

Novel genetic mutation associated with hyperphosphatemic familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome treated with denosumab: a case report

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SUMMARY

In this case report, a novel N-acetylgalactosaminyltransferase 3 homozygous mutation (c.782 G>A; p.R261Q) associated with hyperphosphatemic familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome is described.

The patient had elbow, pelvis, and lower limb pain and a hard mass in the hip and olecranon regions. Increased levels of inorganic phosphorus (Pi) and C-reactive protein were observed. After treating the patient with conventional drugs, we tested denosumab, which reduced but did not normalize the Pi.

Key words: Hyperphosphatemic tumoral calcinosis, GALNT3, denosumab, case report.

Reumatismo, 2024; 76 (2): 137-141

INTRODUCTION

Hyperphosphatemic familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome (HFTC/HHS) is a rare autosomal recessive inherited disorder of dysregulated phosphate metabolism. The onset age, disease severity, and spectrum of symptoms and signs vary widely, encompassing massive ectopic calcifications, hyperostosis, dental disorders, and systemic inflammation. The latter occurs due to local inflammatory reactions around calcifications or inside hyperostotic regions (1). To date, 48 cases of HFTC/HHS attributed to N-acetylgalactosaminyltransferase 3 (GALNT3) mutations (type 1 disease) have been documented, along with 21 cases of HFTC/HHS resulting from fibroblast growth factor 23 (FGF23) mutations (type 2 disease) and a single case involving a Klotho (type 3 disease) mutation (2-5). Moreover, an acquired autoimmune form of HFTC/HHS has been reported, character-

ized by pathogenic autoantibodies targeting FGF23. Notably, this form does not exhibit mutations in FGF23, Klotho, or FGF receptor 1 (6).

Denosumab, a potent anti-resorptive agent that inhibits receptor activator of nuclear factor κ -B ligand, might help reduce plasma phosphates. Denosumab is typically used to manage various forms of osteoporosis, such as post-menopausal osteoporosis, cancer treatment-induced bone loss, and bone metastases. Additionally, it has been used off-label in Paget disease of bone, fibrous dysplasia, and hypercalcemia stemming from various causes.

Herein, we report a case of HFTC/HHS with a novel GALNT3 mutation treated with a single dose of denosumab (60 mg).

CASE REPORT

A 58-year-old man presented with a history of elbow and pelvic pain lasting for 3 years, along with the development of hard swell-

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ing and erythema in his lower limbs, which were warm to the touch and painful.

The patient was a heavy smoker (80 packs per year) and a sedentary subject, without nutritional restriction.

Medical history revealed that the patient had arterial hypertension, hypercholesterolemia, and angioid streaks, which were associated with a significant decrease in vision. The patient was undergoing pharmacological therapy with angiotensin-converting enzyme inhibitors for hypertension and statins to manage hypercholesterolemia.

Clinical examination found the presence of hard masses in the hip and olecranon regions, with a restricted range of motion, melanodermia, and edema in the lower limbs with associated turgidity.

Diagnostic testing

Bone scintigraphy was performed and showed increased uptake at the pelvis and elbows (Figure 1A).

Following bone scintigraphy, a computed

tomography (CT) scan of the pelvis was conducted to further characterize and provide a more detailed characterization of calcifications. The CT scan revealed the presence of tumoral calcinosis in the form of extensive periarticular heterotopic soft tissue calcifications surrounding both hips (Figure 1B). Calcifications were found in both the anterior and posterior compartments (gluteal and quadriceps), with greater density observed on the left side, where they extended widely into the posterior compartment, including the hamstring and adductor muscles (Figure 1C). Such a distribution of heterotopic calcification is a common characteristic of HFTC/HHS and typically occurs in regions subjected to repetitive pressure or microtrauma (7). A tissue biopsy was then performed and revealed the presence of calcium deposits and monocyte proliferation, with no indications of malignancy.

Serum uric acid, creatinine, calcium, urinary calcium, alkaline phosphatase, and

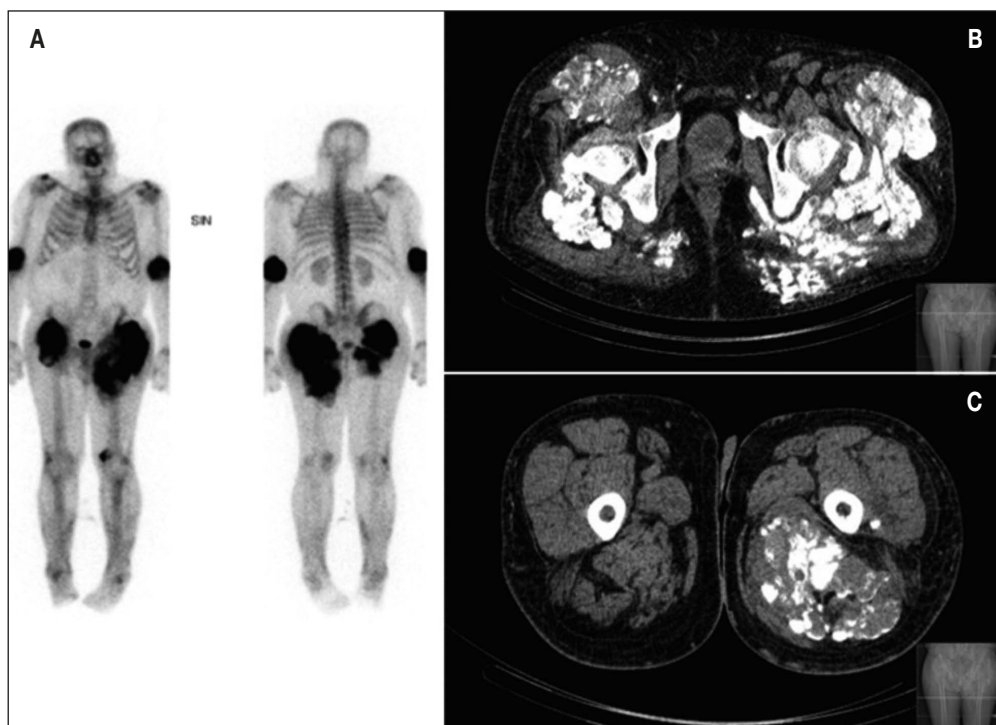


Figura 1 - A) bone scintigraphy using (99m) Tc-labeled methylene diphosphonate shows an increased uptake around the hips and elbows; B, C) axial computed tomography scan of the pelvis shows periarticular calcifications, also known as tumoral calcinosis, of the hip which were larger on the left side.

parathyroid hormone (PTH) were within the normal range. However, serum levels of inorganic phosphorus (Pi) and C-reactive protein were elevated at 6.4 mg/dL (normal range: 2.5–4.5 mg/dL) and 61.4 mg/L (normal range: 0.0–5.0 mg/L), respectively. Intact *FGF23* was 35 pg/mL (normal range: 23.2–95.4 pg/mL).

HFTC/HHS was suspected, and genetic testing was performed on genomic DNA extracted from peripheral leucocytes. A novel homozygous *GALNT3* mutation (c.782 G>A; p.R261Q) was found. Such mutation was predicted to be pathogenic by Varsome, Polyphen2, SIFT, and Mutation Taster bioinformatics tools, while *FGF23* resulted in wild-type. The diagnosis of HFTC/HHS caused by a novel *GALNT3* mutation was done. It was not possible to assess if the variant was *de novo* or inherited because both parents were already deceased: the father for Alzheimer's disease and the mother for senile marasmus. The patient has two brothers in apparent good health and a further brother affected by Churg Strauss syndrome. The son has been screened and was identified as a carrier, presenting the same heterozygous variant.

Therapeutic intervention

Phosphate chelating therapies (aluminum hydroxide and sevelamer) and acetazolamide were initiated promptly after diagnosis. However, these treatments were ineffective in reducing the levels of Pi.

A pharmacological treatment with a single dose of denosumab (60 mg) and prednisone (10 mg/day) was performed. Denosumab was well tolerated. After 15 days from the injection, blood tests were repeated. Pi decreased by approximately 11% (from 6.4 to 5.7 mg/dL). The patient reported symptoms improving at 3 months.

■ DISCUSSION

HFTC/HHS is a rare genetically determined disorder with dysregulated phosphate metabolism. This condition is characterized by the inactivation of *FGF23*, which finely regulates renal phosphate handling. *FGF23* decreases tubular reabsorption of Pi, inhibits

renal 1.25 hydroxylases, and inhibits PTH. HFTC/HHS is indeed characterized by increased serum Pi and normal to high serum calcium levels. Such alterations produce a markedly elevated serum calcium-phosphate product, which, in turn, leads to the development of ectopic calcifications.

This case report contributes to a broader understanding of the genetic spectrum associated with HFTC/HHS by identifying a novel *GALNT3* mutation. The *GALNT3* gene encodes a glycosyltransferase responsible for the O-glycosylation of *FGF23* (8). Such glycosylation significantly influences the enzymatic degradation process of the molecule, possibly leading to the inactivation of *FGF23*. However, the precise mechanism linking *GALNT3* mutations to the pathogenesis of the syndrome remains unknown at present (9).

The diagnosis of HFTC/HHS is generally based on medical history, physical examination, and, most importantly, laboratory biochemistry and imaging. Imaging plays a crucial role in diagnosing HFTC/HHS. CT is the preferred technique for a more precise characterization of calcified masses and the accurate assessment of their characteristics, including size and density (7). Importantly, CT is valuable for assessing the relationship between calcifications and adjacent bones. Typically, patients with HFTC/HHS do not exhibit aggressive soft-tissue mass behavior on bone and cortical destruction (10).

Pain management in HFTC/HHS includes non-steroidal anti-inflammatory drugs, glucocorticoids, and surgical removal of calcifications. To address inflammation, the potential benefits of anti-interleukin (IL)-1 treatment have been explored and have shown promise in improving pain and reducing inflammatory flares of HFTC/HHS (1, 3, 11). However, anti-IL-1 blockade failed to prevent further extension of calcinosis (1). Indeed, treatment should also focus on the reduction of plasma Pi. Hyperphosphatemia is usually controlled by dietary phosphate restriction, blockade of dietary phosphate absorption using phosphate chelators, and the promotion of renal phosphate excretion with medications such as acetazolamide, niacin, and probenecid.

Nonetheless, the clinical response to all these therapeutic measures is quite variable, with limited effectiveness and frequent recurrence of tissue calcification (12).

Phosphate homeostasis depends on a dynamic balance involving the active reabsorption of phosphates in the renal tubules as well as active and passive absorption in the jejunum and bone tissues. Based on these premises, we advised the patient to restrict phosphate intake and initiated treatment with phosphate chelators and acetazolamide. However, Pi did not decrease, and symptoms progressed. Therefore, we initiated denosumab, a potent anti-resorptive agent capable of lowering blood Pi levels. Indeed, denosumab is almost invariably associated with a compensatory increase in PTH serum levels (to counteract relative hypocalcemia). In HFTC/HSS, the increase in PTH is much more desirable due to its phosphaturic effects (13). This effect may be further amplified by a reduction in phosphate release from bone resorption.

The main limitation of this case report is that a single injection of denosumab with too little follow-up can cause only a transient reduction in Pi and, therefore, is not curative in a chronic disease. It will be useful to schedule a longer follow-up to evaluate whether to continue the therapy and to assess if phosphate levels may rise again upon its discontinuation.

In addition, we may have used a suboptimal dose of denosumab. Indeed, it might be interesting to evaluate if higher doses of denosumab (*i.e.*, 120 mg) could have normalized phosphatemia.

Considering that calcium is the electrolyte most prone to change after denosumab, which has never been used in these patients, another aspect to consider is the need to measure blood calcium levels after treatment. Moreover, given denosumab's pharmacokinetics and half-life, it would be useful to assess the persistence of the effect on phosphate reduction not only at 10-15 days (peak of the drug's action, when maximum concentration is reached) but also at 3 months, considering the improvement in symptoms reported by the patient after this period.

■ CONCLUSIONS

In conclusion, we described a patient with HFTC/HHS harboring a novel homozygous *GALNT3* mutation treated with denosumab. This novel mutation of *GALNT3* will help us understand the role of this gene in the pathogenesis of HFTC/HHS.

It is possible that denosumab may merit further future studies for the control of phosphatemia in HFTC/HHS.

Contributions

GF, conceptualization, data curation, investigation, writing - review and editing; AC, data curation, methodology, writing - original draft; CM, data curation, methodology, writing - review and editing; GA, writing - review and editing.

Conflict of interest

GA, Theramex, UCB, Lilly, Galapagos, Fresenius Kabi, Amgen, BMS, Abiogen; the other authors declare no potential conflict of interest.

Ethics approval and consent to participate

The study was conducted following the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

The patient gave his informed consent to the submission of the case report to the journal.

Funding

None.

Availability of data and materials

Data available from the corresponding author upon request.

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