Case Report

Recurrent soft tissue calcification: Keep tumoral calcinosis in your thoughts

ABSTRACT

Hyperphosphatemic familial tumoral calcinosis is a rare condition due to deficiency or resistance to the action of intact fibroblast growth factor 23 (FGF23) in the proximal tubule of the kidney, consequently leading to hyperphosphatemia and metastatic ectopic calcification. A 15-year-old girl presented with recurrent swelling over the lateral aspect of both buttocks at the same site which was operated 5 months ago. Her serum phosphate and 1,25-dihydroxyvitamin D were elevated while serum calcium was normal. The value of intact FGF23, intact parathyroid hormone, and 25-hydroxyvitamin D were normal. MRI of the buttock showed a large, lobular, complex, and solid cystic heterogenous calcified mass with multiple cystic and fluid debris. Clinical exome reveals mutation in GALNT3 gene. She was treated with dietary phosphate restriction and sevelamer with improvement in phosphates. We are reporting this case because of its interesting presentation and rarity.

Keywords: Ectopic calcification, fibroblast growth factor 23, hyperphosphatemic familial tumoral calcinosis

INTRODUCTION

Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare, disabling disorder of intact-fibroblast growth factor 23 (FGF23) deficiency or its resistance. It is characterized by the presence of hyperphosphatemia, chiefly attributable to an inappropriately increased tubular reabsorption of phosphate, along with elevated 1,25-dihydroxyvitamin D, and ectopic calcification[1] HFTC is inherited in an autosomal recessive pattern.[2] FGF23 is a 253 amino acid peptide secreted by osteoblasts and osteocytes.[3,4] In the proximal tubule of the kidney, intact FGF23 binds with FGFR1 and its co-receptor KLOTHO, thereby downregulating the expression of sodium phosphate cotransporter NPT2a and NPT2c, resulting in phosphaturia.[5] Ectopic calcification is frequently seen close to hip joints, though it may involve areas including elbows, shoulders, hands, and tendoachilles.[6,7] Current treatment is aimed at the correction of hyperphosphatemia using phosphate binders such as sevelamer, lanthanum, or agents—aluminum hydroxide, acetazolamide, probenecid, nicotinamide, niacinamide, and surgical excision.[1,7-9]

CASE REPORT

A 15-year-old girl presented to the surgery department with a complaint of swelling over the lateral aspect of both buttocks for the past 5 months. The swelling was painless, but the size was gradually increasing. About 2 years ago, she started developing pain over her shin bones, more so on the right side, and was associated with low-grade fever and localized warmth. After 6 months, she noticed a hard

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swelling over the medial aspect of her right foot, which was surgically excised in a primary care center. X-ray of the right foot revealed amorphous soft tissue calcification on the medial aspect [Figure 1, top], but no evaluation followed. In March 2022, she developed swelling over her left buttock followed by her right buttock, which gradually progressed to the size of approximately 14 cm × 8 cm. A CT scan revealed bilateral calcified masses of similar size involving the subcutaneous tissues and muscles with multiple cystic areas and air-fluid levels within the mass. A skeletal radiograph of her hip joints showed periarticular amorphous and multilobulated calcification [Figure 1, bottom]. FNAC from the lesion revealed acellular smears composed of calcified material deposits. She underwent resection of both swellings in December 2022. However, swelling recurred on both buttocks at the site as the previous one and gradually progressed to the present size of approximately 11 cm × 10 cm on the left side and 10 cm × 8 cm on the right side. She was then referred to the Department of Endocrinology. On examination, right-sided swelling was present on the lateral aspect of the buttock with a size of 10 cm × 8 cm, which was globular in shape, warm to the touch, mildly tender, and consistency was firm in the upper half and hard in the lower half. The overlying skin had previous surgical scars, hyperpigmentation, and stria, but no ulcer. The swelling on the left buttock was similar to the right-sided swelling, except for a larger size of 11 cm × 10 cm. There was another scar over the medial aspect of the right foot. On systemic examination, she had a calcific deposit on her eyelids, more on the upper lid margin than lower lids [Figure 2, top], which led to ocular irritation. The biochemical evaluation showed high serum phosphate and 1,25-dihydroxyvitamin D levels with normal serum calcium, 25-hydroxy vitamin D, and low normal value for intact FGF23 [Tables 1 and 2].

MRI of the buttocks revealed large, lobular, and complex solid cystic heterogenous calcified masses at the lateral aspect of both gluteal regions involving subcutaneous tissue and underlying gluteal muscle. Multiple cystic and fluid debris

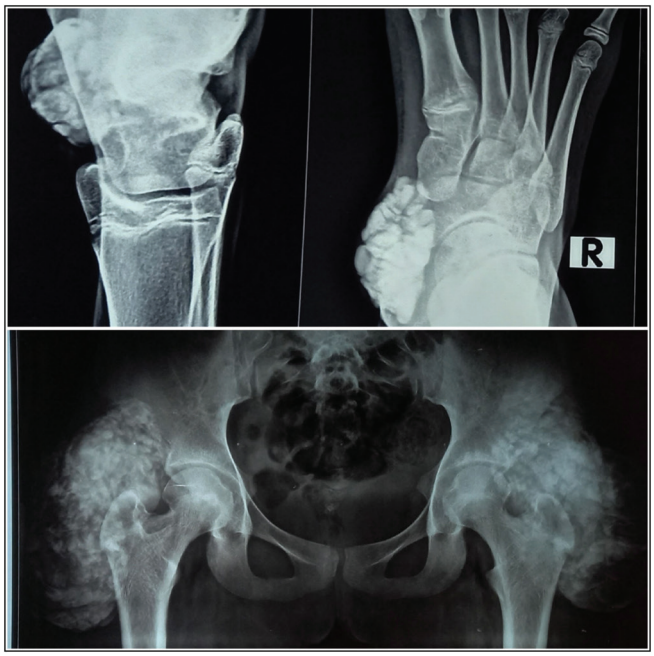


Figure 1: Skeletal radiograph showing amorphous soft tissue calcification on the medial aspect of right foot (top); periarticular amorphous and multilobulated calcification at both hips (bottom)

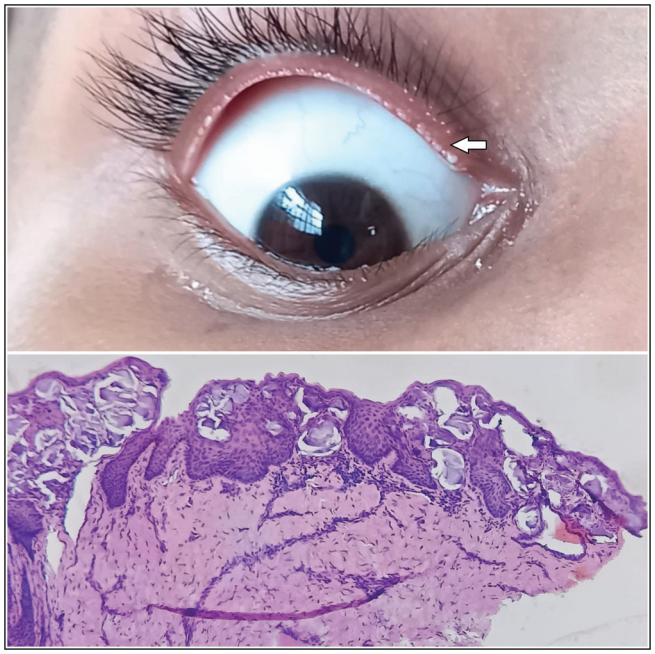


Figure 2: Calcific deposit on eyelids (top); histology of eyelid with calcium deposition in epidermis and dermis (bottom)

Table 1: Calcium and phosphate values at baseline and after the introduction of sevelamer

	Calcium (reference value 8.4–10.2 mg/dL)	Phosphate (reference value 2.5–4.5 mg/dL)
Baseline	10 mg/dL	8.5 mg/dL
After 2 weeks	9.7 mg/dL	4.1 mg/dL
After 2 months	9.6 mg/dL	7.0 mg/dL

Table 2: Values at baseline of intact parathyroid hormone, FGF23, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D

FGF23, intact (reference value 23.20–95.40 pg/mL)	46.84 pg/mL
25-hydroxyvitamin D (reference value 75–270 nmol/L)	48.50 nmol/L
1,25-dihydroxyvitamin D (reference range 47.76–190.32 pmol/L)	239 pmol/L
Intact PTH (reference value 15–68.3 pg/mL)	77.50 pg/mL

PTH, parathyroid hormone

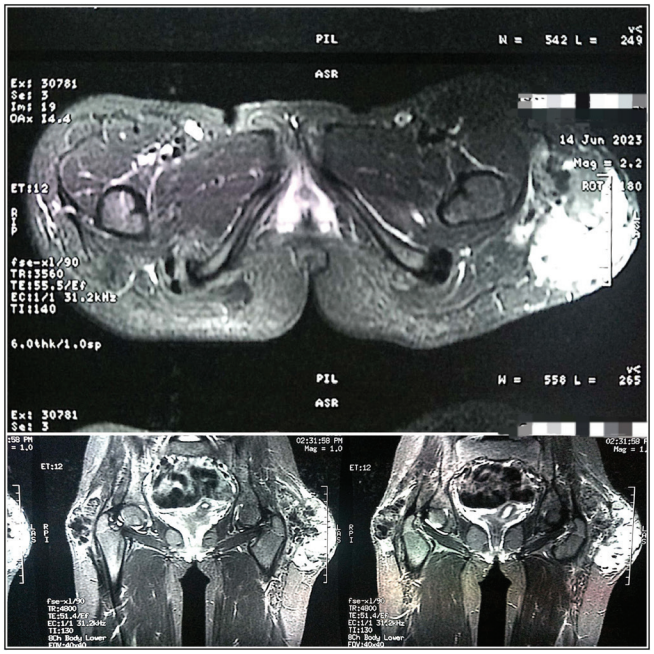


Figure 3: MRI of buttocks showing large, lobular, complex solid cystic heterogenous calcified masses at the lateral aspect of both gluteal regions with involvement of surrounding soft tissues

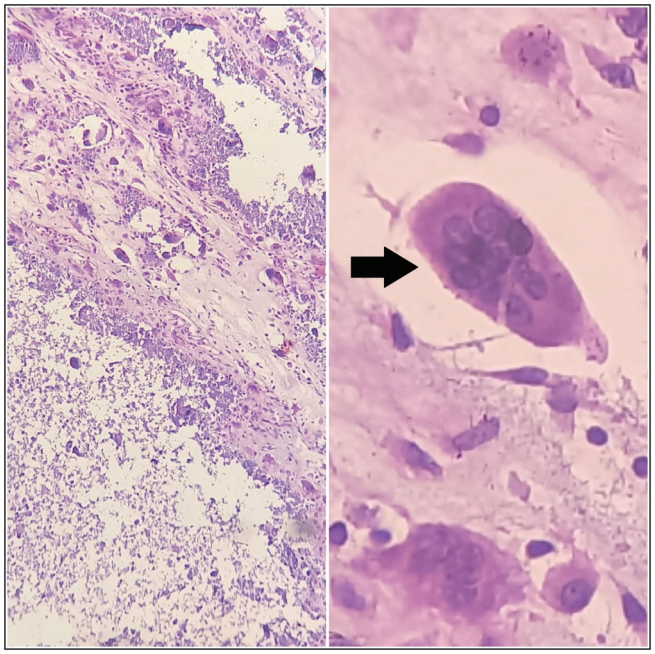


Figure 4: Histopathology of calcific material from both-sided gluteal region showing the rim of histiocytes, lymphocytes, and foreign body giant cells (arrowed) in the adjoined stroma

were seen within the lesion [Figure 3]. In the presence of high phosphate and the characteristic imaging findings, intact FGF23 levels were checked and came as 46.84 pg/mL, which was normal. Histology of eyelid deposits revealed calcium salt deposition in the epidermis and dermis [Figure 2, bottom]. Genetic counseling was offered to our patient. Clinical exome sequencing was done revealing heterozygous frameshift variant c.746_749delTCAG, in the exon 4 of the GALNT3 gene, which results in amino acid p.Val249fs*8 was identified that is a known pathogenic variant for a diagnosis of HFTC. Another variant c.1097T>G p.Leu366Arg was also identified at exon 6 of the gene though this was a variant of uncertain significance. Ultrasound of the kidneys had no evidence of renal calculi or nephrocalcinosis and 2D-echocardiography was normal. Calcification of abdominal and common iliac arteries was evident on MRI. A bone scan was not done in our patient.

A diagnosis of HFTC was made and was advised phosphate restricted diet and sevelamer 400 mg TDS. She responded well and the phosphate level declined transiently, but within a few weeks, the phosphates rose again and the sevelamer dose was titrated to 800 mg TDS. Repeat surgical excision was done for buttock swellings as the patient had cosmetics issues, discomfort while sitting, and on-off pain. Histopathology findings of calcific material adjoining the stroma with a rim of histiocytes, lymphocytes, and foreign body giant cells [Figure 4], again confirmed the diagnosis of HFTC.

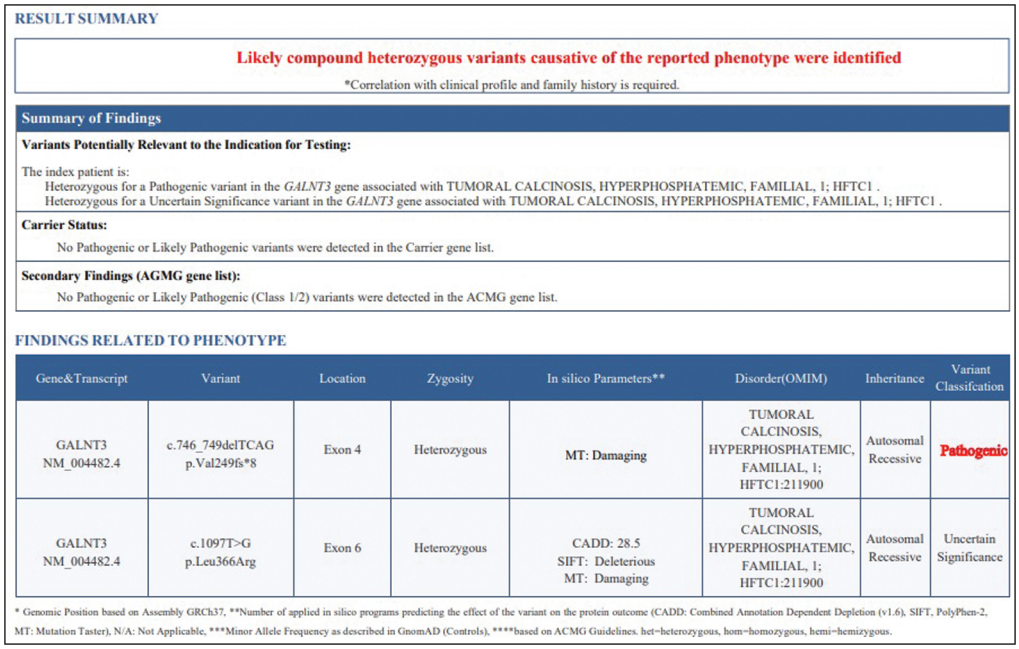
DISCUSSION

HFTC is a rare and disabling genetic disorder resulting from disturbances in FGF23-mediated phosphate regulation. It is due to a deficiency of active, intact FGF23 or a defect in signaling leading to hyperphosphatemia and ectopic calcification.[1] Four types of HFTC are known [Table 3]. Inherited in an autosomal recessive manner but a positive family history might be lacking. FGF23 is a 253 amino acid peptide secreted by osteocytes and osteoblasts.[3,4] In PCT of the kidney, FGF23 binds with FGFR1 and co-receptor KLOTHO, thus downregulating the expression of sodium phosphate.

Cotransporter NPT2A and NPT2c, leading to phosphaturia.[5] FGF23 is transcribed and translated as an active, full-length protein that contains a subtilisin-like proprotein convertase (SPC) cleavage site. FGF23 undergoes O-glycosylation at the Thr178 site in the Golgi apparatus by N-acetylgalactosaminyltransferase 3 (GalNAcT3, encoded by GALNT3). This posttranslational modification stabilizes intact, active protein. A mutated GALNT3 gene leads to the absence of glycosylation of intact FGF23, which can be easily cleaved by furin-like-proprotein convertase to inactive C- and N-terminal fragments.[10] Our patient was diagnosed with a case of HFTC1 due to a GALNT3 mutation. She had low normal FGF23. Two different types of immunoassays for FGF23 are available, one utilizes antibodies targeting the full-length or intact FGF23 and the other uses antibodies targeting the C-terminal of FGF23 molecules. If the C-terminal FGF23

Table 3: Types of HFTC

Types	Gene	Chromosome	Inheritance	Intact FGF23	C-terminal FGF23	Any association
HFTC1	GALNT3	2q24.3	Recessive	Low/normal	High	
HFTC2	FGF23	12p13.32	Recessive	Low/normal	High	
HFTC3	KL	13q13.1	Recessive	High	High	
Autoimmune	–	–	Acquired	High	High	Diabetes mellitus



RESULT SUMMARY

Likely compound heterozygous variants causative of the reported phenotype were identified

*Correlation with clinical profile and family history is required.

Summary of Findings

Variants Potentially Relevant to the Indication for Testing:

The index patient is:
Heterozygous for a Pathogenic variant in the *GALNT3* gene associated with TUMORAL CALCINOSIS, HYPERPHOSPHATEMIC, FAMILIAL, 1; HFTC1 .
Heterozygous for a Uncertain Significance variant in the *GALNT3* gene associated with TUMORAL CALCINOSIS, HYPERPHOSPHATEMIC, FAMILIAL, 1; HFTC1 .

Carrier Status:
No Pathogenic or Likely Pathogenic variants were detected in the Carrier gene list.

Secondary Findings (AGMG gene list):
No Pathogenic or Likely Pathogenic (Class 1/2) variants were detected in the ACMG gene list.

FINDINGS RELATED TO PHENOTYPE

Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classifcation
GALNT3 NM_004482.4	c.746_749delTCAG p.Val249fs*8	Exon 4	Heterozygous	MT: Damaging	TUMORAL CALCINOSIS, HYPERPHOSPHATEMIC, FAMILIAL, 1; HFTC1:211900	Autosomal Recessive	Pathogenic
GALNT3 NM_004482.4	c.1097T>G p.Leu366Arg	Exon 6	Heterozygous	CADD: 28.5 SIFT: Deleterious MT: Damaging	TUMORAL CALCINOSIS, HYPERPHOSPHATEMIC, FAMILIAL, 1; HFTC1:211900	Autosomal Recessive	Uncertain Significance

* Genomic Position based on Assembly GRCh37, **Number of applied in silico programs predicting the effect of the variant on the protein outcome (CADD: Combined Annotation Dependent Depletion (v1.6), SIFT, PolyPhen-2, MT: Mutation Taster), N/A: Not Applicable, ***Minor Allele Frequency as described in GnomAD (Controls), ****based on ACMG Guidelines. het=heterozygous, hom=homozygous, hemi=hemizygous.

Figure 5: Clinical exome electropherograms

method is used, the value will reflect a combination of both intact FGF23 and inactive C-terminal fragments. In HFTC1, that is, GALNT3 mutation, due to increased breakdown, intact FGF23 assay will lead to low/normal value as seen in our patient while C-terminal FGF23 would be high. This is also seen in HFTC2 due to FGF23 mutation but in striking contrast to HFTC3 or autoimmune, where both types of immunoassays will yield high FGF23 values. Most FGF23 immunoassays available commercially do not clearly mention the type of assay that is used in the corresponding laboratory. The assay method is important for the diagnosis as well as for the subtype classification of the disease. The initial complaint in our patient was pain over the shin bone along with fever, likely from tibial hyperostosis. Hyperostosis in HFTC presents with pain and tenderness over the diaphysis of long bones.[7,8] Fever and systemic inflammation are related to macrophage engulfment of hydroxyapatite crystals in calcific lesions.[7] Ectopic calcification in skin and subcutaneous tissue is a common manifestation with lesions occurring in periarticular locations exposed to repeated pressure and trauma.[2] The lateral aspect hip is frequently affected. Our patient had swellings over both buttocks which recurred after resection within a short period at the same site with almost similar features and size. Histopathological features confirmed our diagnosis of HFTC. Other sites of tumoral calcinosis include the elbow, shoulders, hand, and tendoachilles.[6,7] Our patient also had a swelling over the medial aspect of the right foot which is an uncommon site of calcification. She also had eyelid margins calcification histopathologically proven as a calcified nodule in the epidermis and dermis, which is in sync with other findings in this case.[11] Ophthalmological evaluation ruled out the presence of band keratopathy or retinal angioid streaks. MRI in patients reported calcified abdominal aorta and iliac arteries, which is similar to studies stating that calcification may affect small, and large vessels including the aorta, iliac, carotids, cerebral vasculature, and others.[6,7] Screening for coronary and dural calcification in our patient was not possible. She lacked any dental or renal manifestation, commonly seen in HFTC. While the genetic basis of most cases of HFTC is known, the genotype-phenotype correlation between different subtypes and different mutations is not well established due to the rarity of the disease. Similarly, while the gene has been identified relevant hot spots for mutation in these genes are not yet established. Two separate mutations were identified in our patient in the GALNT3 gene, electropherogram [Figure 5]. While one of them is a known pathogenic variant for HFTC the other was a novel mutation with unknown significance.

Further study is required. Current treatment of HFTC focuses on medications lowering phosphates, including phosphate binders-sevelamer, lanthanum, and others such as aluminum hydroxide, acetazolamide, probenecid, and nicotinamide.[1,7-9] Our patient responded well to dietary phosphate restriction and sevelamer without any adverse effects. She had a recurrence of ectopic calcification at the same site within a short span after surgery. No biochemical evaluation was done during the first surgery and she had hyperphosphatemia in the preoperative and postoperative period for several months before receiving phosphate binders.

HFTC is a rare disease, with genetic testing being the gold standard for diagnosis. The diagnosis of HFTC should be kept in mind for patients presenting with extraskeletal calcified masses. Although no definitive therapy is available, maintaining low phosphates can prevent recurrent ectopic calcification.

Learning points

- HFTC, a genetic disorder caused by a defect in intact FGF23 production or signaling leading to hyperphosphatemia and ectopic calcification.
- FGF23 immunoassay that detect intact FGF23 yield low/normal values in HFTC1, and HFTC2 while immunoassay detecting C-terminal FGF23 yields high values for all variants of HFTC. It is thereby important to know, the type of immunoassay used.
- Surgical removal of tumoral masses is the mainstay of therapy and recurrences are common necessitating surgical removal quiescent phase of the disease.
- Surgical removal of tumoral mass without intervention in the form of diet and phosphate binders can precipitate metastatic ectopic calcification at the same site within a short span of time.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Boyce AM, Lee AE, Roszko KL, Gafni RI. Hyperphosphatemic tumoral calcinosis: Pathogenesis, clinical presentation, and challenges in management. Front Endocrinol (Lausanne) 2020;11:293.
2. Ramnitz MS, Gafni RI, Collins MT. Hyperphosphatemic familial tumoral calcinosis. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews®. Seattle, WA: University of Washington, Seattle; 2018. p. 1993-2023.
3. Riminucci M, Collins MT, Fedarko NS, Cherman N, Corsi A, White KE, *et al*. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. J Clin Invest 2003;112:683-92.
4. Yamamoto H, Ramos-Molina B, Lick AN, Prideaux M, Albornoz V, Bonewald L, *et al*. Posttranslational processing of FGF23 in osteocytes during the osteoblast to osteocyte transition. Bone 2016;84:120-30.
5. Bacchetta J, Bardet C, Prié D. Physiology of FGF23 and overview of genetic diseases associated with renal phosphate wasting. Metabolism 2020;103:153865.
6. Ichikawa S, Imel EA, Kreiter ML, Yu X, Mackenzie DS, Sorenson AH, *et al*. A homozygous missense mutation in human KLOTHO causes severe tumoral calcinosis. J Clin Invest 2007;117:2684-91.
7. Ramnitz MS, Gourh P, Goldbach-Mansky R, Wodajo F, Ichikawa S, Econs MJ, *et al*. Phenotypic and genotypic characterization and treatment of a cohort with familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome. J Bone Miner Res 2016;31:1845-54.
8. Ichikawa S, Baujat G, Seyahi A, Garoufali AG, Imel EA, Padgett LR, *et al*. Clinical variability of familial tumoral calcinosis caused by novel GALNT3 mutations. Am J Med Genet A 2010;152:896-903.
9. Favia G, Lacaita MG, Limongelli L, Tempesta A, Laforgia N, Cazzolla AP, *et al*. Hyperphosphatemic familial tumoral calcinosis: Odontostomatologic management and pathological features. Am J Case Rep 2014;15:569-75.
10. Tagliabracci VS, Engel JL, Wiley SE, Xiao J, Gonzalez DJ, Nidumanda Appaiah H, *et al*. Dynamic regulation of FGF23 by Fam20C phosphorylation, GalNAc-T3 glycosylation, and furin proteolysis. Proc Natl Acad Sci USA 2014;111:5520-5.
11. Ichikawa S, Imel EA, Sorenson AH, Severe R, Knudson P, Harris GJ, *et al*. Tumoral calcinosis presenting with eyelid calcifications due to novel missense mutations in the glycosyltransferase domain of the GALNT3 gene. J Clin Endocrinol Metab 2006;91:4472-5.