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Hyperphosphatemia With Normal Kidney Function Associated With Genetic Variants of *GALNT3*

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Iris Schulz[1], Alejandra Kutscher[2], Paola Krall[1,2,3], Daniel Carpio[4] and Leopoldo Ardiles[1,2]

[1]Department of Nephrology, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile; [2]Institute of Medicine, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile; [3]Department of Pediatrics and Child Surgery, Faculty of Medicine, University of Chile, Santiago de Chile, Chile; and [4]Institute of Anatomy and Pathology, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile

Correspondence: Leopoldo Ardiles, Laboratory of Nephrology, Faculty of Medicine, Universidad Austral de Chile, Valdivia, Chile. E-mail: leopoldoardiles@gmail.com

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INTRODUCTION

Hyperphosphatemia commonly affects individuals with advanced chronic kidney disease, mainly those on hemodialysis, but is rarely seen in individuals without renal impairment. Dysfunctional hormones, receptors or coreceptors that mediate renal phosphate excretion can cause hyperphosphatemia in the setting of normal renal function. We report on a case of a 46-year-old woman with a long history of skeletal and skin disease but normal renal function, who was found with hyperphosphatemia with a genetic etiology.

CASE PRESENTATION

A 46-year-old female with a history of chronic osteomyelitis during childhood reported that in her 20s, she was diagnosed with Takayasu's disease because of weak distal pulses and lumbar pain. Oral steroids were initiated as treatment for her presumed vasculitis. Already at that time, her phosphate levels were 7.1 mg/dl, with normal kidney function.

At the age of 41, a computed tomography angiogram revealed a calcified tumor in the left atrium, confirmed by an echocardiogram (Figure 1a and b), and multiple atherosclerotic lesions in the aorta, iliac, femoral arteries, and subcutaneous space (Figure 1c and d), which were not consistent with Takayasu's disease, but surgical treatment was considered unsuitable. She also complained of headache, and a funduscopic examination revealed calcium deposits within the papilla, which were confirmed by ocular ultrasound. Steroids were suspended, and no other medical treatment was pursued until age 46, when she consulted a dermatologist due to ulcerated lesions in both pretibial areas (Figure 1e). Histological analysis was informed as pyoderma gangrenosum, with marked signs of heterotopic calcifications (Figure 1f and g) and she was treated with methotrexate and multiple antibiotic regimens without satisfactory response. Subsequent laboratory tests showed hyperphosphatemia, normal renal function, and normal calcium and parathyroid hormone levels (Supplementary Table S1), but a very low renal phosphate excretion (fractional tubular reabsorption of phosphate 100% [normal values 85%–95%]), ratio of tubular maximum reabsorption of phosphate to glomerular filtration of 6.8 mg/dl (normal values 2.6–3.8 mg/dl). She received treatment with a low-phosphorus diet and non-calcium-based phosphate binders (sevelamer and aluminum hydroxide). Levels of 25-hydroxyvitamin D were low (6.5 ng/ml); however, this was not treated to avoid increases in phosphate. Additional studies revealed slightly elevated serum levels of intact FGF23 (51 pg/ml, internal reference range <30 pg/ml) and C-terminal FGF23 (151 pg/ml, internal reference range <100 pg/ml). A sequencing panel of 358 genes associated with skeletal disorders, including the main candidates involved in phosphorus homeostasis (FGFR1, KLOTHO, FAM20, GALNT3, and FGF23), identified 2 *GALNT3* heterozygous missense variants: c.985G>A (p.G329R) and c.1312C>T (p.R438C). Both variants, G329R and R438C, were classified as likely pathogenic.[1] Counseling was offered to the patient to provide her with information about the genetic findings and the risk of inheritance.

Femoral endarterectomy and femoropopliteal bypass were performed, followed by regression of the cutaneous lesions (Figure 1h). Her serum phosphate at time of hospital discharge was 4.6 mg/dl.

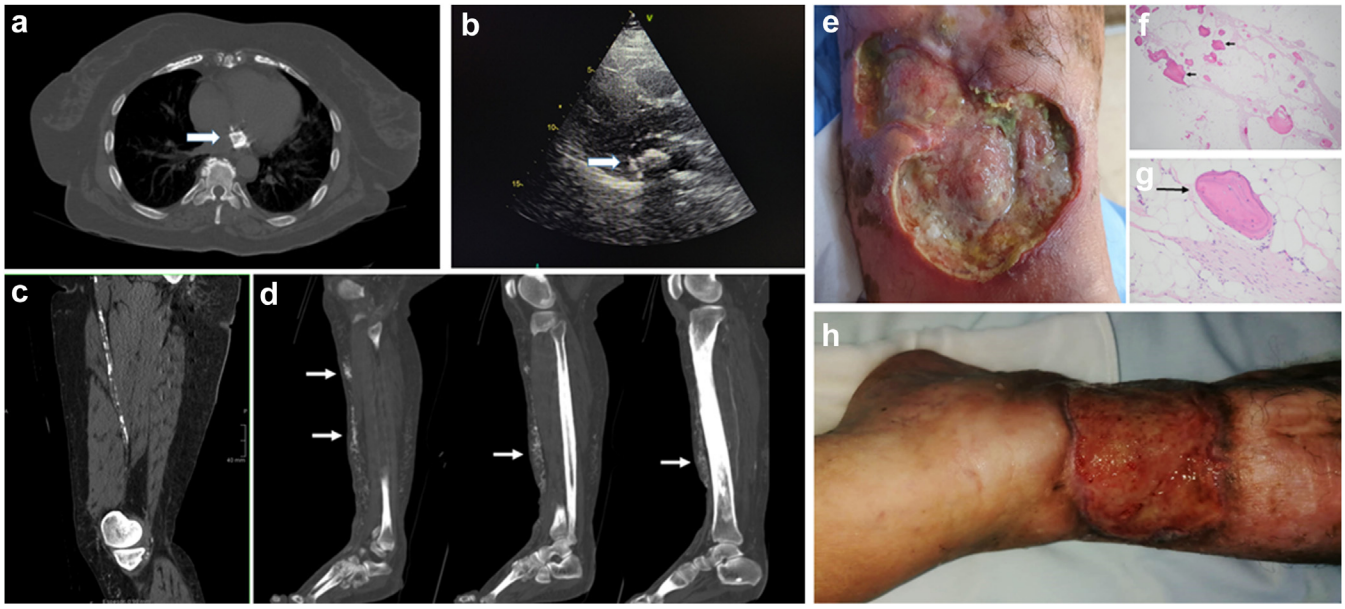

Figure 1. (a) uncontrasted computed thoracic tomography (UCT) showing a refringent calcified intra-atrial mass; (b) cardiac ultrasonography confirming the intra-atrial calcified lesion; (c) calcified right femoral artery in UCT; and (d) arrows showing calcium deposits in pretibial subcutaneous space. (e) active, infected, pretibial ulcer; (f) and (g) histological images (hematoxylin–eosin staining) of subcutaneous tissue from a sample of leg ulcer showing abnormal calcifications (arrows); (h) clinical improvement of the ulcer after surgical toilette, antibiotics, femoral-popliteal bypass, and phosphate quelant therapy.

During the subsequent follow-up visits, we confirmed that the patient had no family history of similar clinical features or diseases. In addition, we found normal serum phosphate levels in her 2 daughters (29 and 17 years old). Due to poor adherence to the low-phosphorus diet, her phosphate levels progressively increased to 5.7 mg/dl 6 months after hospital discharge.

DISCUSSION

This case report illustrates the rare clinical condition of abnormal renal phosphorus excretion in a patient with normal renal function. Our patient presented with hyperphosphatemia, low fractional excretion of phosphorus, and slightly elevated levels of intact FGF23 and C-terminal FGF23.

In response to phosphorus overload or a positive balance, the bone-derived hormone FGF23 acts on the kidney by binding to FGF receptors and the coreceptor KLOTHO to reduce tubular phosphorus reabsorption. The secretion of active FGF23 into the circulation depends on the balance between the synthesis of full-length intact FGF23 (251 aa) and the O-glycosylation by the enzyme GALNT3 that protects FGF23 from proteolysis by the proprotein convertase FURIN. Genetic variants of FGF23, its receptors, or its regulators can disrupt phosphate homeostasis (Supplementary Figure S1), resulting in hyperphosphatemia which can subsequently result in the deposition of calcium phosphate crystals in soft tissues, clinically known as tumoral calcinosis.[2] Familial hyperphosphatemic tumoral calcinosis cases have been associated with variants in *FGF23*, *GALNT3*, and *KLOTHO*.[1,2] Genetic analysis on our patient identified compound heterozygous *GALNT3* variants located on the glycosyl transferase domain.[3] Both *GALNT3* variants, G329R and R438C, are rare alleles with low prevalence in the general population, approximately 0.002% and 0.001%, respectively. In particular, the *GALNT3* R438C variant has been previously documented in patients diagnosed with tumoral calcinosis and hyperphosphatemic hyperostosis.[4,5]

GALNT3 variants can result in defective O-glycosylation of FGF23, leading to decreased stability of FGF23 and increased degradation by FURIN that results in elevated levels of its breakdown products; consequently, an increase in C-terminal FGF23 levels is expected, as observed in our patient. A genetically mediated decrease in GALNT3 activity would favor the secretion of 2 biologically inactive FGF23 fragments. Furthermore, the C-terminal fragment of FGF23 may act as an endogenous inhibitor of FGF23 signaling, blocking the formation of the KLOTHO-FGFR complex and, as a result, suppressing the expression of the type II sodium-phosphate transporters NaPi2a and NaPi2c in the apical membrane, thereby inducing hypophosphaturia and hyperphosphatemia due to increased tubular phosphorus

Table 1. Teaching points

Phosphorus metabolism disorders and their associated complications are common in patients with advanced CKD.
Isolated hyperphosphatemia in a patient with preserved renal function is extremely rare.
Genetic variants in the FGF23 receptor or its regulators can lead to hyperphosphatemia and tumor calcinosis in the absence of significant alterations in renal function.
The clinical manifestations of familial tumoral calcinosis are indistinguishable from those that occur due to impaired calcium-phosphorus metabolism in advanced CKD.
Early genetic diagnosis is of great importance to reduce vascular complications and provide genetic counseling to the family.

CKD, chronic kidney disease.

reabsorption.[6] Typically, calcium levels, parathyroid hormone, and 25-hydroxyvitamin D levels remain within the normal range.[6]

In the presented case of a patient with *GALNT3* genetic variants, slightly elevated intact FGF23 was unexpectedly found. Per the biochemical pathways described above, and although biological variability of plasma intact and C-terminal FGF23 measurements have been described,[7,8,S1] normal or low levels were anticipated. In our opinion, this surprising result might be explained by the sustained hyperphosphatemia, which is a potent stimulus for FGF23 production. Based on this premise, attempts were made to control hyperphosphatemia with the described medical treatment in order to obtain a new sample to measure FGF23 under normophosphatemic conditions; however, this has not been possible.

Clinically, tumoral calcinosis manifests as calcium deposits in the skin and subcutaneous tissue, leading to physical restriction and disability (periarticular deposits) or ischemia due to vascular deposits.[1,2,S2] Calcifications typically begin in the second decade of life and are associated with a systemic inflammatory response induced by the macrophage phagocytosis of hydroxyapatite, resulting in cytokine release.[1,9] The clinical presentations of these manifestations may vary, even among individuals from the same family, because there may be additional variants involved in phosphorus or calcium homeostasis.

Regarding treatment, there is no specific therapy, and current management consists of a low-phosphate diet (600–800 mg/d) and non-calcium-based phosphate binders such as sevelamer or aluminum hydroxide.[S3] Local therapy with sodium thiosulfate has shown favorable results anecdotally[S4]; however, systemic therapy with this salt has not demonstrated benefits.

CONCLUSION

Hyperphosphatemia, in the presence of preserved renal function, is an unusual clinical finding. Early genetic testing to identify the causative mechanism is important in order to provide effective therapies to reduce the associated high cardiovascular risk and to offer the necessary genetic counseling (Table 1).

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patient discussed in the report.

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SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplemental References.

Table S1. Laboratory findings of a patient diagnosed with tumoral calcinosis secondary to GALNT3 genetic variants.

Figure S1. Phosphate homeostasis, FGF23 mediated regulation of renal phosphate handling, and proposed mechanism to explain hyperphosphatemia in the patient carrying GALNT3 variants.

REFERENCES

1. Ramnitz MS, Gourh P, Goldbach-Mansky R, et al. Phenotypic and genotypic characterization and treatment of a cohort with familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome. *J Bone Miner Res*. 2016;31:1845–1854. https://doi.org/10.1002/jbmr.2870

2. Boyce AM, Lee AE, Roszko KL, Gafni RI. Hyperphosphatemic tumoral calcinosis: pathogenesis, clinical presentation, and challenges in management. *Front Endocrinol (Lausanne)*. 2020;11:293. https://doi.org/10.3389/fendo.2020.00293

3. Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Long-term clinical outcome and phenotypic variability in hyperphosphatemic familial tumoral calcinosis and hyperphosphatemic hyperostosis syndrome caused by a novel GALNT3 mutation; case report and review of the literature. *BMC Genet*. 2014;15:98. https://doi.org/10.1186/s12863-014-0098-3

4. Dumitrescu CE, Kelly MH, Khosravi A, et al. A case of familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome due to a compound heterozygous mutation in GALNT3 demonstrating new phenotypic features.

Osteoporos Int. 2009;20:1273–1278. https://doi.org/10.1007/s00198-008-0775-z

5. Yancovitch A, Hershkovitz D, Indelman M, et al. Novel mutations in GALNT3 causing hyperphosphatemic familial tumoral calcinosis. *J Bone Miner Metab*. 2011;29:621–625. https://doi.org/10.1007/s00774-011-0260-1
6. Goetz R, Nakada Y, Hu MC, et al. Isolated C-terminal tail of FGF23 alleviates hypophosphatemia by inhibiting FGF23-FGFR-klotho complex formation. *Proc Natl Acad Sci U S A*. 2010;107:407–412. https://doi.org/10.1073/pnas.0902006107
7. Smith ER, McMahon LP, Holt SG. Method-specific differences in plasma fibroblast growth factor 23 measurement using four commercial ELISAs. *Clin Chem Lab Med*. 2013;51:1971–1981. https://doi.org/10.1515/cclm-2013-0208
8. Smith ER, McMahon LP, Holt SG. Fibroblast growth factor 23. *Ann Clin Biochem*. 2014;51:203–227. https://doi.org/10.1177/0004563213510708
9. Garringer HJ, Fisher C, Larsson TE, et al. The role of mutant UDP-N-acetyl-alpha-D-galactosamine-polypeptide N-acetylgalactosaminyltransferase 3 in regulating serum intact fibroblast growth factor 23 and matrix extracellular phosphoglycoprotein in heritable tumoral calcinosis. *J Clin Endocrinol Metab*. 2006;91:4037–4042. https://doi.org/10.1210/jc.2006-0305