A rare case of Hyperphosphatemic Tumoral Calcinosis in a 13 year old Nigerian boy

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Abstract

Tumoral calcinosis is a rare disorder that presents with ectopic calcifications deposited at different periarticular soft tissue regions of the body- mostly hips, elbows and shoulders. It results from a relative deficiency of, or resistance to, the phosphate-regulating hormone - Fibroblast Growth Factor 23 (FGF23), due to gene mutations, causing hyperphosphatemia. We describe this condition in a 13 year old, Nigerian boy who presented with a 7 year history of multiple body swellings of firm to hard consistency. Laboratory investigations showed hyperphosphatemia with normal serum calcium, vitamin D and parathyroid hormone levels. Radiological and histological findings were consistent with tumoral calcinosis. Having had two previous surgeries to remove the lesions, he was now commenced on low phosphate diet and phosphate binders. It is important to differentiate tumoral calcinosis from other causes of pathological calcification using clinical and laboratory findings especially in environments where molecular genetic testing is not readily available.

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Introduction

Tumoral Calcinosis (TC) is a rare, autosomal recessive disorder where there is deposition of calcium salts primarily of hydroxyapatite (naturally occurring calcium phosphate)[1,2] and/or calcium carbonate[3] in different periarticular soft tissue regions mostly hips, elbows and shoulders. These are usually sites of repeat trauma and/or pressure.

The etiology of TC is uncertain but is reported to be due to disturbances in Fibroblast Growth Factor (FGF) 23-mediated phosphate regulation. Patients develop either deficiency of, or resistance to FGF-23, a phosphaturic hormone, leading to hyperphosphatemia and ectopic calcifications. The lesions slowly increase in size and may be painful and debilitating.[4,5] Some lesions may perforate the skin, and drain liquid hydroxyapatite (also known as "milk of calcium"), which is often confused with purulent drainage. Such lesions often heal poorly. Depending on the size and location, TC can significantly impair range of motion or lead to frozen joints. Calcifications that occur around joint spaces can impair mobility and physical function. Inflammation is also a prominent feature, including painful diaphysitis with cortical hyperostosis.[6] It can be classified based on the blood phosphate levels into:

Primary normo-phosphatemic TC: Normal calcium and phosphate levels are the hallmark of this condition. Usually presenting before the second decade of life in tropical or subtropical regions. Recent literature shows growing evidence of a familial basis for this type of pathology, involving mutations in the gene encoding for SAMD-9 protein.[7]

Primary hyperphosphatemic TC: These patients present with normal calcium levels but abnormally increased phosphate levels. The usual presentation is during the first and second decades of life.[8] Genetic predisposition is a feature of this type of TC where hyperphosphatemia arises due to reduced urinary phosphate excretion caused by recessive mutations in UDP-N-acetyl-alpha-D-Galactosaminyl Transferase 3 (GALNT3) and KLOTHO genes, that causes the inactivation of FGF23, a phosphoturic hormone.[8-10] Mutations in GALNT3 have been identified so far only in patients of Middle Eastern or African-American origin.[8]

Secondary hyperphosphatemic TC: Hyperphosphatemia is due to increased renal phosphate retention in patients with Chronic Renal Failure.

Case Report

A 13 year old boy presented at the Metabolic Clinic at the Department of Chemical Pathology of the University of Nigeria Teaching Hospital, Enugu, southeast Nigeria, with a 7 year history of recurrent, nodular subcutaneous swellings on different parts of his body – both armpits, thigh, back of head, elbows. The swellings were firm, some are matted while others are discrete. They were gradually increasing in size and sometimes painful. Although they do not prevent the patient from carrying out his daily personal activities such as eating and bathing, those on his hands affect his holding objects and writing. There is no history of weight-loss, night sweats, bone pains, oliguria, loss of appetite, or use of medication. The patient is the first of three children (all boys), and there is no family history of similar condition.

On examination, the boy was not in any obvious distress, not dehydrated. There were generalized nodular swellings at different sites of his body: firm to hard matted swellings on the fingers of his right hand (width of about 3.5 cm), discrete firm swellings at the anterior aspect of both armpits ranging from 1 cm to 3 cm in diameter, but no lymphadenopathy (Figure 1). Surgical scars were seen at the left olecranon region, right thigh and back of the head (due to previous excision biopsies).

The following differential diagnoses were considered: gout, pseudogout, tumoral calcinosis, mucolipidosis, and neurofibromatosis.

Investigations

His blood tests revealed the results described in Table 1.

Plain radiographs of the hand and arm lesions showed amorphous, multi-lobulated calcifications in a peri-articular location (Figure 2). Computed Tomography scan was not done due to financial constraints.

Histology sections from three previous excision biopsies (back of the head, left elbow and right thigh) showed nodules of dystrophic calcification within broad bands of fibrocollagenous connective tissue stroma. No evidence of malignancy was seen.

Based on the above investigations, a definitive diagnosis of tumoral calcinosis was made. Genetic molecular testing to identify mutations in the FGF23 genes was not available in any laboratory (public/private/research) in the country. Efforts to conduct the genetic test at specialized laboratories overseas proved abortive, as it was part of national genetic screening programs for the citizens there. Consequently, genetic testing was not done for this patient.

Treatment

The patient and his father were counseled to understand the aetiology of the condition as being genetic, and to know that there was no definitive treatment except surgical excision, of which lesions could recur. He was prescribed with a low phosphate diet, *i.e.* foods with very low phosphorus content such as: egg white, olive oil and vegetable fats, *e.g.* palm oil, soya oil, margarine, protein-free foods, white bread, staples such as beans, yam, white rice, potatoes preferably cooked by boiling, avoid cow's milk but can

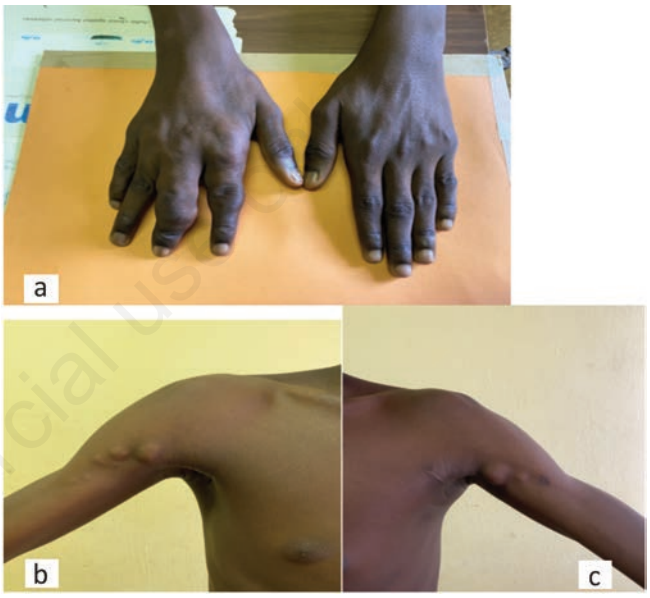

Figure 1. Morphological features show: a) patient's both hands with matted swellings on the right hand, b) patient's right armpit with discrete swellings, c) patient's left armpit with discrete swellings and scar from previous excision.

Table 1. Results of the blood tests performed on the patient.

Biochemical test	Patient's results		Reference ranges	Unit
Sodium	142		135-145	mmol/L
Potassium	3.7		3.5-5.0	mmol/L
Bicarbonate	22		22-28	mmol/L
Chloride	106		97-108	mmol/L
Urea	3.8		2.1-7.1	mmol/L
Creatinine	89		53-150	umol/L
Uric acid	0.29		0.08-0.42	mmol/L
Total calcium	2.5		2.2-2.8	mmol/L
Albumin	46		30-50	g/L
Adjusted calcium	2.38		2.15-2.55	mmol/L
Phosphate	2.8	HIGH	0.8-1.6	mmol/L
Calcium x phosphate product	6.7	HIGH	<4.4	mmol2/L2
Vitamin D	43		30-50	ng/mL
Parathyroid hormone	38		10.4–66.5	ng/mL

take diary milk alternatives such as soya milk, and foods which have very low bioavailable phosphorus such as fruits and vegetables *e.g.* grapes, watermelon, cabbage. Non-calcium phosphate binder (Tab Sevelamer 800 mg) was also prescribed three times daily (every 8 hours) with meals, to reduce intestinal absorption. He was offered physiotherapy exercises for his fingers to improve the range of movement.

Outcome and follow-up

Two weeks later, the patient presented with complaint of pain in the matted swellings of the hands. Both hands were tender and warm to touch. He had not commenced the phosphate binder at this time because he had not been able to source it. he was prescribed with acetazolamide and probenecid for renal phosphate excretion. Anti-inflammatory medication (tab diclofenac 50 mg when needed) was prescribed for the symptomatic hyperostosis.

The major constraint in managing this patient was poor finances and non-availability of prescribed phosphate binders. His genetic mutation is yet to be characterized.

Discussion

Most of the reported cases of TC have been in blacks[11] but it has also been reported in the inhabitants of Papua New Guinea,[12] and in a few whites.[4] The disease process usually begins in the paediatric years between 5 to 10 years of age, and then the patient presents in the first or second decade.There is no sex preference.[13] We observed TC in a male patient similar to another case report,[14] but another study of 7 cases reported it presented usually in females.[12]

Primary hyperphosphatemic TC is caused by genetic mutations in the FGF23,[9] GALNT3,[8] or KLOTHO[10] gene resulting in inactivation of the phosphaturic protein FGF23. The mutations result in relative deficiency of, or resistance to, FGF23, which leads to hyperphosphatemia, due to loss of phosphate negative feedback control mechanisms, resulting in increased renal tubular reabsorption of phosphate and reduced phosphate secretion at the proximal convoluted tubule. As well as elevated or inappropriately normal 1,25 hydroxyvitamin D production, which promotes gastrointestinal absorption of phosphorus and calcium. The net effect is an increase in the calcium phosphate product (hydroxyapatite) that gets deposited in soft tissues (calcinosis).

Affected individuals develop ectopic calcifications and/ or diaphyseal hyperostosis, which may manifest clinically as diaphyseal pain of the long bones and is often erroneously diagnosed as osteomyelitis.[15] The hip has been described as the region of predilection,[12] and was reported to involve both hips in some cases.[16,17] But our index case did not have any deposits in his hip, rather he had at the back of his head, axilla and previously excised deposits at the elbow and thigh. Other sites of calcification deposits that have been described include: elbows, inferior angle of scapulae,[13] shoulders, hands, Achilles tendon, and even teeth.[4,10]

Some of the proposed theories for the pathogenesis of the calcifications include: i) repetitive trauma/chronic pressure leading to hemorrhages in the peri-articular tissue initiating a foamy histiocytic response; ii) the reparative process together with friction forces leads to neobursae formation with an interplay between multifactorial calcification process and collagenolysis.[18]

On radiographs tumoral calcinosis appears as heterogeneous calcified masses.[4] On occasions, calcific deposits around large joints may demonstrate "layering effect".[17] Likewise, despite the type, the histology of the TC lesions in the three groups is identical. Grossly, it appears as an unencapsulated, firm subcutaneous mass that may extend into the adjacent muscles. The cut surface shows nodules separated by fibrous septa and filled with yellow-white chalky material with gritty consistency or milky-yellow white liquid.[19] Microscopically, the active phase of the lesion shows a central area of calcification surrounded by macrophages, osteoclast-like multinucleated giant cells, fibroblasts, and chronic inflammatory cells. The cellularity decreases during the inactive phase, leaving behind amorphous or granular calcified material bordered by dense fibrosis.[19] Histology was our method of definitive diagnosis similar to other reports in resource limited settings like ours.[12,16,17] Ebong *et al.* went on to perform chemical analysis of the excised tumor which showed it consisted of calcium phosphate.[17]

There is no standard treatment for this disease because clinical response to proposed treatments have been variable. Most case reports attempt to lower serum phosphate by administering low phosphate diet, phosphate binders such as sevelamer or aluminium hydroxide which will decrease absorption of dietary phosphorus; acetazolamide- a carbonic anhydrase inhibitor that will increase urinary phosphate excretion; probenecid that promotes renal phosphate excretion; or niacinamide/nicotinamide that reduces renal phosphate reabsorption.[4,5,20-22]

In patients with symptomatic hyperostosis (erythema, pain, warmth, fever), anti-inflammatory medication such as NSAID and glucocorticoids can be given to reduce the inflammatory process.

Surgical debulking may be performed in subjects with functional impairment or severe pain, although some westernized studies have reported that this is not routinely undertaken because calcinosis often recurs.[5,23] In addition, they claim postsurgical morbidity from attempted complete excision or poor wound healing may complicate the condition. However, a case report by Nggada *et al.*, confirmed that their patient had a successful excision with good wound healing, similar to our index case.[24] Also, Ogunlade *et al.* as well as Ebong *et al*. reported that there was no recurrence of the excised tumors in their patients.[16,17]

Although TC is not fatal, patients often have reduced range of motion and/or pain that can severely affect quality of life by impairing activities of daily living, such as walking, eating, and

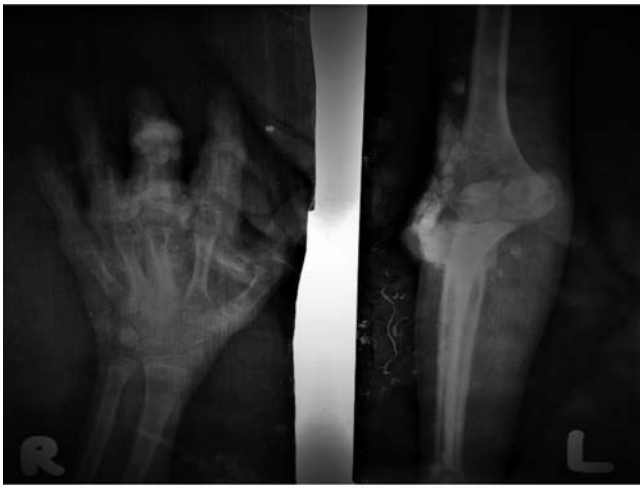

Figure 2. Radiographic films of right hand and left elbow joint showing multiple, oblong, radio-opaque calcific deposits.

routine hygiene, for which conservative management and physical therapy may be helpful.

Conclusions

Tumoral calcinosis is a rare condition that must be differentiated from other varieties of pathological calcification such as chronic vitamin D intoxication, the milk-alkali syndrome, renal insufficiency, chronic nephritis, primary hyperparathyroidism, calcinosis universalis, calcinosis circumscripta and dystrophic calcification. This can be resolved through combining: detailed family, drug and past medical history; typical radiological features of TC; and serum biochemical profile (including serum calcium level, serum phosphorus levels, renal function tests, serum parathormone level and 1,25-dihydroxy-vitamin D levels, cFGF-23 level,[25] especially in resource-limited environments, where molecular genetic tests may be unavailable for confirmatory diagnosis.

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