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Case Report

First report of hyperphosphatemic familial tumoral calcinosis due to homozygous GALNT3 mutation in a 16-year-old boy

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ABSTRACT

Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare disorder HFTC is caused by a loss of function in fibroblast growth factor 23 (FGF23), leading to increased phosphate levels in the body and calcium deposition. It also has an autosomal trait with presentation early in childhood or 2nd decade of life. Mutation of polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) and Klotho (KL) gene are seen in HFTC. We present the first reported case of a 16-year-old boy diagnosed witsh HFTC due to a homozygous GALNT3 gene mutation at exon 5 (Leu366Arg). The patient exhibited calcinosis in the left gluteal region and hyperphosphatemia. Surgical excision and genetic analysis confirmed the diagnosis. Our aim is to highlight the role of genetic screening in HFTC diagnosis and explore novel mutations, advancing research in rare metabolic disorders.

Keywords: Autosomal trait, Gene mutation, Metabolic disorders, Surgical excision, Tumoral calcinosis

INTRODUCTION

HFTC typically has an autosomal recessive inheritance pattern, but autosomal dominant forms have also been reported in some cases of tumoral calcinosis caused by mutations in genes regulating phosphate homeostasis, primarily FGF23, GALNT3, or KL.[1] These mutations lead to hyperphosphatemia and soft tissue calcinosis. It exhibits hyperphosphatemia due to disturbed excessive reabsorption of phosphates from renal tubules and increased levels of 1,25 dihydroxyvitamin D with deposits of calcium and phosphate in the body.[2,3] It typically appears in early childhood to adulthood and manifests as calcinosis under the soft tissue of the legs, feet, and hands. Depending on the site, these may hinder the functioning of the joint causing difficulty in its movement. Physically they look large like tumours but are noncancerous. The FGF23 gene is responsible in making FGF23 which signals the kidneys to stop phospate reabsorption. The proteins produced from the polypeptide GALNT3 and Klotho (KL) gene are required in the process of glycosylation and in the binding of FGF23 to the receptor protein. In HFTC, there is a mutation in the FGF23, GALNT3 or KL gene. Tumoral calcinosis may be primary or secondary to other disorders such as renal damage, hyperparathyroidism or hypervitaminosis. The inherited HFTC due to homozygous mutation of the GALNT3 gene at exon 5 at Leu 366Arg is a unique finding which was detected in our patient. This is the first case of such a unique mutation reported in the literature.

CASE REPORT

A 16-year-old boy presented with a hard, painless lump in the left gluteal area and hyperphosphatemia for the last one year. There were no complaints of associated bone pain, proximal muscle weakness, fracture or constitutional symptoms. His parents had third-degree consanguinity with ancestral roots in the Middle East. Father had small calcinosis in the right hand and mother was asymptomatic. Serum-ionized calcium, alkaline phosphate, intact PTH, 25-OH vitamin D and serum creatinine were normal (Table 1). Laboratory results revealed marked hyperphosphatemia with inappropriately increased TRP (95%) and TMP-GFR (7.2) (Table 2). The reported TRP and TMP-GFR values were interpreted considering the

patient's age, where increased phosphate reabsorption is characteristic of HFTC. Serum C-terminal FGF 23 was 2401 RU/ml (normal: <150). Magnetic resonance imaging (MRI) of the hip showed 5.7×3.7×3 cm lobulated heterogeneous hypointensity near left greater trochanter, consistent with calcified masses typically seen in tumoral calcinosis (Figure 1). 99Tc-MDP bone scan and density parameters were normal. CBCT scan maxilla and mandible showed generalized hypercementosis with irregular root morphology (Figure 2). Mass later excised and it showed tissue calcification next-generation gene sequencing (NGS) and Sanger sequencing revealed normal FGF23 and alpha klotho genes. Exon 5 of GALNT3 gene showed homozygous mutation at Leu 366 Arg.

Table 1: Values at baseline and subsequent follow-ups.

Tests	Unit	12/12/18	19/12/18	31/1/19	3/5/19	22/7/19
Sr. Ca	mg/dl	10.1	9.4	10.4	9.3	9.5
Sr. P	mg/dl	6.8	6.2	6.98	5.4	5.66
Sr. albumin	mg/dl		4.6	4.6	4.1	-
Sr. ALP	Ul		144	155	167	137
Sr. intact PTH	ng/dl	29.4	-	44.68	-	-
Sr. ionized Ca	nmol/dl		-	-	113	119
25 OH vitamin D	ng/ml		6.35	-	34.8	-
1,25 OH vitamin D (47-190)	pmol/dl		-	-	141	-
Sr creatinine (0.6-1.3)	mg/dl	0.7	0.8	0.8	0.7	-

Sr: serum, Ca: Calcium, P: Phosphorus, ALP: Alkaline phosphatase, PTH: Parathyroid hormone

Table 2: Values at follow-ups.

Tests	20/03/19	29/03/19
Spot urine phosphorus (mg)	113	198
Spot urine creatinine (mg)	276	201
Sr. P inorganic (mg/d)	6.1	7.3
Sr. creatinine (mg/d)	0.8	0.8
TRP	95%	90%
Factor	117	0.96
TmP GFR	7.2	7

TRP: Tubular reabsorption phosphate, TMP GFR: tubular maximum reabsorption phosphorus glomerular filtration rate.

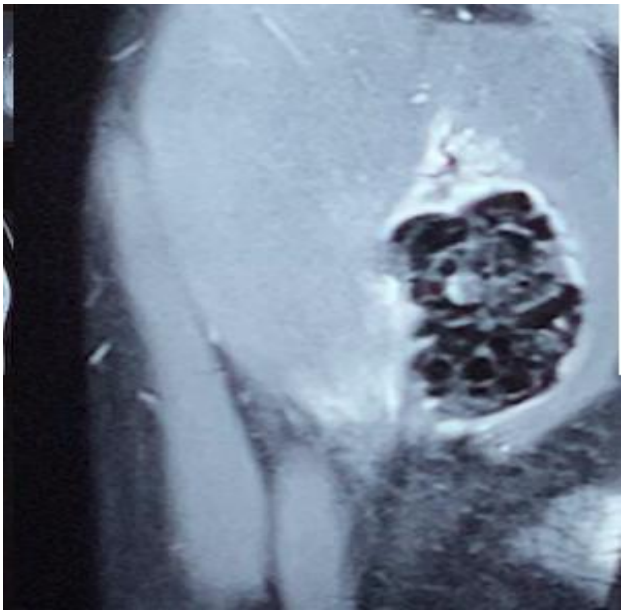

Figure 1: MRI of the hip showing 5.7×3.7×3 cm lobulated heterogeneous hypointensity near the left greater trochanter.

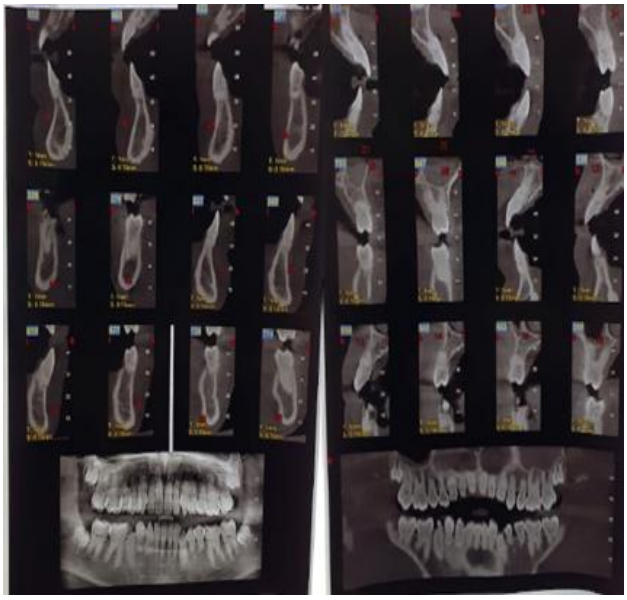

Figure 2: CBCT scans maxilla and mandible showing generalized hypercementosis, disproportionate crown root ratio, and ill-defined roots.

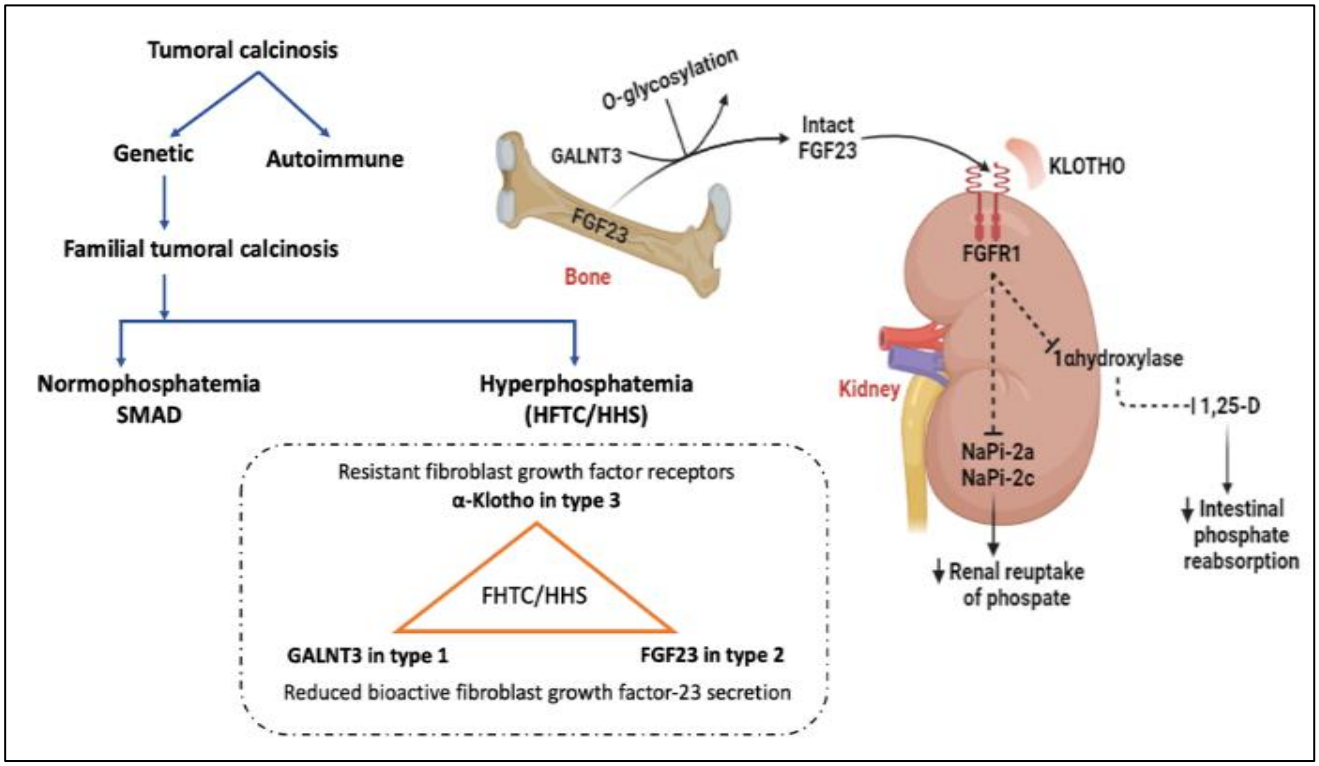

Figure 3: Schematic diagram of pathogenesis of tumoral calcinosis with classification of genetic variant of TC.
FGF23: Fibroblast growth factor 23; GALNT3: polypeptide N-acetylgalactosaminyltransferase 3; NaPi-2a/2c: Potassium cotransporter; HHS: Hyperphosphatemia-hyperostosis syndrome.

DISCUSSION

Hyperphosphatemic tumoral calcinosis is an autosomal recessive metabolic disorder caused by to mutation of the FGF23, GALNT3 or KL gene. This causes uncontrolled production of 1, 25 dihydroxyvitamin D which leads to high reabsorption of phosphates from renal tubules and intestine. Figure 3 shows the schematic illustration of the pathogenesis of HFTC as a result of the mutation of the above-mentioned genes and the classification of the genetic variant of tumoral calcinosis. HFTC manifests in early childhood or before 20 years of age and patients have higher levels of serum phosphate while the circulating calcium and PTH levels are within normal range. The renal functioning in these patients is intact with normal or mildly elevated 1, 25-dihydroxyvitamin D3 values.[4] Patients present with subcutaneous calcifications, dental abnormalities, anemia, regional lymphadenopathy, splenomegaly, amyloidosis, chronic recurrent osteomyelitis and calcification of the eyelids.[5,6] The development of hyperphosphatemia maybe after several years of clinically manifesting with calcinosis or dental abnormalities. Despite calcium deposition in soft tissues, serum calcium levels are typically within the normal range in patients with HFTC.[7]

Diagnosis is mainly based on imaging tools, such as plain radiographs showing typical amorphous, multilobulated, cystic calcified lesions along the peri-articular region. While planning interventional treatment, computed tomography is used to visualize the extent and margins of the lesion. It may appear as cystic loculi with fluid levels, a radiological finding often referred to as the sedimentation sign, are indicative of calcium layering in tumoral calcinosis lesions.[8] Erosion or destruction of the osseous layer of the surrounding structure is absent in tumoral calcinosis.[9]

Treatment is chiefly controlling the phosphate levels and pain. Phosphate-restricted diet and phosphate binders play a major role in causing phosphate depletion. If calcinosis is causing restriction in the joint activity surgical correction can be performed but the possibility of recurrence should be considered. Phosphate binders like sevelamer, lanthanum, or calcium acetate are commonly used to manage hyperphosphatemia along with dietary phosphate restriction.

The HFTC-associated GALNT3 mutations differ in clinical manifestations and severity. Few might present mild symptoms while others might show calcifications.[10,11] With extensive genetic research, the mutations detected in GALNT 3 are increasing yet the disease pathogenesis is unclear. This case report is the first-ever case reported of homozygous mutation of the GALNT3 gene at exon 5 Leu366Arg causing HFTC, thus contributing to a better understanding of the phenotypic manifestations of mutations in this gene. Report of similar homozygous

mutation of GALNT3 has been reported but it was at exon 6 at amino acid positions 415 and 438.[12] Reports of heterozygous GALNT3 mutations are known but the marked heterogeneity seen in the various mutations in GALNT3 indicates the presence of some environmental or genetic modifiers. The symptom severity in the above case was not severe but the nature of the causative mutation may not be the pointer for the GALNT3 expression. As in certain cases, the same mutation in GALNT3 can have a completely different presentation. These findings open the horizon for future genetic research in exploring the varied novel mutations in rare diseases such as tumor calcinosis.

CONCLUSION

HFTC is a rare disorder that due to its autosomal trait requires genetic testing for its diagnosis. With the advancements in genetic studies, newer mutations are been identified which aid in exploring the pathogenesis, especially in rare diseases, which have limited data in the literature. Presenting such a rare and unique mutation of GALNT3 paves the way for future research. There are no specific treatment modalities for HFTC but maintenance with phosphate-lowering drugs and diet can reduce the clinical presentation.

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