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Regression of a Primary Pseudo-Tumoral Calcinosis Progressing During 16 Years under Combined Treatment with Acetazolamide and Aluminum Hydroxide: A Case Report

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ABSTRACT

Primary pseudo-tumoral calcinosis is a rare genetic disease due to a disorder of phosphorus metabolism characterized by the formation and deposition of calcium phosphate crystals in the peri-articular regions. The treatment is based on the reduction of hyperphosphatemia by hygienic and nutritional measures, hypophosphatemic drugs and surgery. We report the case of a 19-year-old patient followed since the age of 3 years for a primary pseudo-tumoral calcinosis that was resistant to surgery and that had well progressed with aluminum hydroxide and acetazolamide. Treatment combining aluminum hydroxide and acetazolamide with hygienic and nutritional measures seems to be an interesting therapeutic option for this pathology.

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KEYWORDS:
Calcinosis, pseudo-tumoral, Acetazolamide, aluminum hydroxide, diet, evolution, FGF23.

INTRODUCTION

Primary pseudo-tumoral calcinosis is one of a rare group of genetic diseases. This disorder is characterized biologically by recurrent hyperphosphatemia and ectopic periarticular calcifications, other visceral and vascular manifestations may be observed, without inflammatory or neoplastic cause [1]. Pseudotumoral calcinosis is characterized by increased renal phosphate reabsorption, hyperphosphatemia, and the formation of tumor-like extraosseous calcifications. The masses are painful and are typically periarticular. Primary pseudo-tumoral calcinosis is associated with inactivating mutations in the fibroblast growth factor 23 (FGF23) gene, or the UDP-Nacetyl-D-galactosam N-acetylgalactosaminyltransferase 3 (GALNT3) gene, or the Klotho (KL) gene [2]. Pseudotumors often necessitate surgical excision because of their volume, aesthetic impact, as well as the associated pain. However, medical treatment to reduce serum phosphorus levels and increase urinary phosphate excretion may limit the necessity for a surgical intervention. Dietary phosphate restriction and phosphate binders are considered as the pillars of treatment. The Literature suggests the possible utilityof oral Acetazolamide to increase urinary phosphate excretion [3], as well as aluminum hydroxide [1]. We report a case of pseudo-tumoral calcinosis in a 19-year-old patient treated with Acetazolamide, aliminium hydroxide with a hypophosphatemic diet, specifying the clinical, biological, radiological and evolutionary aspects of this pathology.

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CASE REPORT

We report the case of a 19-year-old patient, black phototype, without any medical history, followed since the age of 3 years for a primary pseudo-tumoral calcinosis diagnosed in the context of hyperphosphoremia, ectopic peri-articular calcifications and histological examination which had objectified a calcic deposits organized in an amorphous zone compatible with a pseudo-tumoral calcinosis **(figure 1).** The patient had been surgically treated for calcified masses on multiple times at a frequency of once a year. The patient was being admitted to our department for a recurrence. He had a depressed mood on admission, apyretic and stable on hemodynamic and respiratory level. Clinical examination revealed dental avulsion**,** juxta-articular tumefactions on both hips, the largest one measuring 19 cm x 8 cm in diameter, situated in the left trochanteric region and emitting white liquid through a fistula **(Figure 2),** and tumefactions on the

left hand causing tendon retractions. The biological evaluation revealed hyperphosphatemia at 70 mg/l and a low FGF 23 level at 23.1pg . The bacteriological study of the fistula liquid was sterile. The other biological tests are summarized in **(Table 1).** Standard radiography of the pelvis in the frontal incidence had shown ectopic calcification of both hips **(Figure 3).** MRI of both hips had revealed two large bilateral juxta-articular masses of both gluteal regions extended to the posterior and medial muscle lodges of the thigh, with lobulated contours, T1 hypersignal, T2 hypersignal and multiple lodges with liquid-liquid level in T2 hypersignal (sedimentation sign). These formations are heterogeneously enhanced after injection of contrast product, realizing the aspect of honeycomb **(Figure 4).** The patient was treated with aluminum hydroxide 300 mg three times a day and acetazolamide 20 mg/kg/day with phosphorus restriction. Progression was marked by mood and pain improvement, reduction in tumefaction volume **(figure 2),** phosphorus reduction **(Table 2),** and a reduction in calcification size on imagery **(Figure 3, figure 4).**

FIGURES:

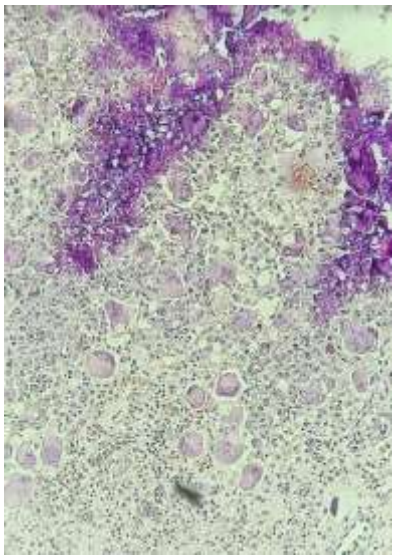

Figure 1: Anatomo-pathological aspect of calcified masses revealing calcic deposits organized in an amorphous zone

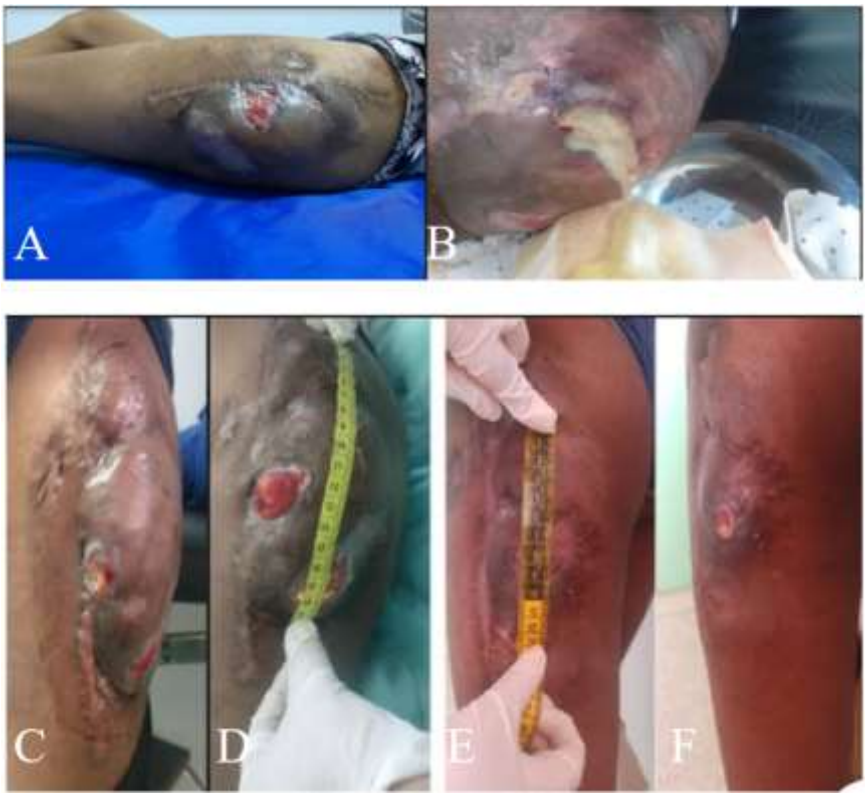

Figure 2: Tumefaction in the left trochanteric region with an aseptic white fluid emerging, with a regression of trochanter masses between the initiation of the treatment (A,B,C,D) and 8 months after the treatment(E,F)

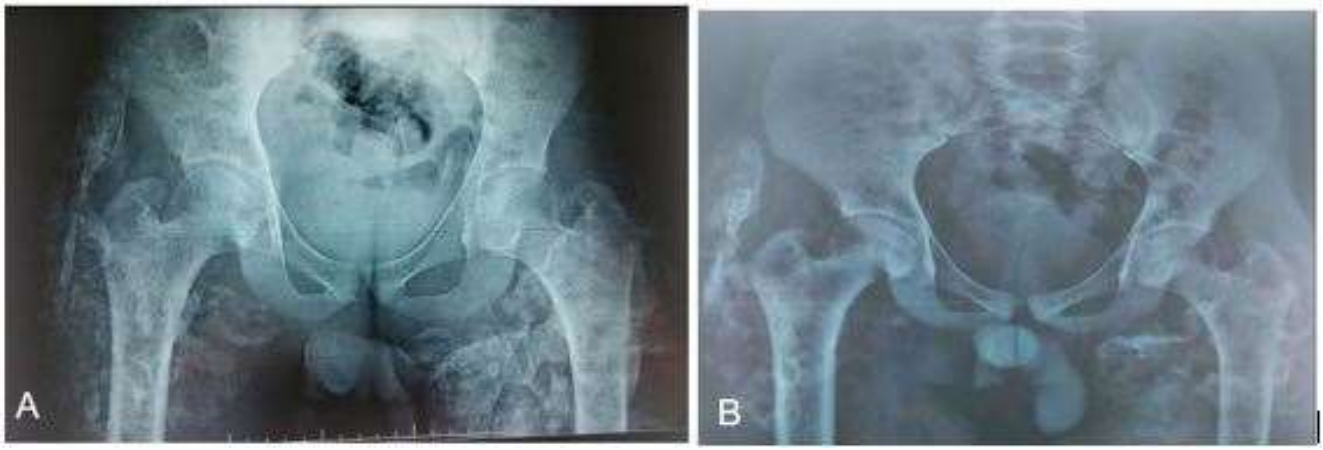

Figure 3: Pre-treatment radiography of the pelvis in the frontal plain (A) and control radiography (B) after 8 months of treatment.

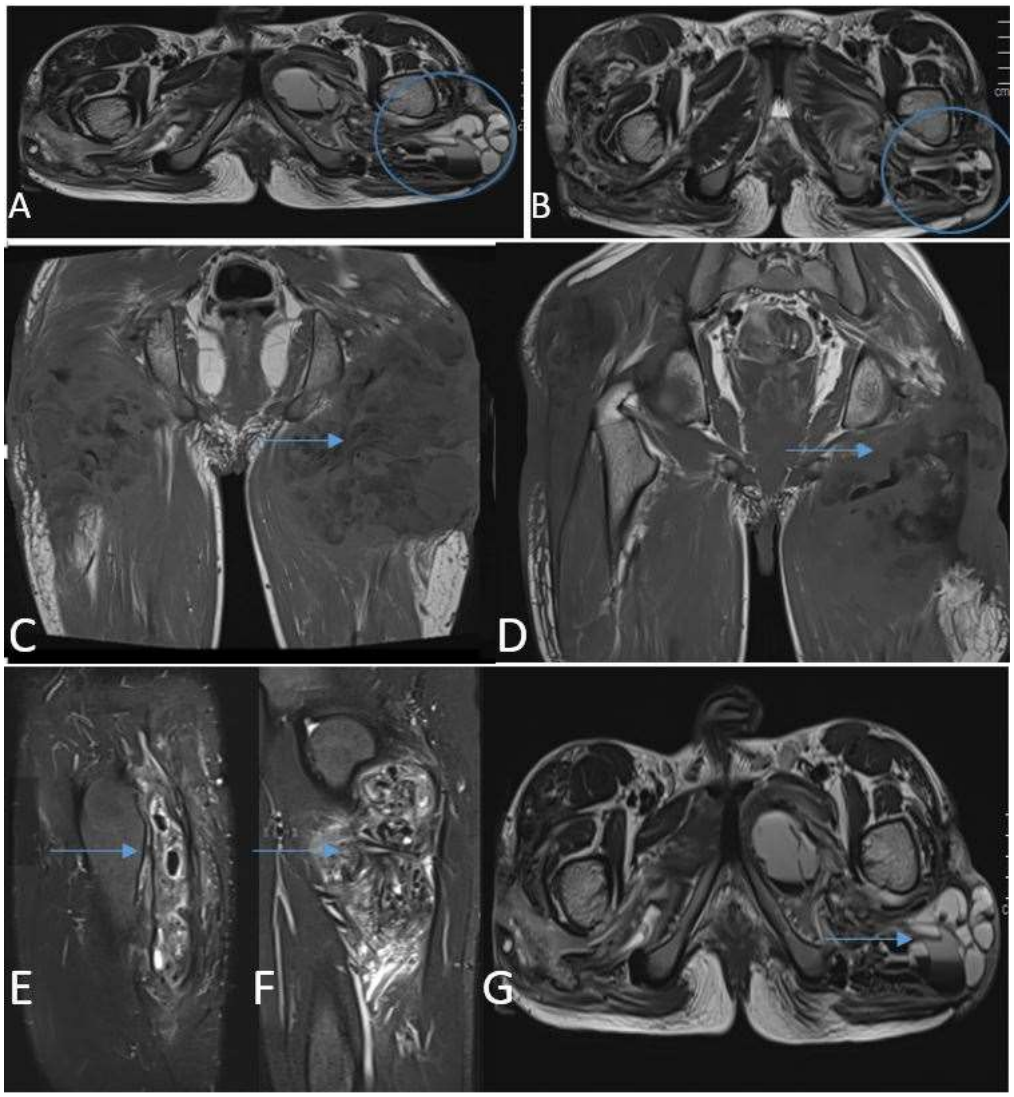

Figure 4 : MRI of the pelvis showing two large masses in the gluteal region extending to the posterior and medial muscular lodges of the thigh in T2 hypersignal (A)and T1 hyposignal(C) with multiple lodges with liquid-liquid levels in T2 hypersignal-hyposignal (sedimentation sign)(A).These formations enhancing heterogeneously after injection of contrast product, realizing the honeycomb aspect(G). Measuring approximately on the right 12x9.3x17cm and 17x9.2x17cm on the left with decrease in size between the first MRI (A,C,E,G) and the control MRI (B,D,F) after 8 months of treatment (on the right 12x9.3x17cm vs. 8x10x17cm and on the left 17x9.2x17cm vs 13x7x14cm).

DISCUSSION

Primary pseudo-tumoral calcinosis is a rare genetic disorder due to inactivating mutations in the FGF23 gene, the FGF23 is synthesized by osteocytes and to a lesser extent by osteoblasts , with three main actions at the renal proximal tubular cell level: inhibition of 1α hydroxylase, stimulation of 24 hydroxylase synthesis, and inhibition of apical membrane expression of Npt2a/Npt2c cotransporters, resulting in both a decrease in 1-25 OH2 vitamin D3 and a decrease in tubular phosphate reabsorption . FGF23 also acts at the parathyroid level, with two main actions: inhibition of parathyroid hormone synthesis and local stimulation of 1α hydroxylase, which locally increases 1-25 OH2 vitamin D3 and thus could locally accentuate the inhibitory effect on PTH synthesis. The gene responsible for its formation is located on 12p13, it is a protein of 251 amino acids (30 kDa) belonging to the family of FGFs (Fibroblast Growth Factors), in the subgroup of the so-called 'endocrine' FGFs (FGF 19 and similar). It shares with all FGFs a highly conserved sequence on the first amino acids; however, it has a unique C-terminal structure**[3]**. Among 100 to 200 cases of primary forms were reported in the literature **[4].** It mainly affects people with black skin and it is characterized by increased phosphate absorption by the renal system, hyperphosphatemia and extra osseous calcifications **[5].** The localization of pseudo-tumors is ubiquitous, but the trochanteric region is affected in 69% of cases **[6]**. The medical treatment of primary familial pseudo-tumoral calcinosis is not well reported in the literature. This report presents a case of primary pseudo-tumoral calcinosis resistant to surgical treatment (frequent resection and recurrence) treated with a combination of acetazolamide (a phosphaturic agent), it a sulphonamide-derivative, acts as a carbonic anhydrase inhibitor in the apical and basolateral membrane of the proximal tubule lumen. It induces natriuresis, kaliuresis, phosphaturia and bicarbonaturia. This causes a reduction in these ions in the body, leading to clinical and biochemical improvement in patients with hyperphosphataemia, and aluminum hydroxide (a phosphorus chelator at the digestive system) with dietary phosphorus restriction. This association seems to have promising results. **T. YAMAGUCHI and al [7]** had reported a case of a 19-year-old patient suffering from primary pseudo-tumoral calcinosis since the age of 10 months with multiple recurrent masses accompanied by pain around the joints of the fingers, knee and toes, the use of oral aluminum hydroxide in monotherapy for a long time had no effect on hyperphosphatemia or calcifying masses but the association with oral acetazolamide had showed a superior efficacy on the biological and clinical level. **Finer.G and al [8]** had also reported a case of primary pseudo-tumoral calcinosis in a 7-year-old African-American boy who presented a severe form that required multiple surgical excisions, the tumors continued to appear and others recurred despite phosphate restriction and sevelamer carbonate (a phosphorus binder). At the age of 9.5 years, acetazolamide (40 mg/kg/day) was started, the patient had a significant clinical improvement, with resolution of pain, cessation of tumor formation and absence of tumor recurrence. But there was a metabolic acidosis as a secondary effect to the treatment. The positive effect of this association is due to the synergy between phosphorus depletion and increased renal excretion. A review of the literature by **Fathi. I and al [9]** had concluded that the indications for surgical excision include recurrent infection, ulceration and functional deficit, it can be beneficial in the quiescent stage of the disease where pseudotumor encapsulation occurs and interferes with the ion exchange process. **Döneray H al [10]** et al report the case of a 13-year-old patient, diagnosed with HFTC at the age of 9, the patient developed mobile calcified masses in both hips and the left elbow, which impaired joint mobility (. Based on previous radiological and CT studies, which showed intra- and periarticular radiopaque lesions related to pseudo-tumoral calcinosis, the patient was subsequently treated with carbonate hydrate (750 mg/die) and ibandronate sodium (150 mg once a month), which significantly reduced the size of the calcified nodules, which were removed surgically. After admission to the hospital, on oral examination, we noticed several dental abnormalities, such as enamel hypoplasia, maxillary and mandibular hypoplasia, and crossbite. Medical treatment by phosphorous depletion (dietary phosphorous deprivation and phosphate-binding chelating agents such as oral aluminum hydroxide) had shown variable success rates, the combination may give a significant synergistic effect. The dental anomalies observed in this patient are also described and they are often precocious, it is caused by calcification of the dental pulp which is responsible for dental fragility **[10].** The differential diagnosis is made with other pathologies that can cause tissue calcifications such as scleroderma, dermatomyositis, hyperparathyroidism, chronic renal failure, hypervitaminosis D and Burnett's syndrome [9, 10].

CONCLUSIONS

Aluminum hydroxide and acetazolamide combined with dietary calcium restriction seems to be an interesting therapeutic option for primary pseudo-tumoral calcinosis. Systemic studies will be needed to confirm these results.

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TABLES

Table 1: Laboratory findings

Plasma markers	**Results**	**Reference values**
Phosphorus mg/l	70	(25-45)
Calcium mg/l	96	(86-100)
25-hydroxy vitamin D	6.82	(30-70)
Albumin g/l	37	(32-45)
Parathormone ng/l	34	(10- 65)
Urea g/l	0.82	(0.25- 0.48)
Creatinine mg/ l	5.1	(7-12)
Sodium mmol/l	143	(135-145)
Potassium mmol/l	4.1	(3,5-4.5)
Bicarbonate mmol/l	23	(22-26)
FGF23 pg/ml	23.1 pg/ml	(23.2- 95.4)
Inflammatory markers	**Results**	**Reference values**
Sedimentation rate mm	32	(0-10)
Protein c-reactive mg/ l	61	(0-5)

Table 2: phosphocalcic test during treatment

	INITIAL ANALYSIS	**AFTER 1 MONTH OF TREATMENT**	**AFTER 8 MONTHS OF TREATMENT**	**REFERENCE VALUES**
phosphorus mg/l	70	61	59	(25-45)
Calcium mg/l	96	92	92	(86-100)
25-hydroxy vitamin D	6.82	10	7,15	(30-70)
Albumin g/l	37	33	35	(32-45)
Parathormone ng/l	34	41	39	(10- 65)