Gigantic hip mass as the initial presentation of hyperphosphatemic familial tumoral calcinosis

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SUMMARY

Introduction: *Hyperphosphatemic familial tumoural calcinosis (HFTC) is a rare autosomal recessive disorder characterised by ectopic calcium phosphate deposition around the joints due to mutations affecting phosphate regulation.*

Case Presentation: *We report a 7-year-old boy who presented with hip pain and swelling, mimicking malignancy. Imaging revealed a large lobulated soft tissue mass involving the left iliac fossa and pelvic musculature. The FDG-PET and MRI findings suggested a neoplastic lesion, but the FNAC revealed only calcific debris. Biochemical analysis revealed elevated serum phosphorus levels and low PTH. Whole-exome sequencing identified a homozygous likely pathogenic mutation in GALNT3 (c.840T>A; p.Cys280Ter). Medical management included phosphate binders and acetazolamide. Despite initial improvement, recurrence occurred one year later. Surgical options were deemed high-risk and conservative treatment was continued.*

Conclusion: *This case highlights the importance of considering HFTC in the differential diagnosis of calcified soft tissue masses in children and the role of genetic testing in diagnosis and management.*

Keywords: *tumoural calcinosis, hyperphosphatemia, GALNT3, paediatric soft tissue mass, phosphate metabolism disorder*

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INTRODUCTION

Tumoural calcinosis (TC) is an uncommon metabolic bone disorder that typically occurs during childhood and adolescence. It is characterised by abnormal calcium deposits in the soft tissues surrounding the joints, particularly in the areas outside the joint capsule. The condition most often involves large joints, including the hips, shoulders, elbows, and gluteal regions (1).

This condition is classified into two main types: primary, likely inherited (familial), and secondary (2). However, according to its pathogenesis, it is classified into three types: primary hyperphosphataemic familial tumoural calcinosis (HFTC), primary normophosphatemic familial TC, and secondary TC.

Hyperphosphataemic familial tumoural calcinosis (HFTC) arises due to either a deficiency or resistance to fibroblast growth factor 23 (FGF23), which disrupts the phosphate balance. This dysregulation is typically caused by pathogenic mutations in the *FGF23*, *GALNT3* (which encodes polypeptide N-acetylgalactosaminyltransferase 3), or *KL* (Klotho) genes. Additional manifestations of tumoural calcinosis can include hyperostosis, localised pain and swelling over bony areas, and dental abnormalities such as discoloured or improperly developed teeth.

A normophosphatemic form of familial TC has also been linked to mutations in *SAMD9* in certain cases. By contrast, secondary TC develops in association with various underlying diseases and metabolic disturbances (3).

Soft-tissue calcinosis has a wide range of causes, making timely identification essential for appropriate management. Evaluating a patient's comorbid conditions is crucial for differentiating between primary and secondary disease processes, as some may mimic the rare clinical and radiographic features of tumoural calcinosis. Differential diagnoses include calcinosis related to chronic kidney disease, calcinosis universalis, calcinosis circumscripta, calcific tendinitis, synovial osteochondromatosis, synovial sarcoma, osteosarcoma, myositis ossificans, calcific myonecrosis, and tophaceous gout. Although many of these lesions are benign, some can be malignant. Therefore, the prompt and accurate diagnosis of calcified soft tissue masses is vital to avoid unnecessary invasive investigations and inappropriate treatment (4).

We report the case of a 7-year-old boy who presented with left hip pain, restricted range of movement, and intermittent fever and was ultimately diagnosed with familial tumoural calcinosis syndrome.

CASE PRESENTATION

A 7-year-old Maldivian boy presented with a one-month history of pain in the left hip, swelling, limited mobility, and intermittent fever.

He was initially evaluated at Malé Hospital, where an abdominal ultrasound performed on 01/02/2024 revealed an ill-defined, heterogeneous lobulated mass measuring 8.8 × 7.9 cm in the left lateral pelvis, contiguous with the left iliac bone, raising suspicion of a malignant bone tumor.

An MRI of the left femur, performed on 03/02/2024, showed a large, heterogeneously enhancing, lobulated solid-cystic multilobular mass measuring 8.4 × 6.7 × 14.3 cm within the left iliac fossa. The lesion demonstrated multiple fluid levels and appeared to arise from the left iliacus and psoas muscles without evidence of bone erosion or marrow oedema, suggesting a soft tissue sarcoma.

The patient was referred to our centre for further evaluation. A whole-body FDG PET-CT conducted on 15/02/2024 demonstrated a metabolically active soft tissue mass with cystic areas and calcification in the left iliac fossa, involving multiple muscles including the iliacus, psoas major, quadratus lumborum, pectineus, and some of the adductor muscles, suggesting a neoplastic aetiology. There was no evidence of metabolically active lymph nodes or distant metastasis (Figure 1).

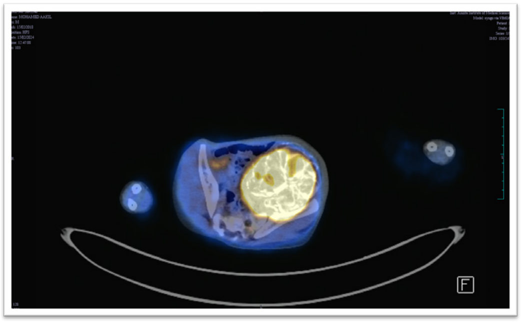

Figure 1. Whole-body PET-CT performed on 15/02/2024 demonstrating a calcified soft tissue mass involving the left pelvic region and upper thigh.

A USG-guided aspiration of the cystic areas of the pelvic mass was performed under general anaesthesia on 16/02/2024. The cytological analysis (FNAC) of the aspirated material revealed only calcific debris and no malignant cells.

The patient consistently exhibited elevated C-reactive protein (CRP) levels, indicating ongoing inflammation, with values of 109.81 mg/L. Additionally, serum inorganic phosphorus was persistently elevated, ranging from 5.8 to 7.9 mg/dL, while the total serum calcium fluctuated between high-normal and mildly elevated levels. Notably, parathyroid hormone (PTH) levels were markedly suppressed (e.g., <1.20 pg/mL), suggesting a non-parathyroid origin of the observed hyperphosphatemia and hypercalcemia. 25-hydroxy Vitamin D was also found to be low (16.14 ng/mL).

Given this atypical presentation, paediatric genetic consultation was sought. Whole Exome Sequencing (WES) identified a homozygous likely pathogenic mutation in the *GALNT3* gene, c.840T>A (p.Cys280Ter), consistent with a diagnosis of familial hyperphosphatemic tumoural calcinosis, an autosomal recessive disorder. Ophthalmology, endocrinology, and dental evaluations were completed as part of the systemic workup.

Following the diagnosis, the patient was initiated on medical management with acetazolamide 250 mg (½ tablet twice daily) and sevelamer 400 mg (three times daily), along with a strict dietary phosphorus restriction. The child demonstrated symptomatic improvement and was discharged in stable condition.

One year later, the patient was readmitted with complaints of left hip pain and swelling. On admission, a thorough clinical evaluation was conducted, and blood investigations were repeated. Empirical antibiotics and symptomatic treatment were initiated. An orthopaedic consultation was obtained, and radiographic imaging was performed as advised. A nephrology review was also conducted due to persistently elevated serum phosphorus levels, and recommendations were implemented accordingly.

Paediatric cardiology consultation, including echocardiography, was performed. After pre-anaesthesia clearance, whole-body PET-MRI was performed under general anaesthesia on 10/02/2025. Imaging revealed a persistent, diffusely FDG-avid, T2-hyperintense multiloculated cystic lesion with a soft tissue component and calcifications involving the muscles of the left pelvis and upper third of the left thigh (both anterior and posterior compartments). There was a minimal further increase in the posterior compartment involvement. The findings were suggestive of either tumoural calcinosis or a primary malignancy with no evidence of metabolically active lymph nodes, pulmonary lesions, or distant metastases (Figure 2).

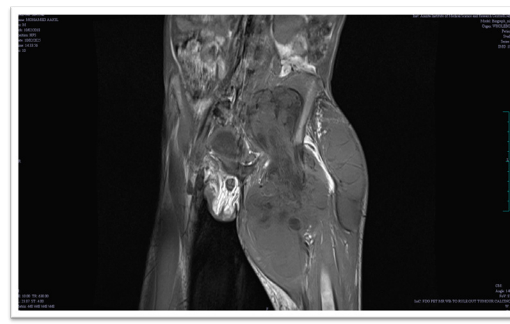

Figure 2. Coronal section of the thigh MRI performed on 10/02/2025, demonstrating disease progression.

During the hospital stay, the blood cultures remained sterile, but the CRP levels were elevated, prompting the escalation of antibiotics to meropenem. Endocrinology consultation was obtained for the management of elevated serum calcium and phosphate levels, and daily monitoring was initiated.

The family received detailed counselling emphasising the importance of strict phosphorus control, continued use of sevelamer and acetazolamide, and potential complications of the disease, including aggressive lesion growth and pelvic destruction, which could lead to significant disability.

The family expressed interest in surgical options, and a plastic surgery consultation was obtained. It was advised that the lesion appeared inoperable at present and that if surgery was attempted, a hemiquadrantectomy might be required. Uro-oncology and orthopaedic opinions were also sought.

The multidisciplinary tumour board recommended conservative management based on the high surgical morbidity, including the risk of amputation and the likelihood of disease recurrence even after surgery.

Despite persistent fever spikes and elevated levels of inflammatory markers, the family requested discharge to obtain a second opinion. The patient was discharged at their request with the following instructions: continuation of sevelamer and acetazolamide, adherence to a low-phosphorus diet, and regular follow-up for monitoring. The progressive and potentially disabling nature of the disease was thoroughly explained to the family.

DISCUSSION

Familial hyperphosphatemic tumoural calcinosis (FHTC) is a rare autosomal recessive metabolic disorder characterised by progressive ectopic calcification in soft tissues, primarily around the large joints. This results from mutations in genes that regulate phosphate homeostasis, most notably *GALNT3*, which encodes a glycosyltransferase essential for the post-translational modification of fibroblast growth factor 23 (FGF23) (5,6).

In the present case, a 7-year-old male from the Maldives exhibited classical clinical features of tumoural calcinosis, including a large, multilobulated periarticular mass over the hip, accompanied by intermittent fever and elevated inflammatory markers, initially mimicking a soft tissue sarcoma. This misdiagnosis is not uncommon, as tumoural calcinosis can present with mass effects, cystic degeneration, and soft tissue infiltration on imaging, features that overlap with malignant neoplasms (7). The absence of bone marrow oedema or cortical destruction on MRI, along with the lack of malignant cells on FNAC, raised the suspicion of a benign yet infiltrative process. The definitive diagnosis was established via Whole Exome Sequencing (WES), which revealed a homozygous nonsense mutation (*c.840T>A; p.Cys280Ter*) in the *GALNT3* gene, consistent with hyperphosphatemic familial tumoural calcinosis (HFTC). This mutation results in a truncated, non-functional GALNT3 protein that disrupts O-glycosylation and impairs the protection of FGF23 from proteolytic degradation. The resulting FGF23 deficiency leads to increased renal phosphate reabsorption and elevated 1,25-dihydroxyvitamin D levels, thereby fostering a biochemical environment conducive to ectopic calcification (8,9).

Clinical manifestations typically begin in childhood or adolescence and include periarticular calcified masses, which may be painful, inflammatory, and prone to secondary complications, such as ulceration, infection, and joint immobility. In this case, the patient's lesion involved multiple pelvic muscles, including the iliacus, psoas, and quadratus lumborum and closely mimicked an aggressive neoplasm. Notably, fever and elevated CRP levels may reflect a sterile inflammatory response secondary to ongoing calcification and tissue necrosis rather than systemic infection, a phenomenon previously documented in the FHTC literature (10).

The management of FHTC is complex and aims to reduce serum phosphate levels using phosphate binders (e.g. sevelamer), carbonic anhydrase inhibitors (e.g. acetazolamide), and strict dietary phosphate restrictions (11). Our patient initially responded well to this regimen with symptom relief and disease stabilisation. However, recurrence and progression, as observed at the one-year follow-up, are common and may require surgical intervention. Surgical resection is often challenging due to poor lesion demarcation and high recurrence rates (12). Surgical options are generally reserved for patients with severe functional impairment or complications. Radical resections, such as hemi-quadrantectomy or amputation, may be considered, as discussed in this case's MDTB meeting, but these interventions carry substantial morbidity. Conservative management should be prioritised, particularly in paediatric patients who are still undergoing skeletal development.

Genetic counselling is essential for families affected by autosomal recessive conditions such as FHTC. Carrier screening and prenatal counselling may be appropriate in regions with high consanguinity or where founder mutations are suspected (13).

CONCLUSION

This case underscores the importance of recognising FHTC in children presenting with atypical soft tissue masses and hyperphosphatemia, especially when the initial cytological findings are inconclusive. It highlights the diagnostic value of early genetic testing in such presentations and emphasises the need for a multidisciplinary care approach, encompassing paediatricians, endocrinologists, nephrologists, geneticists, surgeons, and physiotherapists, for effective long-term management.

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