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Report of an Unusual Case of Primary Normo-phosphatemic Tumoral Calcinosis

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Abstract: ***Tumoral calcinosis is a rare disease characterized by calcium deposition in different peri-articular soft tissue regions. It is classified into three categories: Primary normo-phosphatemic tumoral calcinosis, Primary hyper-phosphatemic tumoral calcinosis and secondary tumoral calcinosis. The primary types mainly manifest in childhood or adolescence as painless, firm, masses around the joints that may lead to joint function limitations specially when large in size. We report an unusual late presentation of primary tumoral calcinosis in a 67-year-old lady. Treatment with one dose of Zolendronic acid seemed to stop disease progression.***

Keywords: Calcinosis cutis, primary Tumoral calcinosis, Zolendronic acid, calcinosis, calcification

1. Introduction

Calcinosis cutis is a group of disorders characterized by calcium deposition in skin and soft tissues. It begins with a calcium phosphate nidus and progresses to hydroxyapatite crystal formation within the collagen matrix [1]. It manifests as a calcified mass in the soft tissue that can be complicated by pain, ulceration and super infection. It also could result in functional disability if the peri-articular areas are involved.

There are 4 types of calcinosis: dystrophic, metastatic, idiopathic and iatrogenic. Dystrophic Calcinosis is the most common type and it is most frequently associated with autoimmune connective tissue disorders [2]. Examples of causes of each type are listed in table 1 [1, 2].

Table 1: Different Types and Causes of Calcinosis Cutis

1. Dystrophic	**3. Metastatic**
Vascular Venous insufficiency	Chronic renal failure Calciphylaxis
Neoplasm Primary bone-forming tumor Tumor necrosis	Primary hyperparathyroidism Secondary hyperparathyroidism
Autoimmune Scleroderma SLE Dermatomyositis Mixed connective tissue disease	Destructive bone disease Paget disease
Infection Parasitic infestation Cysticercosis	Paraneoplastic hypercalcaemia
Trauma	Sarcoidosis
Panniculitis	Milk-alkali syndrome
Inherited diseases of connective tissue Ehlers-Danlos syndrome	Drugs Excessive vitamin D
2. Idiopathic	**4. Iatrogenic**
Tumoral calcinosis	Intravenous extravasation of calcium chloride
Primary normo-phosphatemic	Calcium salt exposure electroencephalography
Primary hyper-phosphatemic	Pentazocine and pitressin
-Secondary	After numerous heel sticks in neonates

Tumoral calcinosis (TC) is one of the causes of idiopathic calcinosis cutis. Its diagnosis could be challenging, as there is a wide range of differential diagnoses. The treatment of the disease is mainly based on lowering serum phosphate levels and/ or surgical excision in some cases.

2. Case report

This a 67-year-old lady presented with diffuse subcutaneous calcification evolving over a decade. She has two exceptionally large masses one at the right axilla and the other at the right hip peri-articular area, measuring 40cm on plain X-ray. She also has digital involvement with calcifications complicated by painful ulceration and white chalky exudate. She has no symptoms suggestive of dermatomyositis, scleroderma or sarcoidosis. She has a normal renal function and she denied taking vitamin D supplements. Her family history is not contributory to the disease. Her laboratory investigations are summarized in table 2.

Table 2: Laboratory Investigations

	Value	Reference range
WBC	$5x10^9$	4.0-9.0
HBG	120 g/l	135-170
Platelets	$250 x10^9$	15-400
Sodium	140 mmol/l	135-145
Potassium	4 mmol/l	3.5-5.0
Chloride	100 mmol/l	98-107
Urea	5 mmol/l	3.0-13
Creatinine	50 umol/l	62-120
Albumin	40 g/l	35-52
Calcium	2.29 mmol/l	2.15-2.55
Phosphate	1.19 mmol/l	0.5-2.2
Alkaline Phosphatase	313 U/l	40-129
C-telopeptide	1221 ng/l	104-1008
PTH	6.7 pmol/l	1.6-6.9
25OH Vit D	25 nmol/l	75-250
1,125 OH Vit D	121 pmol/l	60-208
Creatine Kinase	66 u/l	<190
ESR	26 mm/h	0-20
CRP	<1 mg/l	<6

ANA	Weakly positive	
Anti-ENA	Negative	

X-ray of her right hip and left hand is shown in figure 1 and figure 2. MRI of the right axilla showed a large calcified mass. Her investigations are consistent with primary normo-phosphatemic tumoral calcinosis. The normal renal function and PTH ruled out renal or parathyroid disorders. Her low levels of 25OH Vitamin D also excluded the possibility of Vitamin D hypervitaminosis. All her serological screening for connective tissue disease came back negative. She has a no muscle weakness and a normal CK level which rules out dermatomyositis. She has no clinical symptoms or laboratory findings that support the diagnosis of sarcoidosis. Her chest X-ray did not reveal any hilar adenopathy or findings of interstitial lung disease.

The elevated alkaline phosphatase and the elevated C-telopeptide reflects her active disease, which is evident with her history of progressive calcification over the last 10 years. She had a bone scan and bone mineral density showed evidence of high uptake in the tumor sites and severe osteoporosis.

We treated her with a phosphate lowering strategy despite having a normal phosphate level. We started her on a low phosphate diet (1000mg/day) and Aluminum Hydroxide 300mg 3 times a day with meals and Acetazolamide 250mg twice a day. However, she did not tolerate the medications but she was compliant with the low phosphate diet. Despite these measures, her disease continued to progress. We started her on Zolendronic acid (Aclasta) 5mg intravenously once every year for her osteoporosis. We were hoping with this intervention to decrease the bone formation in her tumor sites and limit the progression of the calcification. Six months later her disease stabilized and she did not develop new lesions.

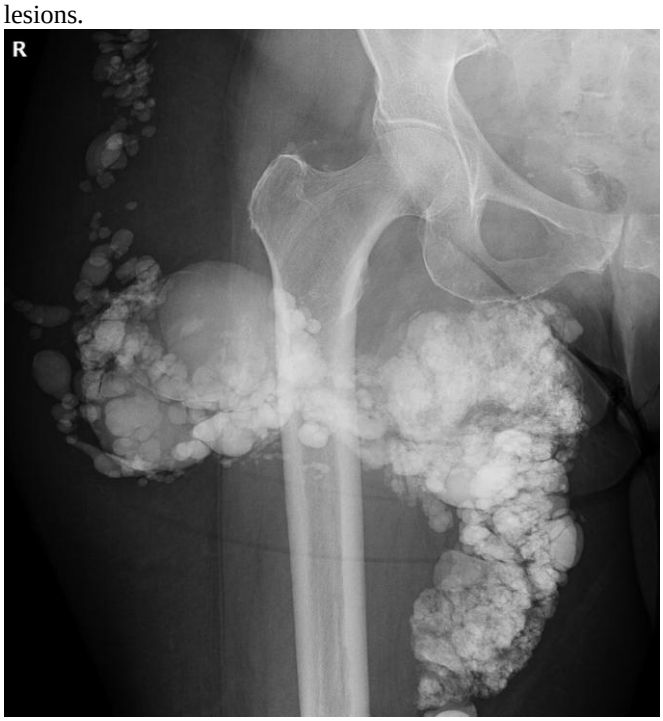

Figure 1: Extensive lobulated soft tissue calcifications in the proximal right thigh

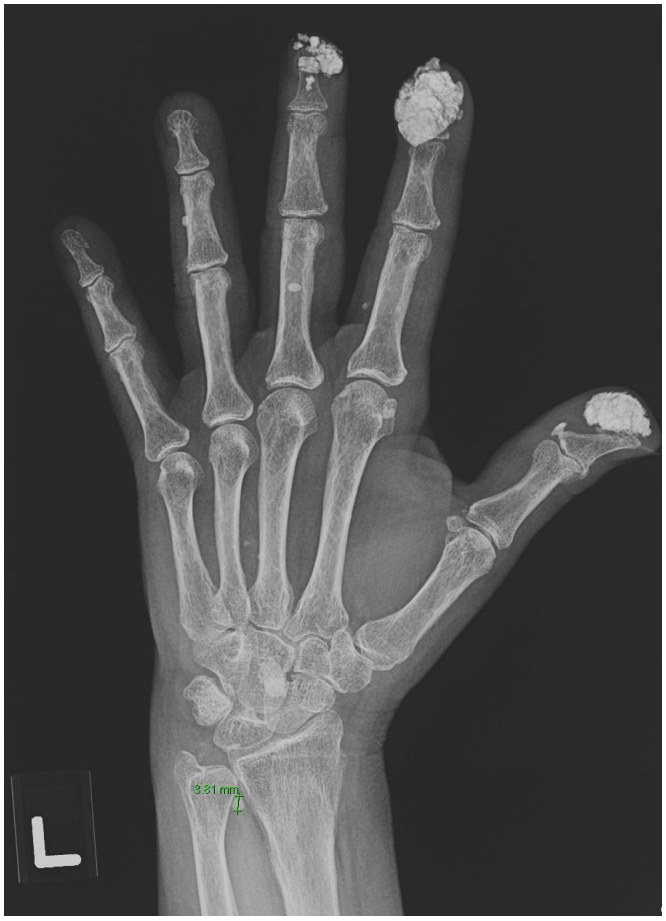

Figure 2: lobulated dense calcification involving the soft tissue of the left thumb and distal phalanx of the second and third finger

3. Discussion

Tumoral calcinosis is a rare syndrome that mainly manifests in childhood or adolescence as painless, firm, tumor-like masses around the joints that may lead to joint function limitations specially when large in size. Areas most commonly involved by this pathology are peri-articular soft tissues of the shoulders, elbows and hip area [3]. Other regions surrounding the metacarpals/metatarsals, spinal and temporo-mandibular joint, has been reported. It occasionally affects the skin and cause ulceration but it spares internal organs.

Tumoral calcinosis is classified into 3 types [4]: the first type is primary normo-phosphatemic TC, which is characterized by normal serum calcium and phosphate levels. They may have transient hyper-phosphatemia initially. Their 1,25 vitamin D levels are usually normal or elevated. They mostly present as solitary masses in the second decade. This type has not been associated with familial basis until recently where mutations in the gene encoding for SAMD9 protein were found [5]. The second type is primary hyper-phosphatemic TC characterized by normal serum calcium but elevated phosphate levels. It is an autosomal recessive disorder with mutations involving GalNAc transferase 3 gene, *GALNT3*, and KLOTHO *[6-8]*. It usually presents in the first or second decade of life. The third type is secondary TC, which occurs

secondary to chronic renal failure, vitamin D deficiency and hyperparathyroidism.

Our patient has tumoral calcinosis that fits the first type (primary normo-phosphatemic TC). She is unique as she developed calcinosis in her fifth decade. She has no family history of a similar condition and her phosphate was not elevated. Her imaging studies were classic for tumoral calcinosis and all other causes calcinosis were ruled out.

The pathogenesis of TC involves minimal repetitive trauma leading to hemorrhages in the peri-articular tissue initiating a foamy histiocytic response, a reparative process is initiated lead to neobursae formation. This results in the characteristic lesions of TC, representing the active stage of the process. Finally, calcified debris fills the loculi leading to bone formation [4, 9].

The diagnosis of tumoral calcinosis is challenging. There is no specific laboratory test to confirm the diagnosis. The diagnosis is usually made by specific radiological findings. Plain x-rays typically show amorphous, multilobulated and cystic calcifications in a peri-articular location while CT usually shows cystic loculi with fluid-fluid levels. It is used to help in determining the extent of the disease.

Magnetic resonance imaging shows inhomogeneous high signal intensity on T2-weighted sequences. Scintigraphy using radiolabeled phosphate compounds (technetium-99m methylene diphosphonate) is of great value in detecting multiple lesions, newly forming lesions, bone marrow affection, and for monitoring therapy reflecting the activity of the lesions [10, 11]. Although biopsy is better avoided because of the risk of infection, it can be done to confirm the diagnosis in some cases. Our patient had classic plain X-rays findings (figure 1). We elected not to perform a biopsy, as imaging studies were conclusive.

The treatment of primary tumoral calcinosis is divided into medical and surgical treatments. The approach to the treatment is dependent on the stage of the disease. For example, an active disease is better treated medically with phosphate lowering agents whereas in stable disease, it is better treated surgically [12]. In some cases the combination of medical and surgical treatment is required.

The medical treatment aim to lower the phosphate levels [13] even in noro-phoshatemic cases; this could be achieved by low phosphate diet and phosphate binders such as oral Aluminum Hydroxide. Acetazolamide is diuretics that promotes phosphaturia and can be used in combination with phosphate binders. Our patient could not tolerate this combination secondary to side effects. We referred her for surgical excision but her disease was deemed very active at this stage and that her risk of recurrence after excision is very high.

We used Zolendronic acid (Aclasta) in our case to treat her osteoporosis and also to try to decrease her bone formation. Bisphosphonates has been used in cases with tumoral calcinosis with successful lesion reduction [14]. Zolendronic acid works by reducing the serum levels of alkaline phosphatase and it is also used to treat Paget disease along with many other bisphosphonates. When compared to Residronate, Zolendronic acid treatment normalized or reduced the serum alkaline phosphatase level more frequently. It also had a shorter time to therapeutic response, a lower frequency of loss of response in follow up (median 190 days) and a sustained suppression of bone turnover markers [15]. Zolendronic acid also showed higher rates of biochemical response and normalization of serum alkaline phosphatase when compared to Pamidronate [16].

4. Conclusion

Tumoral calcinosis is one of the causes of idiopathic calcinosis cutis and should be considered in the differential diagnosis of a calcified mass. Primary TC usually presents in the second decade of life. However our case and other few reported cases presented in older ages. The diagnosis mainly established by radiological imaging and ruling out other causes. The mainstay of treatment is phosphate-lowering strategy and surgical excision. Bisphosphonates has been used in the treatment when other measures fail.

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Author Profile

Roaa S Alsolaimani received the M.B B.S from King Abdulaziz University in 2004 and RCPC degrees in internal medicine and rheumatology and Western University in 2012 and 2013, respectively. During the following years she was working in Vasculitis.