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Case Report

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Two Rare Cases of Tumor Calcinosis

Shanthisree Edara[1], Sherin Philip[1], Sushma Rani Raju[2], Venu Madhav Reddy[2], Anisha Tandon[3] and Harinarayan C V[1,4*]

[1]Institute of Endocrinology, Diabetes, Thyroid and Osteoporosis Disorders, Sakra World Hospital, Bangalore, Karnataka State, India

[2]Department of Nephrology, Sakra World Hospital, Bangalore, Karnataka State, India

[3]Department of Radiology, Sakra World Hospitals, Bangalore, Karnataka State, India

[4]Saveetha Institute of Medical and Technical Sciences University, Saveetha Medical College, Chennai, India

ABSTRACT

Tumour calcinosis is a rare disorder of phosphate metabolism. Familial tumour calcinosis is caused due to gene mutations affecting the activity of FGF23, a phosphoturic hormone. The presentation is hyperphosphatemia and calcified deposits in the periarticular regions. Surgery though being the mainstay of treatment, recurrence is often common without additional treatment. Phosphate restricted diet and phosphate binder before and after surgery would be beneficial. We present two cases of tumour calcinosis with hyperphosphatemia and calcified deposits, evaluated and followed up. We discuss various treatment options available for this rare condition.

***Corresponding author**

Harinarayan C V, Institute of Endocrinology, Diabetes, Thyroid and Osteoporosis Disorders, Sakra World Hospitals, Bangalore 560103, Karnataka State, INDIA. Tel: +91 9731561819, E-mail: cvhari5endo@rediffmail.com

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Introduction

Tumour calcinosis (TC) is a rare disorder of phosphate metabolism. There are deposits of hydroxyapatite or amorphous calcium phosphate crystals in the soft tissue in the periarticular location, around joints, and outside the joint capsule. Most commonly affects the shoulder, elbow, and hip joints, with less predisposition to the spine and other regions. They are frequently seen in patients undergoing renal dialysis. But the term TC actually refers to a hereditary condition associated with massive periarticular calcifications. First described by Inclan et al in 1943, characterized by juxta-articular lobulated calcified masses without visceral or skin calcifications [1]. There are two distinct types of presentation– a) Primary hyperphosphatemic TC - normocalcemia and hyperphosphatemia is the hallmark [2] and b) Primary normophosphataemic TC is characterized by normophosphatemia and normocalcemia [3].

Usually presents in the second and third decades of life where genetic predisposition is a feature. There is hyperphosphatemia due to reduced urinary phosphate excretion because of recessive mutations in the GaLNAc-transferase 3 (GALNT3), Klotho and Galnt3, which causes the inactivation of FGF23, a phosphaturic hormone [4,5]. We present two patients with TC evaluated, treated and followed for a year.

Case Presentation

Patient 1

The patient presented with swelling and inability to move the right shoulder noticed four years back. He was evaluated at another hospital and detected to have high levels of serum phosphorus. MRI revealed -? Dystrophic calcification/TC. He was treated elsewhere with alendronate and phosphate binder for 4 weeks and alternate medicinal therapies. He presented to us with both shoulder swelling, slowly progressing in size and hampering his daily lifestyle. No other family members were affected by a similar illness. Systemic examination was normal. Local examination: Swelling present over both shoulders right more than left, the swelling was non-mobile, non-tender. Restriction of both shoulder movements is present. He could not lift his hand more than 20° to 30°. Laboratory investigations are detailed in Table-1 and radiological pictures are in figure-1a-1k. Surgical removal of the tumour and histopathological examination had the following features: the left hip mass measured 16 x 12 x 4.5 cm. The cut section showed yellowish chalky white areas. Microscopically it showed multiple foci of calcification palisaded by giant cells chronic inflammation including many macrophages laden with hemosiderin and exuberant surrounding fibrosis. Right shoulder mass measured 16 x 12 x 4.5 cm. Microscopy showed multiple foci of calcification palisaded by giant cells chronic inflammation with focal bone formation and exuberant surrounding fibrosis. On follow-up patient's restricted shoulder movements improved to the extent, that he could play shuttle easily.

Patient 2

Presented with cyst-like swelling and pain in the right anterior thigh for 2 years, slowly progressing in size. No previous medication history. No other family member was affected by a similar illness. Systemic examination was normal. Local examination: Swelling was present over the right thigh, and restriction of movements of the hip joint was present. Laboratory investigations are detailed in Table-1 and radiological pictures in figure -1l, m, n, p. Right thigh swelling measured 9 x 9 x 6 cm. histologically, section showed firm calcified areas, fibromuscular tissue with cystic spaces filled with amorphous calcific debris and surrounded by brisk giant cell reaction and neovascularization

Both patients were started on phosphate binders and a low phosphate diet before surgery and continued later on. Dietary consultation was sought for a low phosphate diet. Sevelamer carbonate in doses of 800 mg per meal was used as a phosphate binder with a total dose of 2.4 grams distributed along with meals and snacks the whole day. Acetazolamide 750 mg in divided doses was added to the therapy later on. It was a challenge to optimize protein intake along with a low phosphate diet. Patients were monitored initially for a month and later could not be called back for review because of covid lockdown.

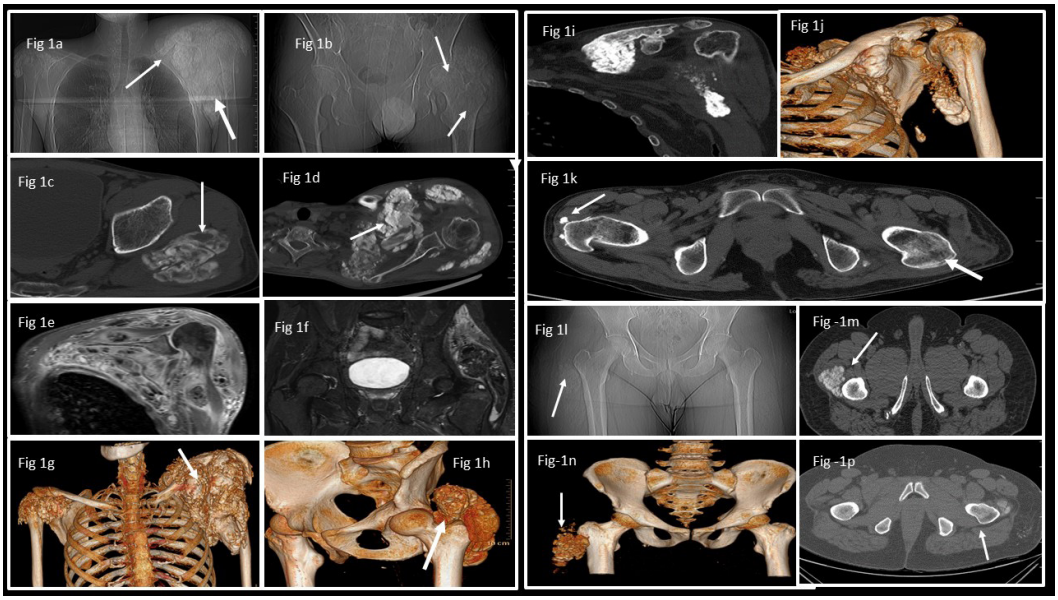

Figure 1a - Patient -1 - AP Radiograph of the Left Shoulder: Large Periarticular Calcified Mass Lesion

Figure 1b - AP Radiograph of the Pelvis with both Hip Joints. Large Periarticular Calcified Mass Lesion around the Left Hip Joint

Figure 1c - Axial CT Sections Left Hip Periarticular Calcified Mass

Figure 1d - Axial CT Sections Left Shoulder Periarticular Calcified Mass

Figure 1e - MRI Left Shoulder: Deposits of Calcium around the Joint

Figure 1f - MRI of the Left Hip Deposits of Calcium around the Joint

Figure 1g - 3D Reconstruction of Left Shoulder Showing Large Periarticular Calcified Masses

Figure 1h - 3D Reconstruction of Left Hip Showing Large Periarticular Calcified Masses

Figure 1i, 1j - Postop Shoulder CT –Significant Reduction in the Calcified Mass

Figure 1k – Post-surgical Pelvis Images after 1 year – Left-Sided Total Lesion Excision. Right Periarticular Calcification has now developed.

Figure 1 l – Patient -2 - AP Radiograph of the Pelvis with both Hip Joints. Large Periarticular Calcified Mass Lesion around the Right Hip Joint

Figure 1 m - CT Images of Right Hip Show Periarticular Calcified Mass seen on Axial Sections

Figure 1 n - 3D Reconstruction of Right Hip Showing Large Periarticular Calcified Masses

Figure 1p- Post-Surgical Images: Right-Sided Calcific Mass has been Surgically Excised and a New Left-Sided Periarticular Calcific Mass has appeared.

Table 1: Biochemical Parameters of Both Cases Pre-Operative and during Follow-Up

	UNITS	Normal RANGE	PATIENT -1					PATIENT-2				
			BASELINE	POST OPER	< 1 month	1 month	17 months	BASELINE	POST OPER	1 month	12 months	33 months
Serum Creatinine	mg/dL	0.44-1	0.39	0.4	0.48	0.41	0.97	0.96	-	1.26	0.95	0.82
Serum Alkaline Phosphatase	IU/L	32-91	112	83	109	94	110	77	54	63	65	81
Serum Protein - Albumin	g/dL	3.5-5	3.6	2.8	3.7	3.9	4.9	4.2	-	3.9	3.7	4.5
Serum Calcium	mg/dL	8.9-10.3	9.4	9	9.8	9.9	10.2	9.8	8.6	10.3	9.6	9.6
Serum Phosphorous	mg/dL	2.4-4.7	7.3	6.2	6.7	8.3	7	6.8	5.4	6.8	6.4	7.4
25(OH) Hydroxy vitamin D	ng/dL	30-100	20.7	35	31.9	38.7	39.5	8.63	-	26.36	20.36	13.7
intact Para Thyroid Hormone	pg/mL	12-88	30.4	11.7	14.3	9.4	18.2	36.9	26.2	11.5	13.8	46.6
FGF23	RU/mL	0-150	1490					1394.6				
PEI		-0.5 to 0.5	-2.15	-1.82	-2.6	-2.6	-2.07	-1.74	-	-1.62	-1.51	-2
TRP	%	82– 95	98.13			95.04	98.49	96.68		96.64	96.16	96.61
TmP/GFR	mg/dL	2.60 – 3.80	7.3			8.29	7	6.8		6.79	6.4	7.4
fepo4	%	10-20	1.87				1.51	3.36		4.36	3.83	3.39

PEI-Phosphate Excretion Index, TRP – Tubular Reabsorption of Phosphate, TmP/GFR Tubular maximum of phosphate/GFR, FGF-Fibroblast Growth Factor

Discussion

Familial tumour calcinosis is a genetically heterogeneous autosomal recessive disorder. It is due to mutation in the genes that affect FGF23 bioactivity. It could be due to reduced intact FGF23 (due to FGF23 and GLANT3 loss of function mutation) presenting as hyperphosphatemic TC or end-organ resistance to serum FGF23 (αKlotho loss of function) presenting as normophosphataemic TC [a defect in sterile α motif domain-containing protein (SMAD9)] [4-6]. Apart from biochemical parameters, plain radiographs are often diagnostic – "chicken wire" appearance due to nodular masses with septae (figure-1). The formation of TC depends on the supersaturation of calcium and phosphate products [2].

Surgical treatment forms the mainstay for resection of the deposits around the joints. Most often the resections are partial because of the involvement of the neurovascular bundle with rapid recurrence.

Medical therapy can be broadly classified as phosphate lowering therapies, anti-inflammatory therapies, anti-mineralization therapies, and physical and occupational therapies [7].

Phosphate lowering therapies – a) low phosphate diet of 700 mg/day in adults and 500 to 1,250 mg/day in children and adolescents. b) Medications inhibiting intestinal phosphate absorption - sevelamer, lanthanum, and aluminium hydroxide – were used with varying degrees of success. To increase the effectiveness, they should be given along with all meals and snacks. Common side effects include nausea, abdominal pain and constipation. Calcium salts used for phosphate lowering in other disorders are to be avoided as they can increase calcium-phosphate products and worsen calcification. Carbonic anhydrase inhibitor acetazolamide is used with variable efficacy. It decreases tubular reabsorption of phosphorus and decreases serum phosphate. The phosphaturic effect of acetazolamide may act synergistically. Monitoring serum bicarbonate and maintaining a level of 18–20 mmol/L to avoid complications. Lanthanum carbonate a non-calcium-based phosphate binder has been used to treat TC with regression of periarticular soft tissue shadows. Compared to sevelamer carbonate the net calcium absorption and hypercalciuria are lower with lanthanum carbonate. Uricosuric agent probenecid that increases renal phosphate excretion is also tried. It should be used with caution as it increases the half-life of other medications leading to potential toxicity. Brief treatment with nicotinamide and niacinamide has also been tried in TC. Sodium thiosulfate or intravenous pamidronate has also been used in the treatment of secondary TC with varying success.

Anti-inflammatory medications like glucocorticoids and NSAIDs have been shown to improve symptomatic hyperostosis. Anakinra blocking the action of interleukin-1 (IL-1), an IL-1 receptor antagonist, and monoclonal antibodies against IL-β (canakinumab), have been shown to reduce inflammation and improve quality of life.

Anti-mineralization therapies like sodium thiosulphate are supposed to increase the solubility and excretion of calcium through chelation by unconfirmed mechanisms.

Medical therapy before the excision and followed up after surgery may be beneficial. Both patients were started with a low phosphate diet and phosphate binders before surgery and continued later on with the addition of acetazolamide.

Conclusion

Tumour calcinosis is a disturbing disorder due to disturbances in phosphate regulation. It is due to either deficiency or resistance to FGF 23 due to genetic mutations. It usually presents in the second and third decade of life presenting as hyperphosphatemia and ectopic calcifications in periarticular regions. In this case report, we have discussed the challenges in the management and limitations of this rare condition.

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