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Familial tumoral calcinosis in three patients in the same family

Aynı aileden üç olguda ailesel tümöral kalsinozis

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Tümöral kalsinozis esas olarak periartiküler bölgelerde, iri kalsifiye yumuşak doku kitleleri şeklinde görülen nadir bir hastalıktır Bu yazıda, ailesel tümöral kalsinozisli bir baba ve iki çocuğu sunuldu. Kırk beş yaşındaki baba, 10 yaşından başlayarak çeşitli aralıklarla sağ dirsek posteriorunda, her iki kalçada, sol gluteal bölgede, perineal bölgede ortaya çıkan kitleler nedeniyle çok sayıda ameliyat geçirmişti. On altı yaşındaki erkek çocukta ise, ilk kez 10 yaşındayken olmak üzere, dirsek posteriorunda ortaya çıkan lezyon çıkarılmasından iki yıl sonra tekrarlamış ve yeniden ameliyat edilmişti. Daha sonra hasta sağ dirseğinde, sağ ayak dorsalinde ortaya çıkan lezyonlar için ameliyat edildi. On iki yaşındaki kız çocukta lezyon aynı yaşta, sağ ayak dorsalinde ortaya çıktı ve cerrahi tedaviyle çıkarıldı. Üç olguda da bütün ameliyatların patoloji sonuçları tümöral kalsinozis olarak bildirildi. Üç hastada da normokalsemi, hiperfosfatemi ve vitamin D hipervitaminozu vardı.

Anahtar sözcükler: Kemik neoplazileri/patoloji; kalsinozis/genetik/patoloji.

Tumoral calcinosis is a rare condition characterized by large calcific soft tissue deposits occurring predominantly in a periarticular location. Familial tumoral calcinosis was detected in three members of a family, namely, the father and two offsprings. The father underwent many operations since age 10 for occurrences or recurrences of mass lesions in the right posterior elbow, both hips, left gluteal region, and perineal region. His 16-year-old son underwent his first operation at the age of 10 for a lesion in the posterior elbow, which recurred at the same site and required another operation two years later. He underwent subsequent surgeries for lesions that appeared in the right elbow and right dorsal foot. Finally, the 12-year-old daughter was treated with surgery for a lesion in the right dorsal foot. In all the patients, pathologic diagnoses of all surgical specimens were reported as tumoral calcinosis. All had normocalcemia, hyperphosphatemia, and D hypervitaminosis.

Key words: Bone neoplasms/pathology; calcinosis/genetics/pathology.

The term tumoral calcinosis was first used by Inclan in 1943 to describe slow growing, progressive masses found usually adjacent to large joints such as hips, shoulders and elbows. The first study conducted in Turkey by Ugur Hacihanefioglu was published in JBJS in 1978.[1] The disease is rare; there is no consensus on the etiology and pathogenesis thereof. It generally occurs within the second or third decades; hardly ever found in early childhood phases. Infantile cases reported in literature are 16 in total.[2] While well-identified cases have been published pronouncing variety of names such as lipogranulomatosis, lipocalcinogranulomatosis, bursitis, tuberculosis, tumoral lipocalcinosis, calcified bursa, calcified collagenosis, metastatic calcification; the most common term has been tumoral calcinosis.[3] The cases comprise three clinically different forms. Tumoral calcinosis in the first group develops as a complication of renal dialysis. The second group comprising about one third of the cases is familial; found more frequently in black populations and in males. The third group on the other hand is sporadic; with no identified calcium or phosphor anomaly. In the clinical evaluation, hard and pain-

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less masses related to joint movements are found in the vicinity of joints. The lesion tends to recur subsequent to inadequate resection. In this study, a father and two siblings diagnosed with familial tumoral calcinosis which occupies a significant place in the differential diagnosis of soft tissue masses. According to the information obtained from the family, it follows that a brother of the father has suffered from the same condition. Having been operated several times due to masses occurring in various parts of his body, the patient died at the age of 46. This family member was not included in our study as it has been not possible to access his records.

Presentation of the cases

Case 1– The father is 45 years old, with alive and healthy parents. One of the four brothers suffers from tumoral calcinosis while one of the sisters is diagnosed with chronic renal failure. Being first operated at the age of 10 due to a mass developing at the right elbow posterior, the patient had undergone a total of five operations between the ages of 10 and 15 owing to masses developing and recurring on both hips. The disease was suppressed during the next 20 years with no signs of complications; however, with the mass developing at the left gluteal region being operated in 1999, the histological analysis material complied with tumoral calcinosis.

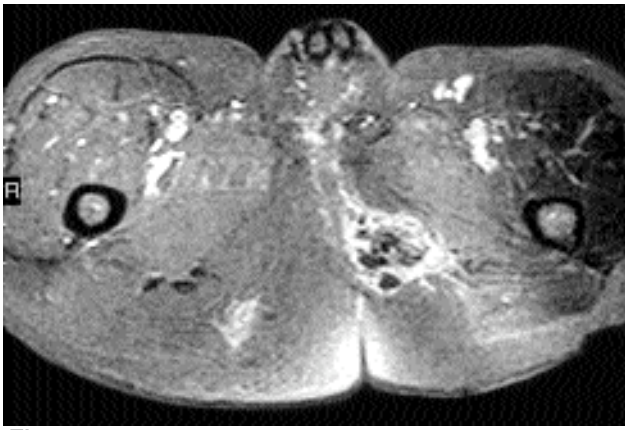

Figure 1. MR image of the lesion at the perineal region in the father

Through the recurrence of this lesion, a further mass with a dimension of 20x10x8cm was developed in 2003 for which extensive resection was employed. Being mutually assessed with the endocrinology clinic of the department of internal medicine, the patient was prescribed with a low phosphorus diet for his hyperphosphatemia, normocalcemia and high level of Vitamin D while sevelamer hydrochloride (Renagel Tablet) was administered in order to reduce phosphor absorption and to avoid accumulation in the tissues. Using this medication for two years, the patient then was unable to obtain it and a new lesion with a dimension of 4x4x3 cm developed in the perineal area during the last 4 months (Figure 1) and resection was applied.

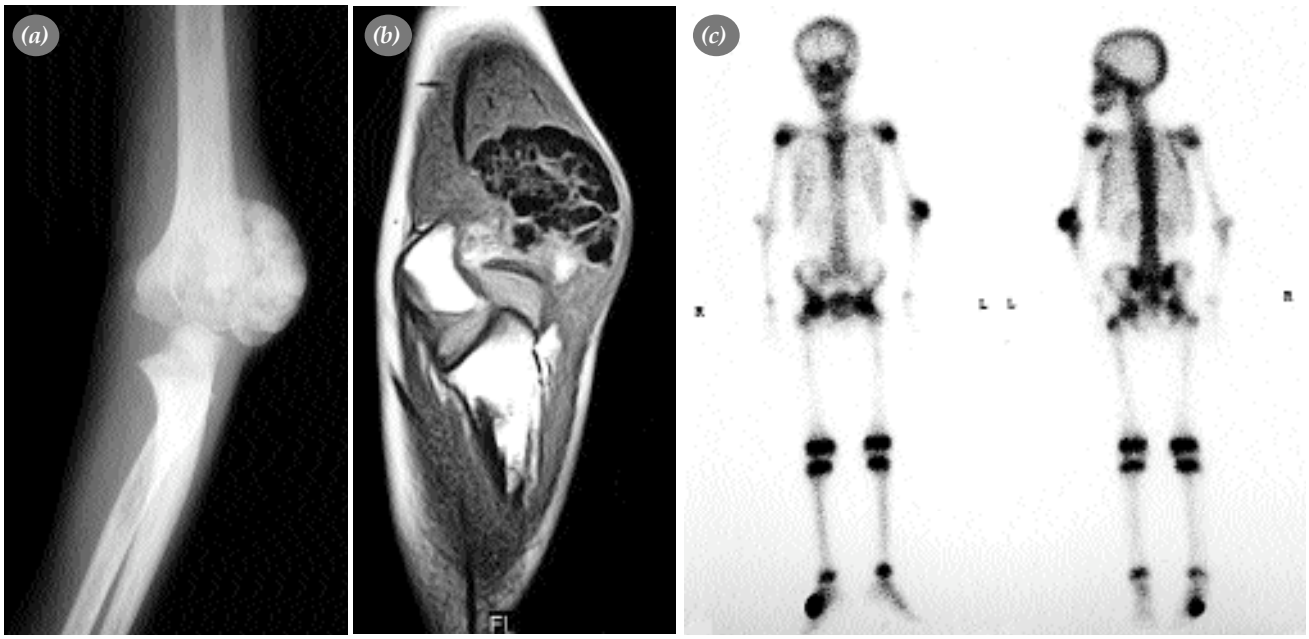

Figure 2. Mass at the elbow accompanied by the soft tissue calcification in the son a)radiographic **(b)** magnetic resonance **(c)** whole body bone scintigraphy images.There is increased uptake at the left elbow.

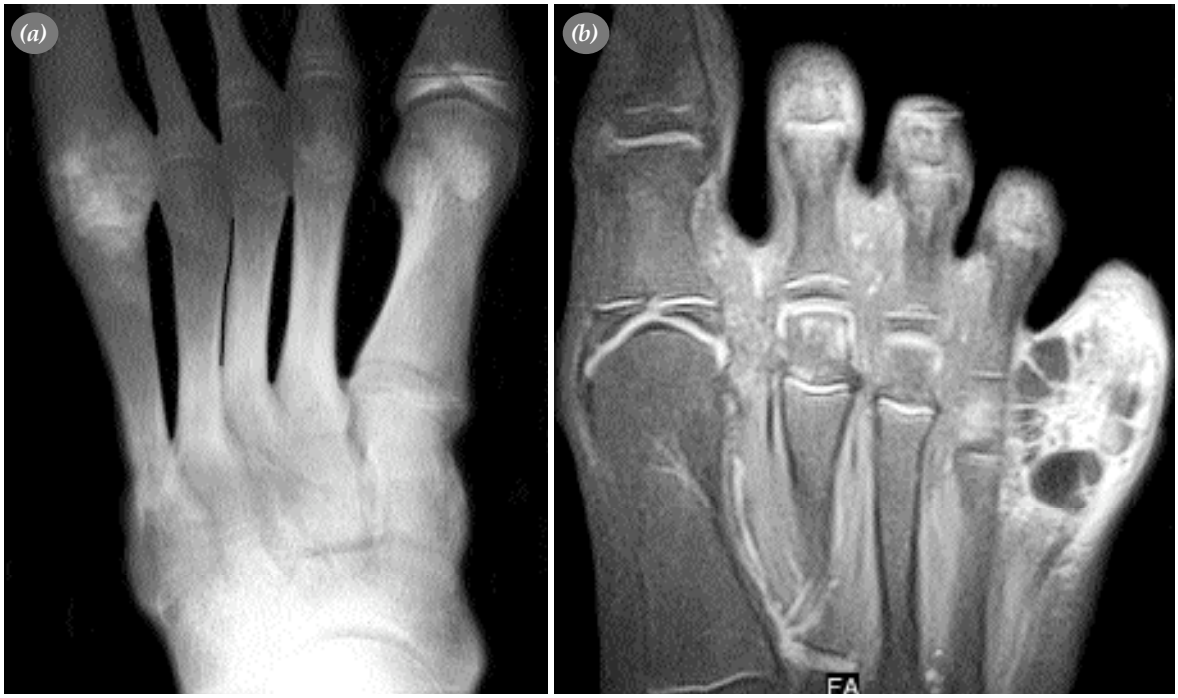

Figure 3. The lesion at the foot at the daughter **(a)** radiographic **(b)** magnetic resonance images.

Case 2– Son, 16 years old. The first lesion occurred in the left elbow posterior at the age of 10. In radiological examinations, a multi-lobular calcified mass was detected within the soft tissue at the elbow posterior. No pathology was observed in the joint or in the adjoining bones (Figure 2). In T1 and T2 weighed MRI images, the dimensions of this lesion presenting hypo-intense characteristics due to calcification and wherein patches of inflammatory aspects were observed was 5x5x3 cm (Figure 3). An osteoblastic activity in the left elbow soft tissue was detected in the whole body skeletal scintigraphy (Figure 4). The patient was initially operated in 1998 and the pathology was reported as tumoral calcinosis. The lesion reaching the dimensions of 4x4x3 cm by recurring two years later was removed with a second operation in 2000. The patient once again checked in our clinic in 2001, this time with a 5x4x2 cm. mass in the right elbow. This lesion was also removed. While there has been no further recurrence of the lesions in any of the elbows, the patient was operated in our clinic in 2002 due to a 4x2x2 cm. mass on the 4th and 5th metatarsal bones of the dorsal surface of the right foot. With the further recurrence of this lesion, the patient was operated once again in 2004. All pathology results were reported as tumoral calcinosis.

Case 3– Daughter, 12 years old. The first lesion occurred at this age in the 4th - 5th metatarsal space of the dorsal surface of the right foot. With the patient consulting the clinic with a 4x2x2 cm lesion, a calcified and multi-lobular mass localized in the soft tissue at this region was detected in the x-ray examinations (Figure 5). The skin was involved and one fistula was present. Through MRI examinations, the case was assessed as a mass presenting hypo-intensive calcification in all sequences, accompanied by inflammatory symptoms, presenting heterogeneous contrasting on administration of IV contrast material, closely related to the 5th metatarsal bone while not generating any destruction (Figure 6). Similar to the other patients, this patient was also diagnosed with normocalcemia, hyperphosphatemia and Vitamin D hypervitaminosis. The pathology result of the lesion was reported as tumoral calcinosis.

The older daughter of the family is 14 years old with no symptom of a disease at present.

Discussion

Tumoral calcinosis is a highly controversial entity. Masses lacking a direct relation with the adjacent joint might be observed generally in the periarticular localities and particularly in regions under compres-

sion. The most common locality is the hip, being followed respectively by the elbow, shoulder and scapula.[3] Spinal involvement is highly uncommon.[4] The most common locality in our cases has been the elbow. Either a white grained substance with the color and consistency of milk or cream, or calcified tissue is present within these masses. The condition might be present as solitary or multiple lesions. The skin over the mass is generally intact; only getting ulcerated or infected occasionally. There are three different forms of tumoral calcinosis.[5] About one third of the cases emerge as a component of a genetic metabolic disease. Heritage might be passed on as autosomal recessive or more probably as autosomal dominant. Hyperphosphatemia and elevated levels of serum 1.25-dihydroxyvitamin D are observed in biochemical examinations of the patients.[5] Serum calcium and parathormone levels are normal. The major regulator of serum 1,25-dihydroxyvitamin D in healthy individuals is PTH and the hyperparathyroidism serum level increases Furthermore, hypophosphatemia stimulates the generation of 1,25-dihydroxivitamin D. The elevation of phosphor level in tumoral calcinosis is due to increased renal tubular re-absorption. In terms of biochemistry, it has been asserted that a defect occurring in the regulation of the 25-hydroxy-1-_-hydrolase enzyme which plays a part in Vitamin D metabolism leads to this condition.[6] Our patients are included in this group in view of the fact that the disease is familial, due to the biochemical aspects thereof and the lack of any accompanying disease. The second form of the disorder is tumoral calcinosis accompanied by other diseases. It is most frequently observed in cases with renal failure which are under dialysis treatment wherein Vitamin D treatment is also being administered. Furthermore, this condition might be present in some ligament diseases, in Engelmann disease (progressive diaphyseal dysplasia) and in patients with Down syndrome. The disease is sporadic in the third group, occurring at different ages, no hyperphosphatemia being observed in these patients. The disorder might be assessed as a neoplasic case stemming from the bone or the soft tissue. Consequently, differential diagnosing should be conducted through clinical, laboratory and radiological studies with regards to diseases which lead to calcification in the soft tissue, such as hyperparathyroidism, hypervitaminosis D, chronic renal failure, milk-alkali syndrome, calcium pyrophosphate dihydrate crystal deposition disease and synovial chondromatosis. Treatment of tumoral calcinosis is complex and contentious. Spontaneous regression of the mass has not been reported in literature. Surgical excision in general is the preferred method of treatment. While the lesions are enveloped in pseudo-capsules, extensions into soft tissues are seen in some cases, leading to difficulties with regards to complete excision.[7] Furthermore, tumoral calcinosis may occasionally act as a rapidly developing local aggressive neoplasm and recurring lesions may be larger and more destructive. Various drug regimens and radiotherapy have been used in order to prevent recurrences. Successful results have been reported with phosphate binding antacids along with low phosphate and low calcium diets in some patients.[8] Treating a patient in this manner for a period of three months, Gregosiewicz observed that the dimensions of the mass diminished significantly and removed the remaining mass surgical intervention.[9] In another study however, the same treatment was reported to be inadequate and possibly disadvantageous in children.[10] Subsequent to treating a case of tumoral calcinosis accompanied by chronic renal failure with vinpocetine, Seyahi et al. reported a regression in the mass following a treatment period of five months.[11] The father in our group used sevelamer hydrochloride for two years and had a diet low in phosphate and calcium. Not progressing during the said period, the disease recurred in the period when he discontinued the medication.

The pathogenesis of the calcification process in tumoral calcinosis is still very enigmatic. While some justified this condition as a calcific dystrophy due to trauma; this assumption fails to explain factors such as the lesion's being vascular, increasing in dimensions and the presence of calcified fluid in it.[5] Some authors on the other hand, asserted that the condition is triggered by a traumatic collagenosis; however, collagenosis seems to be a minor incident.[12] The mineral deposits in tumoral calcinosis are essentially consists of calcium phosphate organized in the form of hydroxyapatite. Hence, while there were some to claim that tumoral calcinosis is a hydroxyapatite disease, this theory also fails to account for the morphological aspects and periarticular placement of the disease.[7] Reporting a case of tumoral calcinosis in cervical vertebrae, Kokubun stated that the correlation between calcium pyrophosphate dihydrate (CPPD) crystal deposition disease and tumoral calcinosis

should be discussed.[1 3] Subsequent to histopathological studies, Slavin assessed tumoral calcinosis as an exaggerated reparative reaction against hemorrhages incurred by minor injuries and evaluated the disease in three phases.[5] Foamy histiocytoses generated during and after hemorrhage transform, with the addition of collagenolysis, into cystic cavities with their peripheries surrounded by giant cells and histiocytoses. These lesions seem like adventitial bursa in this form. With the periarticular localization of tumoral calcinosis, the forces caused by movement and friction are factoes triggering this transformation. Probably hyperphosphatemia as well as a case of calcification led by endogenous hypervitaminosis develop simultaneously, and with the cavities in the lesion losing their synovia-like lining finally and being encapsulated by the fibrous tissue, ossification occurs.

Recurrence is common in patients with genetic anomalies or those undergoing renal dialysis, as the stimulus leading to calcium precipitation is not eliminated. On the other hand, recurrence in sporadic cases is comparatively rare.[2] When assessed in terms of phases, surgical treatment during the first two stages of the disease might be more problematic as the encapsulation is incomplete and the lesion is progressive. On the other hand, reducing the level of serum phosphor diminishes the calcified component of the lesion by affecting the formation of hydroxyapatite. It might be rather uncomplicated to remove the lesion during the third phase when the mass is capsulated and in a relatively inactive stage. Furthermore, as movement sets off a stimulus in terms of neobursa formation leading to a hemorrhage stemming from the impact of the moving calcified masses upon small veins, all these factors inducing the formation of a new lesion, it is important to keep the operated section at rest. The lesion is sometimes firmly attached to fascia, muscles and tendons, requiring that some significant periarticular structures to be sacrificed during the excision of the lesions.[14]

Familial tumoral calcinosis is a hereditary metabolic disease and this aspect should not be ignored during the treatment thereof. The resection of the developing masses might frequently be inadequate and recurrence might be observed in case a treatment focused on the metabolism is not employed. In our cases, this principle was intended to be employed for the father, whereas drug treatment for the children was determined to be employed in the adulthood as it was considered to be disadvantageous. Once being witnessed, tumoral calcinosis is a condition not to be forgotten again and it must definitely be taken into account in terms of differential diagnosis when a mass progressing in parallel with intensive calcification.

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