A Case of Arterial Calcification due to Deficiency of CD73 in an Omani Woman

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Abstract

Calcification of Joints and Arteries (CALJA) is a rare autosomal recessive disorder caused by NT5E mutations that reduce extracellular adenosine and promote ectopic calcification. Fewer than 25 cases have been reported. We describe a 41-year-old Omani woman with a 23-year history of recurrent seronegative polyarthritis affecting multiple peripheral joints and symptoms of lower limb claudication. Her family history included consanguineous parents and a brother with a homozygous NT5E variant. Despite persistently normal inflammatory markers and rheumatologic tests, imaging revealed multifocal periarticular calcifications and mild vascular stenosis. Genetic testing confirmed a homozygous NT5E c.1360G>A variant, establishing the diagnosis of CALJA. Standard therapies with prednisolone and methotrexate offered limited benefit, whereas colchicine improved joint symptoms. Zoledronic acid was initiated to address skeletal and vascular calcifications. This case emphasizes the need to consider CALJA in patients with chronic seronegative polyarthritis and claudication, particularly with a supportive family history.

Keywords: NT5E mutation, CD73 deficiency, Arterial calcification, CALJA, Colchicine, Zoledronic acid

Introduction

Calcification of Joints and Arteries (CALJA) is a rare disease that leads to chronic arthritis and lower limb claudication due to hydroxyapatite crystal deposition.[1]

Mutations in the NT5E gene, which encodes ecto-5'-nucleotidase (CD73), have been linked to arterial calcification due to CD73 deficiency (ACDC), a rare autosomal recessive disorder characterized by vascular and periarticular calcifications.[2]

The NT5E gene mutation reduces extracellular adenosine, which normally inhibits tissue-nonspecific alkaline phosphatase (TNAP) activity. This inhibition is crucial for preventing calcification. Without CD73, adenosine levels decrease, leading to increased TNAP activity, which breaks down pyrophosphate (PPi), a potent calcification inhibitor, ultimately resulting in calcium and phosphate accumulation in arteries and joint capsules.

The prevalence of Calcification of Joints and Arteries (CALJA) is extremely low, estimated to be approximately 1 in 2,500,000 in East Asian populations, reflecting its status as a very rare genetic disorder.[3] To best of our knowledge affecting fewer than 25 patients reported to date.[21]

This extreme rarity contributes significantly to diagnostic challenges and limited awareness of the condition.

We report a case of a 41-year-old Omani woman with long-standing recurrent polyarthritis, initially treated as inflammatory arthritis, later found to have clinical features and family history suggestive of NT5E-related calcification syndrome.

Case Report

A 41-year-old Omani woman complained of recurrent joint pain since the age of 18 years, affecting the hands, elbows, ankles, and toes. The episodes occurred every 2–3 weeks, lasting up to 2 weeks, and were associated with swelling, redness, and morning stiffness. Symptoms worsened with activities, cold weather and pregnancy.

She had symptoms suggestive of lower limb claudication. She had no history of rash, fever, or systemic symptoms. Family history was notable for consanguineous parents and a brother homozygous for an NT5E variant associated with autosomal recessive calcification of joints and arteries. Her sister had chronic arthritis without genetic testing. Physical examination revealed no joint deformities, swelling, or nodules.

Laboratory investigations, including ESR, CRP, rheumatoid factor, anti-CCP, ANA, CBC, liver and renal function, calcium-phosphate metabolism, were normal. Lipid profile was mildly elevated.

Radiographs revealed periarticular calcification of metatarsophalangeal and interphalangeal joints bilaterally as shown in Figures 1, 2, as well as focal calcifications around the talus. Her chest x ray revealed no calcification above the diaphragm. CT coronary calcium scoring and sacroiliac joint imaging were normal. CT angiography reveals mild atherosclerotic changes involving the mid/distal superficial femoral arteries with mild stenosis. The rest of the arteries appear unremarkable Figure 3.

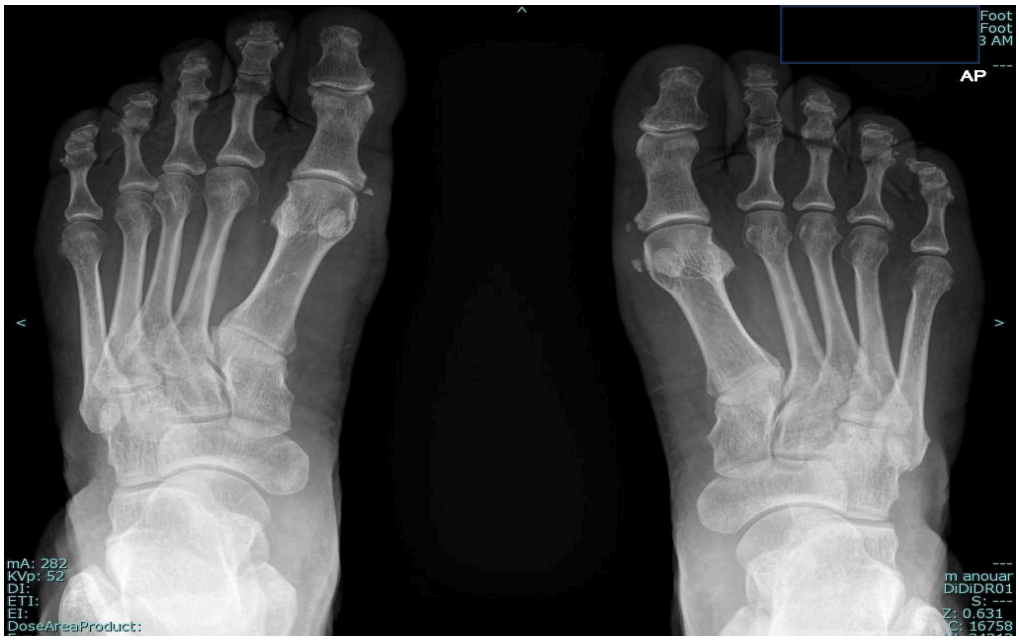

Figure 1: X ray feet showing periarticular calcification of metatarsophalangeal joints.

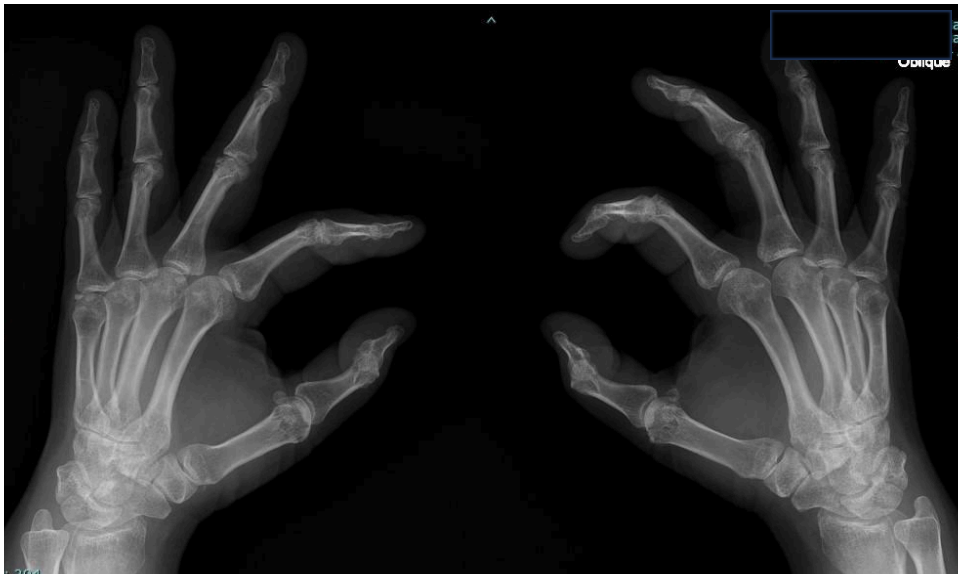

Figure 2: X-ray of hands revealed periarticular calcification of interphalangeal joints bilaterally.

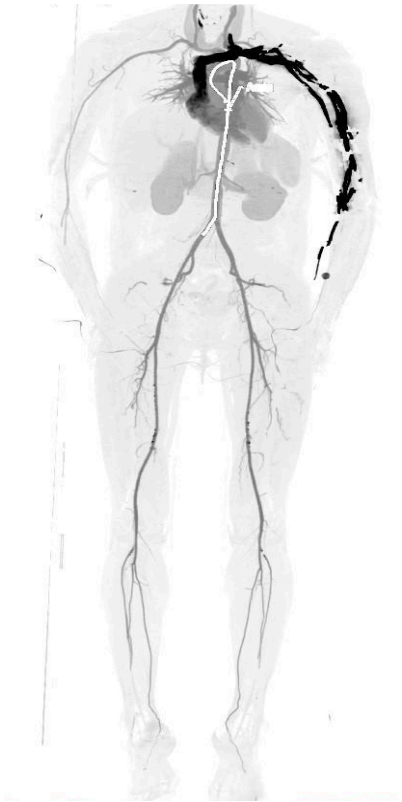

Figure 3: CT angiography revealed mild atherosclerotic changes involving the mid/distal superficial femoral arteries with mild stenosis and non-opacification of the left lower limb arteries.

Genetic testing revealed a homozygous NT5E c.1360G>A variant consistent with autosomal recessive calcification of joints and arteries. This variant has been reported in association with CD73 deficiency and is classified as likely pathogenic according to the American College of Genetics and Genomics (ACMG) criteria.

She had been treated with prednisolone at a dose of 10 mg daily and methotrexate 6 mg weekly with partial improvement of her symptoms when seen earlier in a private clinic. We trialed her on colchicine which helped with her articular symptoms. She also received a dose of intravenous zoledronic acid to help reduce the severity of vascular and skeletal calcifications.

Patient consent for publication purposes was obtained.

Discussion

Calcification of joints and arteries (CALJA), also referred to as arterial calcification due to CD73 deficiency (ACDC), is an autosomal recessive disorder caused by mutations in the NT5E gene encoding the enzyme ecto-5′-nucleotidase (CD73). To date, only a limited number of genetic variants have been reported worldwide.[3]

The transmembrane protein CD73 is expressed by stromal cells, endothelial cells, and lymphocytes and catalyzes the hydrolysis of adenosine monophosphate to adenosine and inorganic phosphate (Pi). Adenosine normally inhibits tissue non-specific alkaline phosphatase (TNAP), which catalyzes the hydrolysis of PPi to Pi. Mutations in the NT5E gene increase TNAP activity, reducing PPi and promoting mineralization at ectopic sites.[4]

Historically, medial arterial calcification associated with periarticular deposits was first described by Magnus-Levy (1914) and Levitin (1945). (5-6) The familial nature of the condition was later supported by Sharp (1954).[7] Subsequent reports before the genomic era described similar phenotypes without molecular confirmation. The molecular basis of CALJA was first identified in 2011 by St. Hilaire et al., who demonstrated that NT5E mutations underlie this phenotype.[2] Their patients presented with intermittent claudication and intense articular pain involving the hands and lower extremities, with characteristic juxta-articular calcifications and sparing of large central arteries.

In our patient, articular manifestations began in adolescence and were characterized by recurrent episodes of polyarthritis affecting the small and large joints of the hands and feet, with no evidence of erosive changes or intra-articular mineralization, which is consistent with the established literature.[8]

Imaging demonstrated periarticular, capsular, and ligamentous calcifications without erosive changes or intra-articular mineralization, aligning with published findings. Axial skeletal involvement, including osteophytes, syndesmophytes, and ligamentous calcifications, has been reported in some cases but was absent in our patient.[9]

The episodic arthritic flares, typically lasting up to two weeks, are a hallmark of ACDC.[9] Pain correlates with periarticular calcification, which may regress over time, suggesting a potential for partial reversibility.[10] Vascular manifestations usually involve calcification of large lower-limb arteries, particularly the femoral and popliteal arteries, leading to claudication.[9]

In our patient, CT angiography showed mild stenosis of superficial femoral artery involvement and non-opacification of the left upper limb arteries, consistent with reports of both lower and upper extremity disease.[13,14,15] Even though the stenosis was only mild, these findings are clinically relevant as arterial calcification in CALJA usually impacts the arteries of the lower limbs and may lead to serious vascular issues. Timely detection of vascular involvement is crucial, as increasing calcification may result in aggravated claudication and critical limb ischemia over time. Consequently, vascular imaging is crucial not only for aiding in diagnosis but also for monitoring disease progression and directing long-term care.

Aortic valve calcification has also been described in two Japanese sisters with ACDC, aged 77 and 71 years. These were reported as the first cases undergoing aortic valve replacement (AVR) for severe aortic stenosis. [11]

Given its rarity, no standardized diagnostic criteria exist. The diagnosis should be suspected in patients presenting with early-onset seronegative arthritis and features of peripheral vascular disease, particularly in consanguineous families. Genetic confirmation remains essential.

In 2025, we encountered a Japanese woman who presented with a leg ulcer attributable to CALJA (calcification of joints and arteries), further underscoring the progressive, debilitating nature of vascular calcification in this rare genetic condition.[12]

In CALJA, laboratory findings are typically normal with negative RF, anti-CCP antibodies and ANA. An increase in inflammatory markers could be observed during episodes of arthritis, with normal values during the inter-critical phases as documented by local treating healthcare providers at the time of the acute arthritic flare. In our patient, however, they remained persistently normal over the years.[9]

Although ACDC imposes a considerable impact on patient quality of life, there is currently no established treatment. The associated arthritis is generally responsive to non-steroidal anti-inflammatory drugs (NSAIDS) or low-dose glucocorticoid.[9,10]

In our patient, colchicine therapy proved effective in relieving articular symptoms. This observation suggests that colchicine may play a role in decreasing the frequency of hydroxyapatite arthritis episodes. Moreover, consistent with findings from recent studies, colchicine might also help attenuate vascular inflammation and could potentially have a preventive role in cardiovascular complications among patients with CAJA. [15]

Methotrexate MTX, which enhances intracellular adenosine concentration,[16] did not appear to effectively control the arthritic episodes in our patients. It is possible that in these patients, extracellular adenosine resulting from MTX activation may be insufficient to compensate for the physiological loss of adenosine from CD73 deficiency.[9]

In a pilot study Etidronate treatment appeared to have slowed the progression of further vascular calcification but did not have an effect in reversing vascular and/or periarticular joint calcifications in small ACDC cohort.[17]

Furthermore, long term etidronate use has been associated with impaired bone mineralization and osteomalacia, restricting its safety for chronic administration.[18]

Given these limitations and the restricted availability of etidronate in many centers, Zoledronic acid, a potent third-generation nitrogen -containing bisphosphonate, was selected as an alternative. Zoledronic acid exhibits a stronger inhibitory effect on osteoclastic bone resorption, a longer duration of action, and better skeletal safety data compared with etidronate.[19]

Additionally, emerging evidence suggests that newer bisphosphonates, including zoledronic acid, may exert anti-atherogenic and anti-osteogenic effects on vascular tissues, potentially contributing to attenuation of vascular calcification.[20]

Therefore, zoledronic acid was used in our patient as a more potent and practical bisphosphonate option, aiming to mitigate both skeletal and vascular calcifications while ensuring long term treatment safety and feasibility.

Conclusion

This case highlights the importance of considering CALJA in patients with long-standing, seronegative polyarthritis and claudication, particularly in consanguineous families. Genetic testing for NT5E variants is essential for diagnosis. Colchicine and bisphosphonates may provide symptomatic and potential disease-modifying benefits.

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