries.

Authors' contributions

Author 1 wrote the manuscript.
Author 2 procured the case and edited.

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None

Disclosures

None

Consent

None

Human and animal rights

If reporting experiments on human or animal subjects, please indicate if ethical standards followed the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

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FIGURES

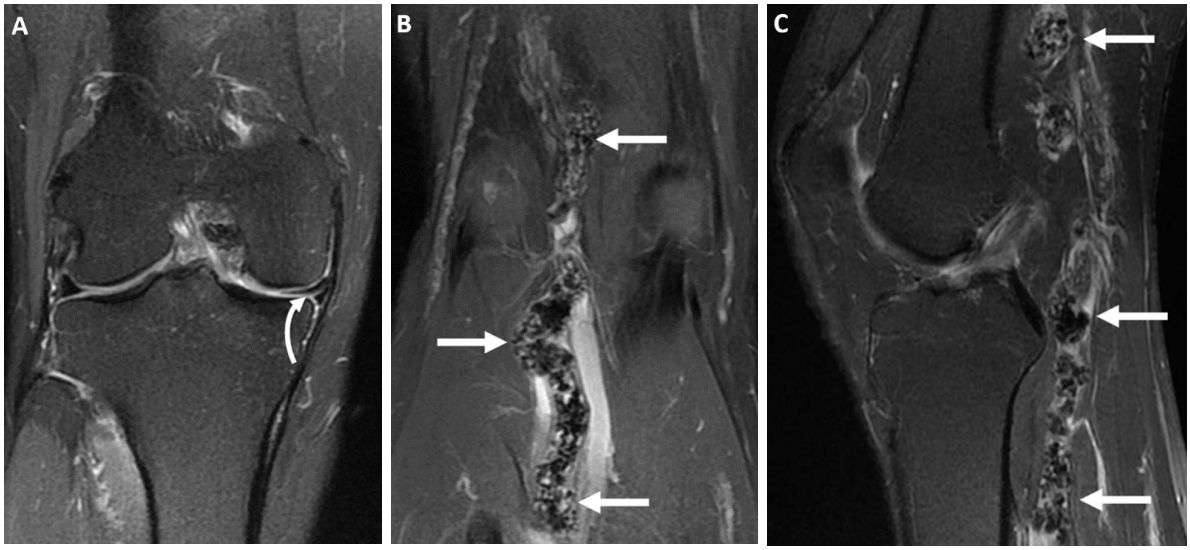

Figure 1: 52-year-old male with right medial knee pain. (a and b) Coronal fat-saturated proton density-weighted and (c) sagittal fat-saturated T2-weighted images of the right knee demonstrate a horizontal tear in the body of the medial meniscus (curved arrow). The popliteal artery has heavy calcification (arrows) and appears markedly tortuous.

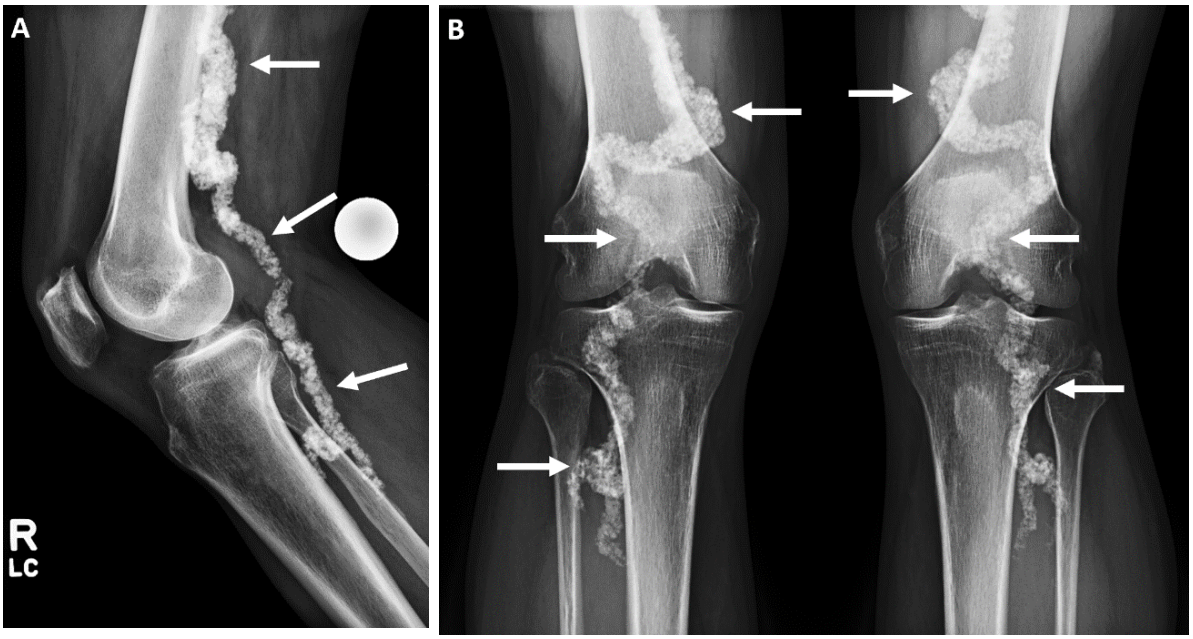

Figure 2: 52-year-old male with Arterial Calcification due to Deficiency of CD73. (a) Lateral radiograph of the right knee and b) AP radiograph of the bilateral knees demonstrates marked tortuosity and extensive arterial calcification in the bilateral popliteal arteries (arrows).

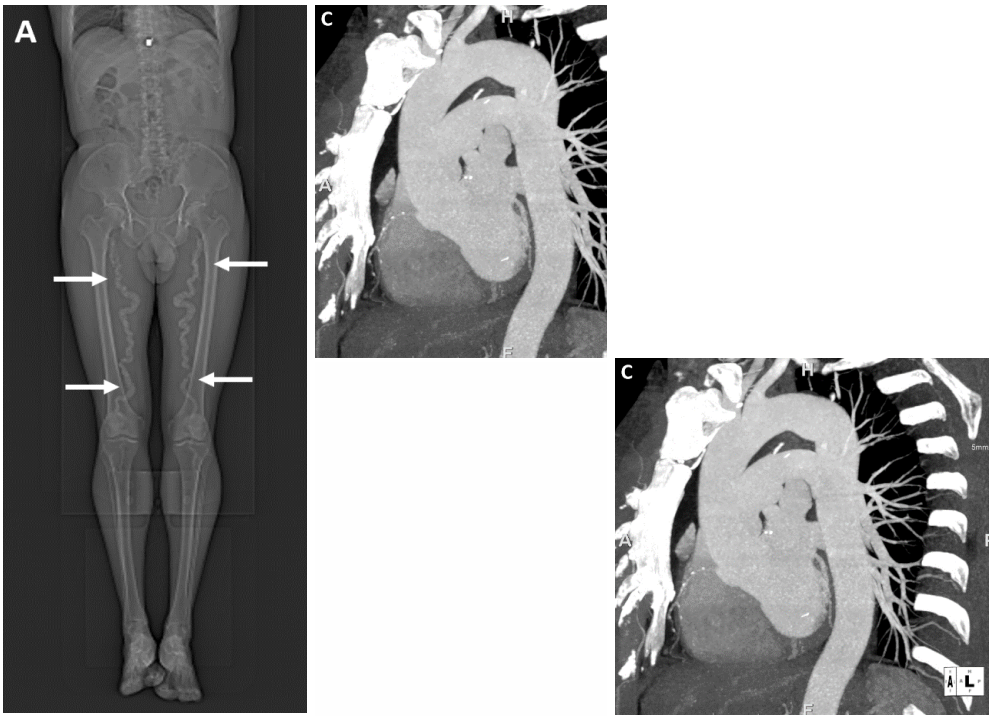

Figure 3: 52-year-old male with Arterial Calcification due to Deficiency of CD73. (a) Scout images and 3D coronal reformatted images from a CT study of the lower extremities without contrast demonstrates tortuous calcification in the femoral and popliteal arteries bilaterally (arrows), but no calcification in the abdominal aorta (curved arrow). (c) Sagittal reformats from a CT angiogram of the chest demonstrates no aortic calcifications.

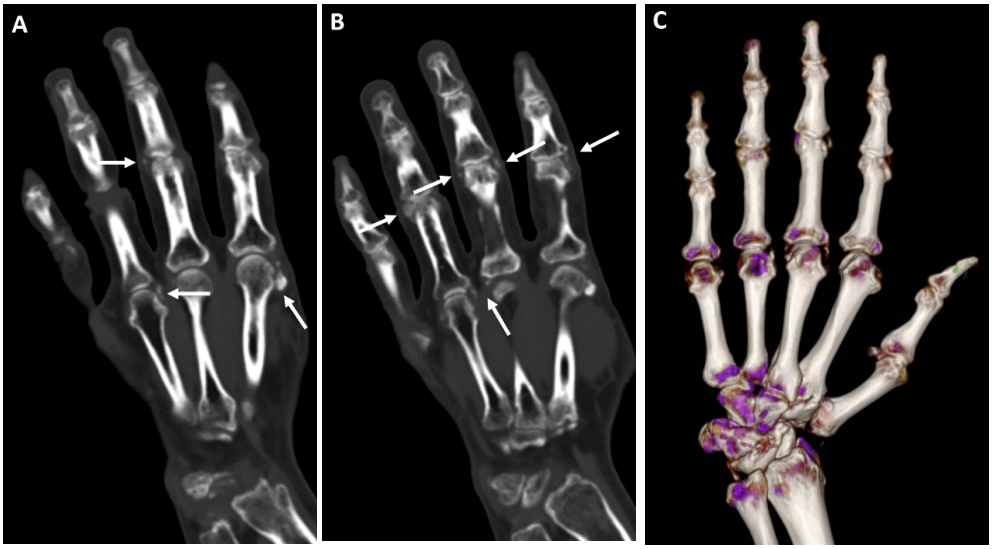

Figure 4: 52-year-old male with Arterial Calcification due to Deficiency of CD73. (a, b) Coronal CT reformatted images of the left hand demonstrate calcifications in the periarticular soft tissues (arrows) at the metacarpophalangeal and proximal interphalangeal joints in the hand. (c) The corresponding 3D reformatted image of the left hand shows an absence of green periarticular monosodium urate crystals in these locations, which would indicate gout.

Table 1: Summary table of Arterial Calcification Due to Deficiency of CD73

Summary Table	**Arterial Calcification due to Deficiency of CD73**
Etiology	Mutation of NT5E causing CD73 deficiency
Incidence	20 cases currently recorded
Age Predilection	Adult-onset disease
Risk Factors	Unknown
Treatment	Bisphosphonates with dual anti-platelet therapy
Prognosis	Unknown
Findings on Imaging	Peripheral artery calcifications of the lower extremities and periarticular calcifications of the small joint capsules of the extremities

Table 2: Differential diagnosis table for Arterial Calcification Due to Deficiency of CD73

Differential Disease	**Etiology**	**Systemic Findings**	**Imaging Findings**
ACDC	Mutation of NT5E gene causing CD73 deficiency	Coronary and peripheral vascular calcifications and peripheral joint calcifications	Tortuosity and arterial calcification of the lower extremity (popliteal, superficial femoral) and periarticular calcifications of the small joints of the extremities on CT and radiographs
Chronic Renal Failure	Reduced phosphate excretion due to renal failure leading to increased parathyroid hormone secretion	Increased calcium and parathyroid hormone in the serum with soft tissue and periarticular calcifications. This often shows up with labs signifying renal failure such as increased creatinine and serum urea.	Subperiosteal demineralization and resorption of the phalanges and periarticular and intraarticular erosions with soft tissue calcification on radiograph and CT scan
Pseudoxanthoma Elasticum	Mutation of ABCC6 or ENPP1	Vascular, dermatologic, and cardiovascular involvement, as well as fundoscopic irregularities	Diffuse vascular and periarticular soft-tissue calcifications on radiographs and CT scan
Generalized Arterial Calcification of Infancy	Mutation of ABCC6 or ENPP1	Vascular and cardiovascular involvement	Diffuse vascular and periarticular soft-tissue calcifications on radiographs and CT scan
Tophaceous Gout	Multifactorial including genetic risk factors, diet, and medical comorbidities	Destructive arthropathy of affected joints with massive tophi	Well-defined periarticular erosions, with eccentric and asymmetric nodular deposits of calcium urate (tophi) in the surrounding soft tissues of affected joints on radiographs
Scleroderma (Systemic Sclerosis)	Unknown	The limited form of scleroderma results in CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), whereas the diffuse form results in fibrosis of visceral organs, including the kidneys, gastrointestinal tract, heart, lungs	Well defined soft tissue calcifications (calcinosis) in the hands and wrists, soft tissue resorption over the distal digits with acro-osteolysis (resorption of the terminal tufts and phalanges)
Wilson's disease	Mutation in ATP7B	Neurologic, hepatic, and endocrine dysfunction with skeletal demineralization and bony abnormalities	Skeletal demineralization with osteoarthrosis and periarticular abnormalities on radiographs or CT
Calcium Pyrophosphate Deposition Disease	Unknown	Acute crystal-induced synovitis (pseudogout), cartilage calcification in joints (chondrocalcinosis) and structural joint abnormalities (pyrophosphate arthropathy)	Chondrocalcinosis in articular cartilage, as well as fibrocartilage structures (menisci, triangular fibrocartilage and labrum), pericapsular calcification, and structural joint abnormalities including marked subchondral cysts, subchondral collapse and fragmentation simulating a neuropathic joint

KEYWORDS

Arterial Calcification due to Deficiency of CD73, Claudication, Peripheral Artery Disease, Calcification, NT5E

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