CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 23 (2016) 56–60

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

A 23-year-old patient with secondary tumoral calcinosis: Regression after subtotal parathyroidectomy
A case report

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ARTICLE INFO

Article history:
Received 21 March 2016
Accepted 7 April 2016
Available online 11 April 2016

Keywords:
Tumoral calcinosis
Chronic kidney disease
Parathyroidectomy
Case report
Teutschlaender disease

ABSTRACT

INTRODUCTION: Tumoral calcinosis (TC) is a rare disorder defined by hyperphosphatemia and ectopic calcifications in various locations. The most common form of TC is associated with disorders such as renal insufficiency, hyperparathyroidism, or hypervitaminosis D. The primary (hereditary) TC is caused by inactivating mutations in either the fibroblast growth factor 23 (*FGF23*), the GalNAc transferase 3 (*GALNT3*) or the KLOTHO (*KL*) gene.
PRESENTATION OF CASE: We report here a case of secondary TC in end-stage renal disease. The patient was on regular hemodialysis and presented with severe painful soft-tissue calcifications around her left hip and shoulder that had been increasing over the last two years. Initially, she was treated with dietary phosphate restriction and phosphate binders. Because of high phosphate blood levels, which were not yet managed with dialysis and medical therapy, a subtotal parathyroidectomy (sP) was performed. This approach demonstrated significant response. Three months after surgery a rapid regression of the tumors was observed.
DISSCUSION: Regardless of the etiology, the two types of TC do not differ in their radiologic or histopathologic presentations but need to be diagnosed correctly to initiate targeted and effective treatment. Considering the primary TC, primary treatment is early and complete surgical excision. In case of secondary TC surgical excision of the tumoral masses should be avoid because of extensive complications. These patients benefit from sP.
CONCLUSION: After initial conservative therapy chronic kidney disease patients with TC might benefit from sP to avoid prolonged suffering and potential mutilations.

1. Introduction

TC is a rare disorder with disturbance in the phosphate metabolism defined by hyperphosphatemia and ectopic calcification in various locations [1,2]. As originally described, TC is a primary or hereditary entity caused by autosomal recessive mutations in three genes involving phosphate metabolism: *FGF23*, *GALNT3* and *KL* [3]. Mutations in *FGF23* or *GALNT3* genes result either in inadequate intact FGF23 or limited secretion. Mutations in *KL* gene effect resistance to FGF23 activity at the fibroblast growth factor receptor/α-Klotho complex [4]. The limitation in FGF23 activity induces increased renal tubular reabsorption of phosphate and thus hyperphosphatemia. The result is typically calcification of the entire body [5,6].

Erroneously, TC or Teutschlaender disease [7–9] have been widely used in the literature to describe any massive collection of peri-articular calcifications. Though, most reported cases are in fact secondary TC due to chronic renal insufficiency, hyperparathyroidism, or hypervitaminosis D [10]. Regardless of the etiology, these two types of TC do not differ in their radiologic or histopathologic presentations [11], but need to be diagnosed correctly to initiate targeted and effective treatment.

Abbreviations: TC, tumoral calcinosis; sP, subtotal parathyroidectomy; FGF23, fibroblast growth factor 23; GALNT3, GalNAc transferase 3; KL, KLOTHO; THR, total hip replacement; ROM, range of motion; CRP, C reactive protein; WBC, white blood cells; PTH, parathyroid hormone; CT, computed tomography.

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http://dx.doi.org/10.1016/j.ijscr.2016.04.011

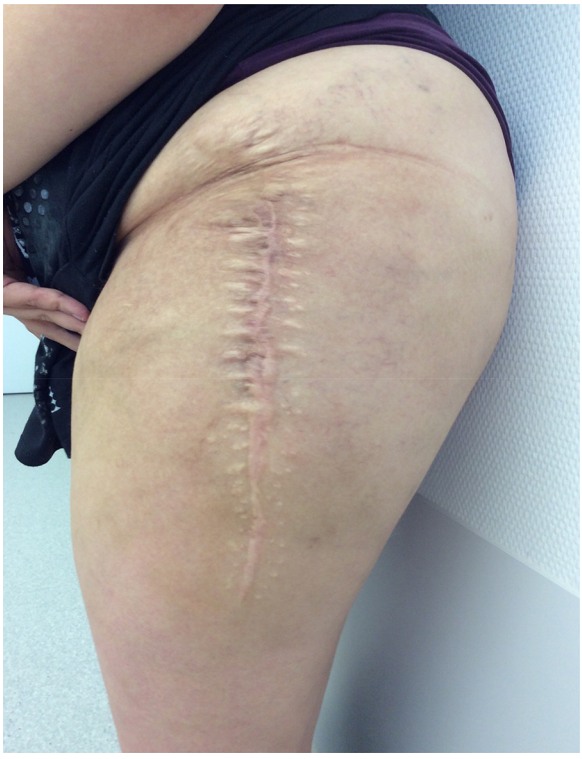

Fig. 1. Preoperative appearance of the swollen left hip joint.

2. Presentation of case

In 2011 a 19-year-old female with an acute renal insufficiency due to nephronophthisis presented herself with septic arthritis of the left hip because of a shaldon catheter-related bloodstream infection. After hip resection arthroplasty and antibiotic cement spacer implantation the patient received a total hip replacement (THR). After wound healing and 4 months of physical exercises, near normal range of motion (ROM) and good function were achieved. Thereafter, she was on hemodialysis three times per week because of end-stage renal disease. Three years later, the patient returned to our hospital with the complaint of severe pain in the left groin and lateral hip. Physical examination detected tenderness over the left greater trochanter and the surgical scar. The whole left leg was enormously swollen (Fig. 1). No symptoms of infection were found. Hip range of motion was normal. Blood tests revealed: hemoglobin 9.2 g/dl, creatinine 6.7 mg/dl, C reactive protein (CRP) 8.7 mg/dl, white blood cells (WBC) 7.9/nl, calcium 2.78 mmol/l, phosphate 6.3 mg/dl (2.5–5.0 mg/dl), calcium-phosphate serum product 6.24 $mmol^2/l^2$ (0–4.4 $mmol^2/l^2$), intact parathyroid hormone (PTH) 779 ng/l (15–65 ng/l), 25-hydroxyvitamin D3 57 ng/ml (30–70 ng/ml). Rheumatoid factor and antinuclear antibody were absent. X-rays of the left hip and proximal upper limb revealed pronounced peri-articular soft-tissue calcifications similar to a cauliflower. Computed tomography (CT) scans demonstrated amorphous and multilobulated calcified masses around the left hip join and in the region of the iliac muscle (Fig. 2a and b). Abdominal organs were normal. Bone scintigraphy with radiolabeled phosphate compounds (technetium—99 m methylene diphosphonate) was performed to detect further lesions and found increased uptake in the peri-articular soft-tissue of the left shoulder. The patient reported a fall on the left shoulder several years ago. Standard radiography of the left shoulder revealed tumoral masses similar to the ones described for the left hip joint (Fig. 3a). An incision biopsy of the tumor located at the left hip joint was performed. During surgery a white and yellow chalky substance (Fig. 4) appeared. Microbiology of the biopsy was sterile. Histopathologic evaluation of the excised mass showed numerous psammoma bodies with inflammatory and histiocytic reaction.

Due to increased PTH level a parathyroid sestamibi scan was initiated and revealed parathyroid hyperplasia of the caudal right parathyroid gland. Additionally, a conciliar examination was ordered. Ophthalmological examination revealed obvious conjunctival calcific deposits and retinal angioid streaks in both eyes.

Measurement of c-terminal fibroblast growth factor (FGF)-23 was elevated (1345 kRU/l) (26–110 kRU/l). Thereupon, the patient was screened for mutations in all exons of *FGF23*, *GALNT3* and *KL*. No mutations were found. A diagnosis of secondary TC was made and a non-operative approach was initially indicated. Her medical treatments were changed toward decreasing intestinal phosphate absorption and increasing phosphate excretion. Calcium- and phosphate-restricted diets were started. The patient was treated with Renagel® 1600 mg (Sevelamer hydrochlorid) and OsvaRen® 435/235 mg (Calcium diacetat x-Wasser, Magnesium carbonat) (each taken three times a day) but serum phosphate levels remained high. In the following, Mimpara® 60 mg (Cinacalcet hydrochlorid) (once a day) was prescribed and blood calcium levels in the high normal range were achieved.

The initially conducted therapy of dietary deprivation of phosphate and phosphate-binding medication was not able to prevent the progression of the calcifications. Therefore, a sP (removing 3 1/2 glands) was performed. Three months after surgery, the patient was free of complaints. In particular, she did not feel any pain in the left hip or shoulder and her left leg was only slightly swollen. X-ray of the left shoulder and left hip revealed reduced tumoral masses (Fig. 2c). Peri-articular soft-tissue calcifications of the left shoulder were barely visible (Fig. 3b). Although, the laboratory profile showed no changes with this development. Directly after sP PTH level fell to 135 ng/l (preoperative: 779 ng/l) but four days after surgery PTH concentration increased again to 533 ng/l. Though, there was no evidence for ectopic parathyroid glands in the neck or mediastinum. On order of a nephrologist we discontinued Mimpara® and OsvaRen® and started medical treatment of Fosrenol® 1000 mg (Lanthan(III) carbonat x-Wasser) (three times a day).

3. Discussion

Calcified masses near large joins were early on recognized and described by Duret in 1899 [12]. Teutschländer [9] introduced the term progressive lipocalcinogranulomatosis in 1935, while Alberto in 1943 [13] proposed the current name tumoral calcinosis.

TC is an uncommon lesion that is either primary (hereditary) or secondary to other diseases. The primary TC is caused by autosomal recessive mutations in three genes involving phosphate metabolism, namely *FGF23*, *GALNT3* and *KL* [3]. Secondary TC is associated with renal failure and prolonged hemodialysis. Although, other conditions such as hyperparathyroidism, sarcoidosis, hypervitaminosis D and scleroderma have been reported to be accompanied by TC [14]. Regardless of etiology, patients typically present with progressively increasing tumor-like masses in peri-articular locations. Patients often complain about localized swelling and reduced mobility around the involved joints. Furthermore, calcifying organ manifestation is typically found in eyes [6], as was seen as well in our patient.

In renal secondary hyperparathyroidism, impaired renal phosphate elimination due to the reduced clearance function of the kidneys is the reason for an increased phosphate concentration in the serum. The inhibited renal synthesis of 1,25-dihydroxyvitamin D leads to a reduced enteral calcium absorption. The resulting hypocalcaemia leads to a stimulation of the parathyroid glands,