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

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A B S T R A C T

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 GaINAc 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.

DISSCUSSION: 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.

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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 etiology 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.
Microbiology of the biopsy was sterile. Histopathologic evaluation of the excised mass showed numerous psammonia 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 g) 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 joints 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,
Fig. 2. Standard x-ray (a) and CT scan (b) of the left hip and proximal upper limb before and after subtotal parathyroidectomy (c).

Fig. 3. Standard x-ray of the left shoulder before (a) and after subtotal parathyroidectomy (b).
increasing PTH-level. PTH again, causes an osseous calcium mobilization and thus leads to osteopenia. Additionally, the persisting low vitamin D level leads to a skeletal resistance to PTH, which means that hypocalcaemia cannot be compensated for, resulting in increased PTH levels [15]. In renal failure patients an elevated calcium-phosphate serum product explains the occurrence of soft-tissue calcifications. A calcium-phosphate serum product >5.8 mmol/l² may lead to extrasosseous calcifications [16].

In the presented case, a young patient with secondary TC due to secondary hyperparathyroidism as a result of end-stage renal disease was treated. After sP a regression of the TC was observed. Three months after surgery, the tumor around the left hip joint showed a significant decrease in size and radiographic appearance, whereas a rapid complete regression of the tumoral masses around the left shoulder was observed. We thus complement the preceded literature.

In 1994, Benkert et al. [16] observed a regression up to complete dissolution of TC after sP. Three years later, in 1997, a female patient with end-stage renal failure and tumoral calcifications in the clavicular region was treated with total parathyroidectomy. In this case TC disappeared after surgery [17]. Further, Cohen and Parikh performed a partial parathyroidectomy and achieved regression of tumoral calcifications [18]. Moelckel et al. [15] treated two renal failure patients with TC as a result of secondary hyperparathyroidism. After initial conservative therapy they performed a sP in one of the cases, after which a complete regression was achieved. The second patient obtained surgical excision of the foci, whereby local recurrences were observed.

If TC is assumed, a biochemical profile (including serum calcium and phosphate levels, serum PTH levels and 1,25-hydroxyvitamin D levels) and renal function should be examined. Detailed family, drug and past history should also be obtained. Without signs for a primary disease a screening for mutations in FGFR3, GALNT3 and KIF gene should be considered. In case of a secondary TC an initial conservative approach is indicated. Medical treatment includes the use of phosphate binders, an optimization of dialysis and a phosphate restricted diet. If this fails or the therapeutic outcome is unsatisfactory, sP should be considered. In these patients surgical excision or biopsies of the tumoral masses should be kept as a last resort because of extensive complications (delayed wound healing, secondary infections, fistula formation). Considering the primary TC, primary treatment is early and complete surgical excision [19]. Partial excision of large lesions may lead to pain relief but incomplete excision involves the risk of high recurrence rates or even faster growth [1,15,20].

4. Conclusion

The two types of TC need to be diagnosed correctly to initiate the right treatment. Especially, in chronic kidney disease patients with a secondary TC early sP may be an approach to treatment to avoid prolonged suffering and potential mutilations.

Conflicts of interest

None.

Funding

Nothing to declare.

Ethical approval

N/A.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors’ contributions

Katharina E. Niemann helped with data collection, interpretation and writing the paper. Feride Kröpil contributed to study concept/design, data analysis and interpretation. Martin F. Hoffmann, Marlon O. Coulibaly and Thomas A. Schildhauer helped with interpretation and contributed to review of the final manuscript and final submission of the paper.

Guarantor

Katharina E. Niemann and Thomas A. Schildhauer.

References


Fig. 4. Intraoperative result: white and yellow chalky substance.

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