J. Univ. Med. Dent. Coll., Vol.13(2), 399-402;2022
ISSN (Print) 2221-7827, ISSN (Online) 2310-5542
DOI: 10.37723/jumdc.v13i2.705
http://www.jumdc.com/

Case Report

Open Access

Long follow-up of Multiple Recurrent Calcific Masses–A rare case report of Hyperphosphatemic Familial Tumoral Calcinosis

Saad Ahmed[a], Ayesha Saeed[b], Shafique Farooq[c], Zeeshan Yaqoob[d], Fatima tul Zohra[d], Muhammad Waqas[d]

[a]Registrar Department of Pediatric Orthopedics the Children's Hospital and The Institute of Child Health, Faisalabad.
[b]Assistant Professor and Head Department of Pediatric Orthopedics the Children's Hospital and The Institute of Child Health, Faisalabad.
[c]Senior Registrar Department of Pediatric Orthopedics, The Children's Hospital and The Institute of Child Health, Faisalabad.
[d]Medical Officer Department of Pediatric Orthopedics, The Children's Hospital and The Institute of Child Health, Faisalabad.
Corresponding author* drayeshasaeed@gmail.com

ABSTRACT

Hyperphosphatemic familial tumoral calcinosis (HFTC) is an autosomal recessive benign condition of dysregulated phosphate metabolism (biallelic mutation in GLANT3, KLOTHO or FGF23) due to deficiency or resistance of intact fibroblast growth factor 23 resulting in deposition of large amount of ectopic calcium salts in periarticular soft tissues. We present a 21-year male with multiple recurrent masses around both hips, feet, left knee, and left elbow. His serum inorganic phosphate levels and ratio of renal tubular reabsorption rate of phosphate to corrected glomerular filtration rate were markedly elevated. Medical treatment to lower serum phosphate levels by placing him on tablet sevelamer hydrochloride and acetazolamide and surgical excision of the periarticular masses lead to disease remission. At 4 years follow up he has no recurrence and his functional scores (SF 36 and Harris Hip Score) have tremendously improved. Tumoral calcinosis, though rare must be kept in mind as a differential in abnormal calcific masses and with good radiological and laboratory support can be diagnosed early.
KEYWORDS: Hyperphosphatemic Familial Tumoral Calcinosis (HFTC), Hyperostosis Hyperphosphatemia syndrome (HHS), Hyperphosphatemia.

INTRODUCTION

Hyperphosphatemic familial tumoral calcinosis (HFTC)/ hyperostosis hyperphosphatemia syndrome (HHS) is an autosomal recessive benign condition of dysregulated phosphate metabolism (biallelic mutation in GLANT3, KLOTHO or FGF23) due to deficiency or resistance of intact fibroblast growth factor 23 (iFGF23) resulting in deposition of large amount of ectopic calcium salts (hydroxyapatite crystals) in periarticular soft tissues [1,2]. One third of these cases are familial autosomal dominant (SAMD9) with hyperphosphatemia and reports of autoimmune variant are documented as well [2]. First case was reported by Duret in 1899 as "Endothelium Calcifie" and later Inclan in 1943 labelled it as "Tumoral Calcinosis (TC)" that was accepted world-wide [3]. This is also known as Teutsecherlaender disease, calcifying bursitis, lipocalcino granulomatosis [4]. They resemble tumor but are not true neoplasms as they don't have dividing cells [3].

Tumoral Calcinosis presents as firm rubbery masses usually painless, non-tender but cause pressure symptoms and decrease range of motion of affected joint. They mostly occur around hips, elbow, shoulder, foot and wrist with predilection for extensor surfaces. Grossly they are lobules of calcific material separated by fibrous septa and demonstrate milky white material. On histology the lobules are surrounded by histiocytic giant cells containing psammomatous calcifications. The radiographs appear as heterotrophic amorphous and multilobulated (cloud like) calcified masses [5]. On computed tomography there is no erosion or osseous destruction with cystic appearance and multiple fluid calcium levels caused by calcium layering (Sedimentation Sign) [5]. Differentials include hyperparathyroidism, chronic renal failure, calcium pyrophosphate deposition disease, myositis ossificans, calcinosis circumscripta and universalis, milk-alkali syndrome, hyper-vitaminosis D, calcific tendonitis,

Ahmed S, Saeed A, Farooq S, Yaqoob Z, Zohra F, Waqas M et al. long follow-up of Multiple Recurrent Calcific Masses–A rare case report of Hyperphosphatemic Familial Tumoral Calcinosis. Journal of University Medical & Dental College. 2022; 13(2):399-402.

synovial sarcoma, osteosarcoma, calcific myonecrosis, tophaceous gout, dystrophic calcification associated with connective tissue disorders, and synovial chondromatosis [5,6]. Treatments to lower serum phosphorus by blocking dietary phosphate absorption and increasing renal phosphate excretion have limited effectiveness. Surgery is usually reserved for patients with significant pain or limited function [7]. Awareness of this rare disorder is important to ensure appropriate biochemical investigations and to avoid unnecessary invasive diagnostic procedures [5].

We present a case of tumoral calcinosis with multiple recurring periarticular masses that underwent repeated surgeries and later responded to phosphate lowering drugs with good outcome.

CASE REPORT

A 21 years old male presented in May 2017 with complains of massive swelling, mild pain and limitation of movement in bilateral hips and left elbow joint developed gradually over 5 years. Clinical examination revealed non-tender, hard mass in the left gluteal region with painful, restricted rotation and abduction movements of the hip. There was history of 5 previous surgeries for similar swellings on bilateral feet in 1999, left knee in 2012 and 2016 and left elbow in 2015. Previous histopathology reports reveled fibro-collagenization with extensive calcification and foreign body giant cell type reaction. So far the biochemical workup was inadequate therefore no definite diagnosis was reached. He was also prescribed anti tuberculous therapy empirically in 1999 for 1 year with no successful outcome.

The present radiographs showed amorphous calcifications all around both hip joints, posterior aspect of left elbow and anterolateral aspect of left knee. MRI left hip showed large well-marginated lobulated masses heterogeneously hypointense located deep to left half of gluteal region approaching subcutaneous plane laterally. Medially abutting femoral attachment of piriformis muscle and body of ischium, enveloping superolateral aspect of greater trochanter. There was no bony or joint capsule involvement. MRI right hip showed similar hypointense heterogeneous signals as well as sedimentation signals. Mass measured 16 x 9 x20 cm involving all gluteal muscles, piriformis, quadratus femoris, obturator externus muscles extending just below iliac crest to upper thigh posteriorly with normal hip joint.

Serum urea, creatinine, uric acid, total calcium, alkaline phosphate, and parathyroid hormone concentrations were normal. However, serum inorganic phosphorus was elevated at 7.4 mg/dl (normal range 2.7 – 4.5/L). The ratio of the renal tubular maximum reabsorption rate of phosphate to corrected glomerular filtration rate was also elevated at 2.24 mmol/L (normal range 1.07–1.89 mmol/L), suggestive of increased renal tubular phosphate reabsorption. Considering the patient's age, presence of multiple, recurrent periarticular soft tissue, calcific masses, hyperphosphataemia with increased tubular phosphate reabsorption, and the absence of indications that the ectopic calcification was secondary to any other causes, the patient was diagnosed with hyperphosphataemic tumoral calcinosis. Endocrine consultation was sought and tablet sevelamer hydrochloride (non-calcium-based phosphate binder) 800mg/day was started with oral acetazolamide (40mg/kg/day) to induce phosphaturia.

The surgical excision of left hip mass was planned first. In general anesthesia in a right lateral position using the Moore's approach marginal total resection of the tumor was done. A mass of 17 ×8×19 cm was removed in two pieces as the multi-planar involvement made the dissection difficult. After 5 months in January 2018 mass of 16×9×20 cm was removed from the right hip as well. Both masses had chalky white material contained as shown in figure. Histopathology showed well defined capsules with thick septa, lobules of calcific material surrounded by histiocytic giant cell containing small psammomatous calcifications suggestive of Tumoral Calcinosis.

Mass of 4×3 cm behind left elbow was not painful and was not affecting the range of motion so was not removed. Patient is still on sevelamer 800 mg/day with phosphorus level monitoring every 6 months. There is no recurrence of mass as shown in follow-up photograph taken after 4 years in January 2021, size of mass behind elbow has regressed and the phosphate levels are normal (4.5 mg/dl).

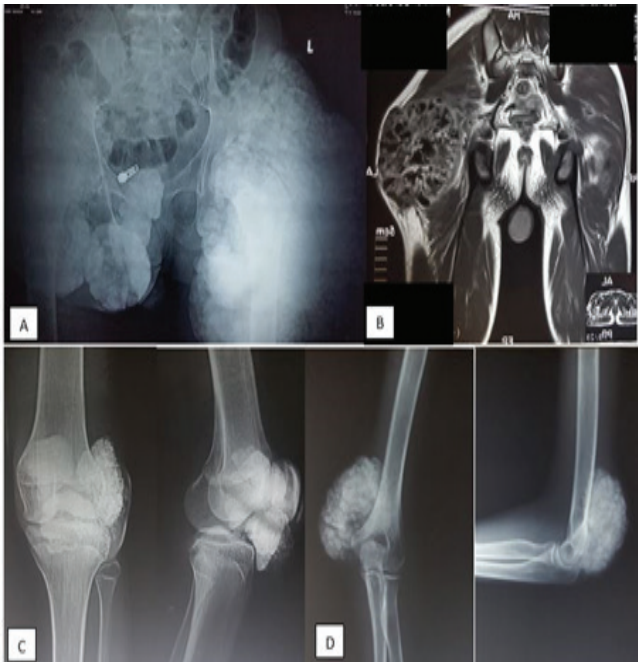

Figure-I: A) Radiographs of both hips at presentation showing huge calcific clouds around hip joints sparing the bone, **B)** Sagittal section MRI hip soft tissue relationship **C & D)** Radiographs of knee & elbow showing well-circumscribed lesion.

Patient's Short Form (SF) 36 score also improved significantly with physical functioning improving from 50 to 95, role limitations due to physical health improving from 56 to 100, and role limitation due to emotional problems improved from 45 to 96, pain improved from 42 to 100. Highest scores for energy were 80, emotional wellbeing was 64, social functioning was 75, general health 65 and health change 75 were obtained after surgery, all attributed to length of time of patient suffering [8]. Harris hip score for right hip improved from 34.15 to 94 and left hip improved from 36 to 93 after surgery.

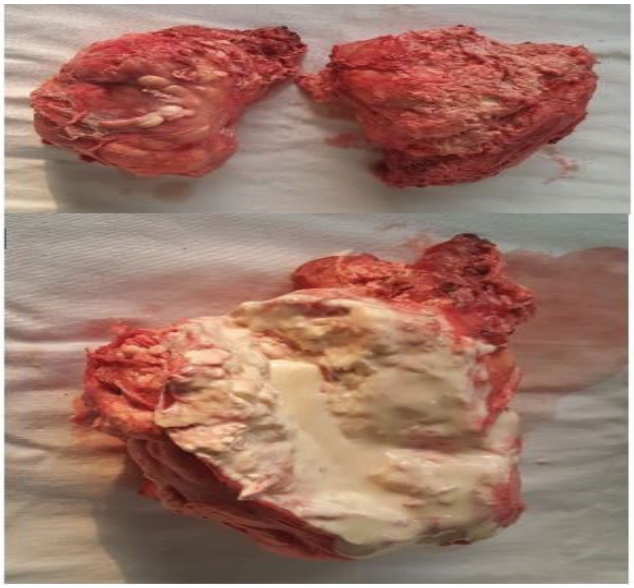

Figure-II: Right hip surgical specimen piece-meal removal, transverse section shows milky white material discharge.

DISCUSSION

Multifocal calcification due to raised calcium phosphorus deposition with hyperphosphatemia can be explained by genetic mutations in FGF23, GLANT3 and KLOTHO genes[1]. Various theories like repetitive trauma leading to hemorrhages initiating foamy histiocytic response or frictional forces leading to neo-bursa formation and periarticular deposition in normo-phosphatemic variety [9]. HFTC is marked by hyperphosphatemia, excessive renal tubular phosphate reabsorption and tumor like extraosseous masses. A baseline biochemical workup like serum calcium, phosphorus, parathormone, 1, 25 dihydroxy vitamin D levels and renal function tests is mandatory to exclude differentials. History and clinical examination when in doubt of connective tissue disorder antinuclear, antismith, anticentrome and antiscleroderma antibodies are to be done [4,10].

Medical management in HFTC aims at lowering serum phosphorus and increasing urinary phosphate excretion may limit the need for surgical intervention. Dietary restriction of phosphate and phosphate binders are considered mainstays of treatment, although some evidence suggests the possible utility of oral acetazolamide in enhancing urinary phosphate

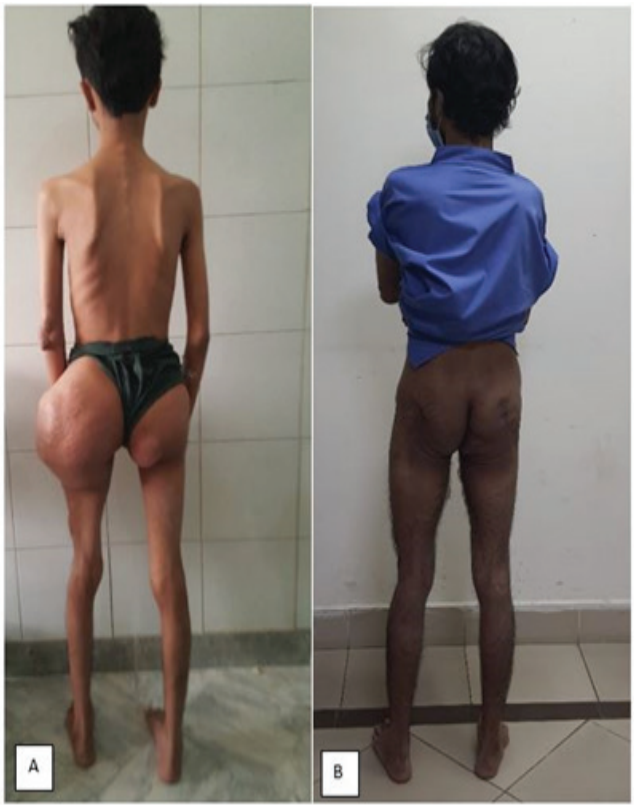

Figure-III: A) Preoperative photograph at presentation in 2017 B) Postoperative follow up photograph in January 2021.

excretion. Other treatment alternatives include calcitonin, bisphosphonates, calcium channels blockers, corticosteroids, and colchicine. Medical agents that lower phosphorus include sevelamer, calcium acetate, aluminium hydroxide and acetazolamide to induce phosphaturia are used and shown to decrease recurrence. Resistance to medical therapy has been proposed if the lesion gets encapsulated preventing ion exchange [11].

In secondary variety, surgical excision is usually complicated by infection, sinus formation and recurrence [9]. Medical treatment includes calcium and phosphorus restricted diets, dialysis and phosphate binders except aluminium. Drugs like vinpocentine, sodium thiosulphate and intravenous pamidronate have shown some success in studies. Renal transplantation and total/ subtotal parathyroidectomy are to be done if medical treatment fails [1,2,4].

In the reported case, marginal total excision along with continuous treatment with oral sevelamer hydrochloride (phosphate binding agent) and acetazolamide resulted in good outcome and no recurrence or appearance of masses. Similar approach as been described by multiple case reports in literature [13-14].

The limitation in this case was inability to conduct genetic testing due to which exact labelling of genetic mutation was not possible.

CONCLUSION

Tumoral calcinosis, though rare must be kept in mind as a differential in abnormal calcific masses and with good radiological and laboratory support can be diagnosed early. Surgical excision with marginal resection relieves the pressure symptoms and improve functional status. Medical management with phosphate lowering agents in close follow-up prevent recurrence.

ACKNOWLEDGEMENT: None.
CONFLICT OF INTEREST: All authors declare no conflict of interest.
GRANT SUPPORT & FINANCIAL DISCLOSURE: None.

References

1. Albaramki J, Dmour H, Shboul M, Bonnard C, Venkatesh B, Odeh R. Recessive mutation in GALNT3 causes hyperphosphatemic familial tumoral calcinosis associated with chronic recurrent multifocal osteomyelitis. The Turkish Journal of Pediatrics. 2019;61(1):130-133. Doi: 10.24953/turkjped.2019.01.022
2. Roberts MS, Burbelo PD, Egli-Spichtig D, Perwad F, Romero CJ, Ichikawa S, et al. Autoimmune hyperphosphatemic tumoral calcinosis in a patient with FGF23 autoantibodies. The Journal of Clinical Investigation. 2018;128(12):5368-5373.
3. Inclan A, Leon P, Camejo MG. Tumoral calcinosis. Journal of the American Medical Association. 1943;121(7):490-495. Doi:10.1001/jama.1943.02840070018005
4. Tiwari V, Goyal A, Nagar M, Santoshi JA. Hyperphosphataemic tumoral calcinosis. Lancet (London, England). 2019;393(10167):168.
5. Olsen KM, Chew FS. Tumoral calcinosis: pearls, polemics, and alternative possibilities. Radiographics. 2006;26(3):871-885.
6. Savaci N, Avunduk MC, Tosun Z, Hosnuter M. Hyperphosphatemic tumoral calcinosis. Plastic and Reconstructive Surgery. 2000;105(1):162-165.
7. Finer G, Price HE, Shore RM, White KE, Langman CB. Hyperphosphatemic familial tumoral calcinosis: response to acetazolamide and postulated mechanisms. American Journal of Medical Genetics Part A. 2014;164(6):1545-1549.
8. Ware J, Kosinski M, Keller S. SF-36 physical and mental health summary scales. A user's Manual. 2001:1994.
9. Fathi I, Sakr M. Review of tumoral calcinosis: A rare clinico-pathological entity. World Journal of Clinical Cases. 2014;2(9):409-14.
10. Sobhani Eraghi A, Athari B, Kheirkhah Rahimabad P. Tumoral calcinosis of the foot: An unusual differential diagnosis of calcaneal mass. International Journal of Surgery Case Reports. 2015;10:219-22.
11. Farzan M, Farhoud AR. Tumoral calcinosis: what is the treatment? Report of two cases of different types and review of the literature. American Journal of Orthopedics (Belle Mead NJ). 2011;40(9):E170-E176.
12. Gupta M, Thakur S, Sharma R, Gupta A. Idiopathic tumoral calcinosis presenting in early childhood. BMJ Case Reports. 2019;12(1).
13. Rajaonarison Ny Ony Narindra LH, Nirinaharimanitra VS, Hunald FA, Ahmad A. Two new cases of pediatric tumoral calcinosis. Journal of Surgical Case Reports. 2020:(12):rjaa481.
14. Sandomenico F, Corvino A, Ronza FM, Catalano O, Fazioli F, De Chiara A, et al. Recurrence of tumoral calcinosis: a case report. Acta bio-medica : Atenei Parmensis. 2019;90(4):587-594.

Author's Contribution:

Saad Ahmed: Drafted the manuscript, design and acquisition of data, interpretation of data and literature search.
Ayesha Saeed: Drafted the manuscript, design and acquisition of data, interpretation of data and literature search, final approval, patient management.
Shafique Farooq: Drafted the manuscript, acquisition of data, interpretation of data and literature search.
Zeeshan Yaqoob: Drafted the manuscript, acquisition of data, interpretation of data and literature search.
Fatima tul Zohra: Drafted the manuscript & did literature search.
Muhammad Waqas: Drafted the manuscript & did literature search.

Submitted for publication: 17-12-2021
Accepted after revision: 19-05-2022