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CASE REPORT

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Familial hyperphosphatemic tumoral calcinosis: A rare case report from Syria

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Key Clinical Message

Tumoral calcinosis is a very rare disease mainly caused by a disturbance in phosphate metabolism. It is advisable to contemplate screening more organs such as testes, thyroid, and spleen in patients with TC. This study provides insight into tumoral calcinosis for physicians in the region and encourages future work on the matter.

Abstract

Familial hyperphosphatemic tumoral calcinosis (FHTC) characterized by progressive deposition of calcium phosphate crystals in soft tissues. Tumoral calcinosis (TC) is often underdiagnosed in Syria as it cannot be confirmed without genetic testing, which is unavailable in Syria. We present the first reported case from Syria of a man with TC. This case has findings that were not reported in other cases such as testicular calcification, brain calcification, enlarged thyroid, and splenomegaly. Determining these genes in the case presented wasn't possible and future studies need to overcome this hurdle.

KEYWORDS

hyperphosphatemic tumoral calcinosis, phosphate, splenomegaly, testicular calcification, tumoral calcinosis

1 | INTRODUCTION

Tumoral clacinosis (TC) is a rare disorder of phosphate metabolism that was first described in 1943.TC is classified as primary and secondary subtypes. Secondary TC is mainly caused by chronic renal disease. On the other hand, primary TC is also classified into normophosphatemic TC, and familial hyperphosphatemic TC (FHTC).[1]

There are 75 individuals with a molecularly confirmed diagnosis of FHTC without an apparent sex predominance. FHTC usually manifests in the first two decades of life. Symptoms vary depending on the site of calcifications. It can also be asymptomatic. Calcifications typically occur in peri-articular areas such as hips and shoulders.[2,3]

Laboratory and radiologic studies play a role in establishing the diagnosis, the diagnosis is then confirmed with molecular genetic testing.

No guidelines for TC management are available. Therefore, management decisions are made case by case.

We report a case of 36-year-old man with FHTC associated with an unusual manifestations.

2 | CASE HISTORY / EXAMINATION

A 36-year-old man from Syria presented with a 17-year history of hard and tender masses. In 2006, the first presentation was a mass in the left buttock. The mass was surgically excised without further treatment or follow up. In 2015, other masses appeared in the right buttock, shoulders, right elbow and right wrist. One of the lesions was also removed surgically and the pathological report at that time showed a highly cellular lesion composed of large number non-neoplastic osteoclast-like giant cells which was consistent with giant cell tumor. In 2018, he presented with multiple nodules on elbow and fingers mimicking gout tophi. The patient was diagnosed with gout and was prescribed allopurinol 300 mg once daily and colchicine 0.5 mg twice daily. In 2023, the size of the masses was increased with marked limitation of right hip movement. Family and medical history were unremarkable. The parents of the patient were not relatives. There was no history of trauma or an autoimmune disease.

Upon admission, the vital signs were normal. On physical examination hard masses were palpable at the right buttock and both shoulders, the thyroid was enlarged and hard, and the spleen was palpable three fingers below the left costal margin.

3 | METHODS

Laboratory findings are shown in Table 1. It showed that the serum phosphor level is elevated (6.1 mg/dL) with increased reabsorption of phosphate from the renal tubules (TRP = 0.87).

X-ray and CT revealed calcified masses in the right buttock, shoulders, with marked calcifications in the brain and testis. The CT report confirmed a spleen enlargement measuring 17 cm without calcifications (Figure 1). Ultrasound of the thyroid gland showed enlargement of the gland with microcalcifications. Testicular ultrasound showed diffuse microlithiasis. These calcifications in both the thyroid and the testes were totally asymptomatic.

The former biopsy was reevaluated by another pathologist and it showed calcific substances surrounded by highly proliferative macrophages and giant cells resembling osteoclasts. Proliferative chronic inflammatory fibrous tissue separates these areas.

Hence, the diagnosis of FHTC was made based on clinical, laboratory, radiological and histopathological findings.

Confirming the diagnosis with the genetic testing was virtually impossible because it was not available in our country, and sending it to another country was too expensive.

The splenomegaly work-up including: protein electrophoresis, blood smear, aspiration and biopsy of bone marrow, were normal. In addition, the JAK2 mutation was done to exclude a myeloproliferative disease and came back negative. Ultrasound and Doppler Ultrasound for the abdomen and the portal vein (to rule out portal vein hypertension as a cause for splenomegaly) showed no signs of cirrhosis or portal hypertension.

4 | CONCLUSION AND RESULTS

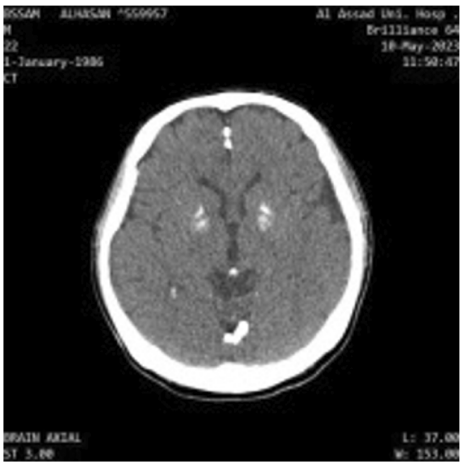
The patient was treated with Acetazolamide 250 mg twice daily to increase the phosphate excretion, Sevelamer 800 twice daily to reduce the phosphate absorption,

TABLE 1 Laboratory findings.

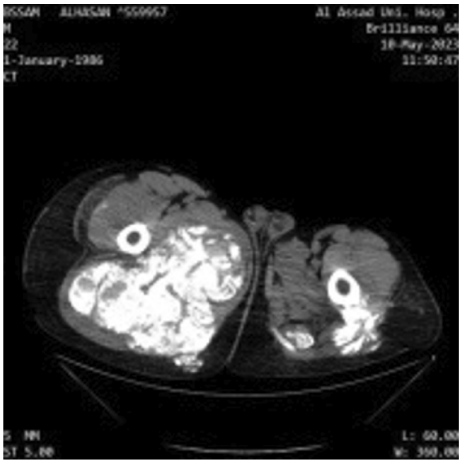
WBC	5.3 × 103/mL	Urea	37 mg/dL	CRP	9.9 mg/dL	Fe	12
L/N	16/77	Creatinine	1.23 mg/dL	Alb	4.9 mg/dL	Ferritin	827
RBC	2.3 × 106/ml	ESR	70	UA	6 mg/dL	TIBC	364
Hb	8.9 mg/dL	Ca	9.3 mg/dL	PTH	20 pg/mL		
MCV	65 fl	P	6.1 mg/dL	25-OH vit D	11.4 pg/mL		
Plt	232 × 106 /mL	ALP	120 mg/dL				
24 h urine collection							
Urine volume	1600 mL	UA	138	Total protein	248	TRP	0.87
Creatinine	1159	Ca	102	Citrate	1075	TMP/GFR	1.83

Note: Wbc (4–10) × 103/mL; Rbc (3.5–5.5) × 106/mL; Hb (12.5–16) mg/d; MCV (80–100) Fl; Plt (150–450) × 106/mL; Urea (20–40) mg/dL; Creatinine (0.5–1.1)—in urine (800–2000); ESR: Age/2 for male, Age/2 + 10 for female; Ca: (8.5–10) mg/dL—in urine (60–250); P (2.5–4.5) mg/dL; ALP (−) mg/dL; CRP (0–5) mg/dL; Alb (3.5–5.5) mg/dL; UA (3–8) mg/dL—in urine (250–750); PTH (15–65) pg/mL; Citrate (320–1240); TRP (78–91); TMP/gFR (0.8–1.35).

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; Ca, calcium; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; L, lymphocytes; MCV, mean corpuscular volume; N, neutrophils; P, phosphor; Plt, platelets; PTH, parathyroid hormone; RBC, Red blood cells; TMP, total maximum phosphorus; TRP, tubular reabsorption of phosphate; UA, uric acid; WBC, white blood cells.



(A)



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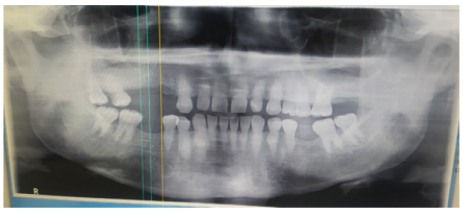

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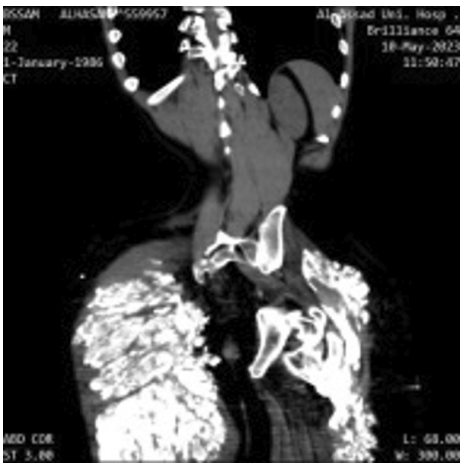

(D)

FIGURE 1 (A) Intracranial calcification in computed tomography. (B) Computed tomography showing large calcifications at the buttocks. (C) Panoramic dental radiograph showing short, bulbous roots, with obliteration of dental pulp chambers. (D) Computed tomography with calcification in testicular microlithiasis.

Allopurinol 300 mg once daily and colchicine 0.5 mg once daily. Surgical options were limited by the proximity of the right buttock lesion to nerves and major vessels.

On follow up, the patient showed a decrease in serum phosphate after 6 months without a change in the size of the masses.

5 | DISCUSSION

FHTC is an autosomal recessive disease caused by a mutation in one of three genes (FGF23, GALNT3, and KL) which induces errors in phosphate metabolism.

Genetic predisposition is a feature of this type of TC where hyperphosphatemia arises due to reduced urinary phosphate excretion caused by recessive mutations in GalNAc transferase 3 gene, GALNT3, and KLOTHO, that causes the inactivation of FGF23, a phosphoturic hormone.

FHTC has a wide range of manifestations depending on the site of calcifications, which typically occur around large joints, commonly hip, elbow, and shoulder. These calcifications can impair mobility and physical function.

Calcifications in the vessels can cause ischemia. Other reported sites of calcifications are kidneys, eyelids, intracranial dura and testis. Teeth are commonly affected causing short bulbous roots, pulp stones, and obliteration of pulp chambers.[4]

In the reported case, the intracranial and thyroid calcifications were asymptomatic. Thyroid calcifications were not reported in medical literature. Testicular microlithiasis was reported only once in a 14-year-oldboywith a mutation in theGALNT3 gene and was associated with oligospermia. The Sperm count was normal.[5]

For diagnosis, plain radiograph of long bones and dental radiograph are commonly used. Computed tomography (CT) is the most preferred diagnostic measure. CT is helpful in identifying vascular calcifications.[4] CT helps in determining the extent of lesions and serves as a guide for surgical planning. MRI can be done in difficult cases. Scintigraphy can be used to assess the disease activity.[6]

The age of the patient in this case, and the clinical manifestations are almost typical. History, laboratory tests and radiologic findings excluded the main mimickers of soft tissue calcification. These include myositis ossificans,

lymphangioma, tophaceous gout, osteosarcoma, and vitamin D hypervitaminosis.

In this case, the patient had splenomegaly with a full negative workup for the most common causes. Splenectomy had only a diagnostic value as it was asymptomatic and no hypersplenism was evident. There are no published cases of the relationship between splenomegaly and tumoral calcinosis. To our knowledge, there was only one case diagnosed with tumoral calcinosis associated with cirrhosis causing splenomegaly.

Future studies could focus on determining the exact relation between tumoral calcinosis and splenomegaly.[7]

Emerging evidence demonstrates that FGF23 is affected by inflammation and iron metabolism, which may be relevant for patients with FHTC who may demonstrate both chronic inflammation and anemia.[8]

The treatment decisions for the patient were guided by previous observational studies, case series, and case reports. Medical therapies mainly focus on lowering serum phosphate levels and decreasing the levels of inflammatory markers.

The medications for phosphate reduction include sevelamer, lanthanum, aluminum hydroxide, acetazolamide, probenecid, nicotinamide, and niacinamide. Dietary phosphate reduction is also recommended.[4]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat the pain and edema associated with hyperostosis. Interleukin-1 (IL-1) antagonists were used to treat two patients with overwhelming systemic inflammation after one of them did not respond to NSAIDs and glucocorticoids. Other rarely used drugs with limited efficacy include bisphosphonates, calcitonin, and calcium-channel blockers.[9]

Phosphate lowering agents were prescribed to the patient. No data are available on the management or the prognosis of testicular microlithiasis in TC patients.[4]

6 | CONCLUSION

In conclusion, TC should be considered in patients with calcified masses. This study provides insight into TC for physicians in the region and encourages future work on the matter.

AUTHOR CONTRIBUTIONS

Balkis Al Abdulrahman: Writing – original draft. **Hiba Eed:** Writing – original draft. **Rama Kurdy:** Writing – original draft. **Yazan Alwadi:** Writing – original draft. **Salwa Alcheikh:** Writing – review and editing.

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DATA AVAILABILITY STATEMENT

The data can be made available upon reasonable request.

ETHICS STATEMENT

Informed consent was taken for this research. Our study ethical aspects were reviewed and approved by Damascus University deanship, Damascus, Syria.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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