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Normophosphatemic type tumoral calcinosis associated with chronic recurrent multifocal osteomyelitis: a case report

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Chronic recurrent multifocal osteomyelitis (CRMO) and tumoral calcinosis are two distinct musculoskeletal diseases with unclear etiopathogenesis. Previously, two CRMO cases with associated tumoral calcinosis were reported. We report a patient who developed tumoral calcinosis after the surgical treatment of CRMO. To our knowledge it is the third patient in whom tumoral calcinosis developed sporadically during follow-up for CRMO.

Key words: Chronic recurrent multifocal osteomyelitis; tumoral calcinosis.

Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory disease mostly involving the long bones. Its course includes exacerbations and convalescences in which no infectious pathogen could be determined.[1,2] Tumoral calcinosis is an extraarticular calcification with unclear etiopathogenesis. They are adjacent to, but not in direct relation with major joints.[3] In the literature, two cases of hyperphosphatemic type tumoral calcinosis after CRMO have been reported[4,5] (Table 1). To our knowledge the presented case is the third patient, in whom tumoral calcinosis occurred after CRMO. The current case differs from previous ones due to the absence of familial inheritance and hyperphosphatemia, which are listed among the etiologic factors for tumoral calcinosis.

Case report

A 9-year-old girl admitted with a one week left forearm pain. The pain was increasing at night. Clinical examination revealed local warmth and sensitivity with palpation in her left forearm. Her clinical history revealed that previously she had had similar complaints in both legs and the right forearm. She had been diagnosed with osteomyelitis and operated on 4 times in the last 2 years at different centers. The patient had also had a painful mass in her right elbow which was surgically removed 6 months ago. Her pathology reports of the two previous tibia operations suggested osteomyelitis. The pathological examination of the right elbow mass revealed a foreign body type granulation with multinuclear giant cell granulomas with many calcification fields.

The radiographs of the left forearm revealed sclerosis and new bone formation at the ulna diaphysis suggesting osteomyelitis (Fig. 1). Due to previous surgery, the patient had old incision scars on both lower extremities and there was a cavitary lesion on the direct radiographs of the right tibia (Figs. 2, 3a and b). Magnetic resonance imaging which was done for the differential diagnosis supported osteomyelitis (Fig. 4). The patient was consulted with other depart-

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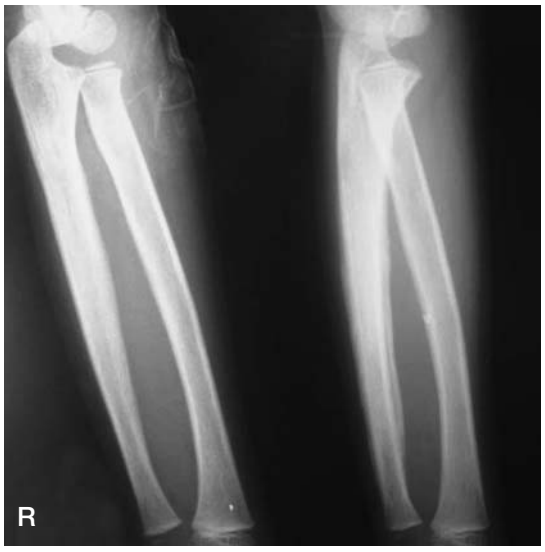

Fig. 1. Subperiosteal new bone formation and sclerosis of the left ulna and CRMO sequel in the right ulna.

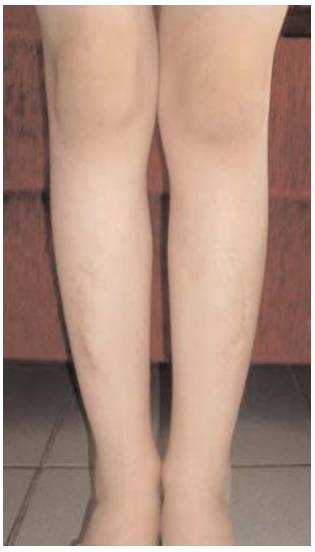

Fig. 2. Clinical photograph of the lower extremities. [Color figure can be viewed in the online issue, which is available at www.aott. org.tr]

ments to determine the primary hematogenous origin of the infection. In her blood, the white blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values were normal. Her urinary and throat cultures were sterile. Following clinical, radiological, and laboratory evaluations, the patient was hospitalized with diagnosis of chronic recurrent multifocal osteomyelitis. During her hospitalization, she did not have a high systemic fever. None of her first degree living relatives showed signs of CRMO. The patient was treated with non-steroidal anti-inflammatory drugs and was discharged on the 3rd day after her complaints had resolved. Following discharge, her drug therapy was extended to 10 days.

The patient reapplied to our clinic, 5 months after her first admittance with a recurring painful mass in her right elbow. Physical examination revealed that the mass was hyperemic, with partly ulcerous skin weeping a whitish discharge (Figs. 5a and b). Her elbow was extremely sensitive with palpation and movement. On elbow radiographs, there was a calcified mass at the posterior area of the joint (Figs. 6a and b). Kidney function tests, ESR, CRP, white blood cell count, serum parathormone and 1.25-

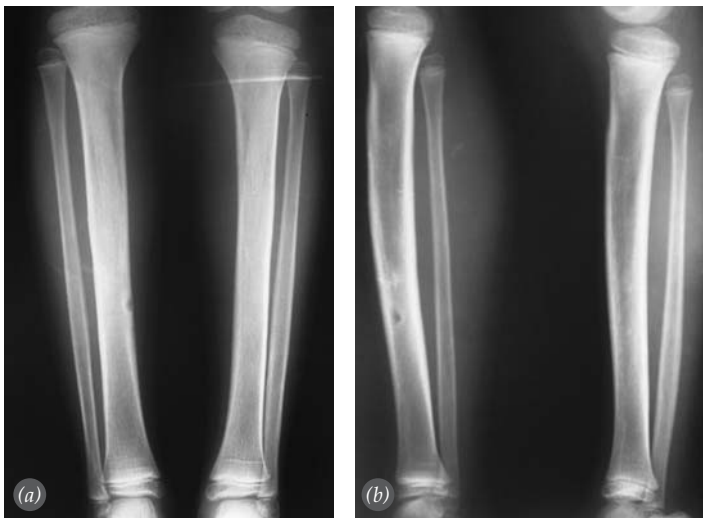

Fig. 3. Anteroposterior **(a)** and lateral **(b)** radiographs of both tibias after surgery. Note the curettage cavity in the right tibia.

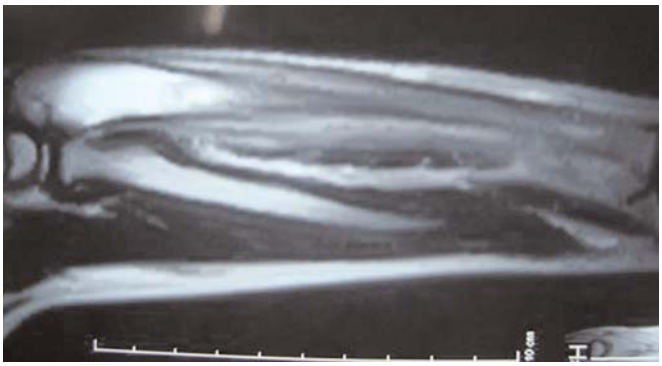

Fig. 4. MRI view of the bone marrow showing edema and cortical irregularities. [Color figure can be viewed in the online issue, which is available at www. aott. org.tr]

dihydroxyvitamin D levels, and especially blood calcium and phosphorus levels were within normal limits. No other mass lesion was revealed in any of the major joint and vertebral radiographs.

The probable diagnosis of the mass was tumoral calcinosis. A vertical incision was made on the mass, and the ulcerous parts and the skin with fistula were excised. The lesion was not encapsulated and the invasion of the surrounding tissue did not allow its en bloc removal. After the complete removal of the mass the incision was anatomically closed. The new pathology report was similar to the previous one: there were amorphous calcification foci at the center and surrounding multinuclear histiocytes in places, suggesting chronic inflammatory mononuclear cell infiltration (Fig. 7). At her 2nd week follow-up, her pain had completely resolved and her elbow range of motion was full. Last follow-up at the end of the first year, there were no clinical or radiological findings of CRMO or tumoral calcinosis.

Table 1. Clinical aspects and treatment of patients with tumoral calcinosis associated with chronic recurrent multifocal osteomyelitis.

Author	Year	Age	Ethnic origin	Type of tumoral calcinosis	Joints involved	Main symptoms	Treatment
Majeed SA[4]	1994	13	Jordanian	Hyperphosphatemic	Elbow	Limitation of motion	Surgical excision
Maus U[5]	2007	11	Turkish	Hyperphosphatemic	Hip and ankle	Limitation of motion	Surgical excision
Yüksel HY et al.	2010	9	Turkish	Normophosphatemic	Elbow	Pain and limitation of motion	Surgical excision

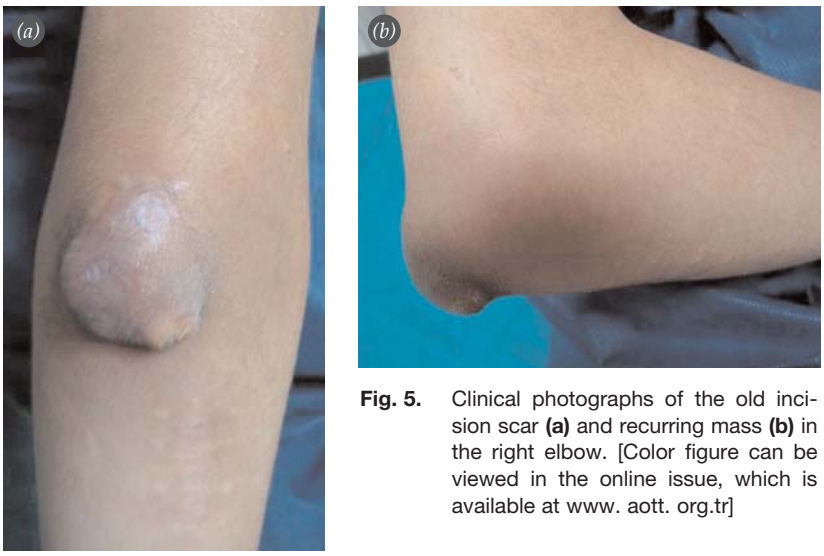

Fig. 5. Clinical photographs of the old incision scar **(a)** and recurring mass **(b)** in the right elbow. [Color figure can be viewed in the online issue, which is available at www. aott. org.tr]

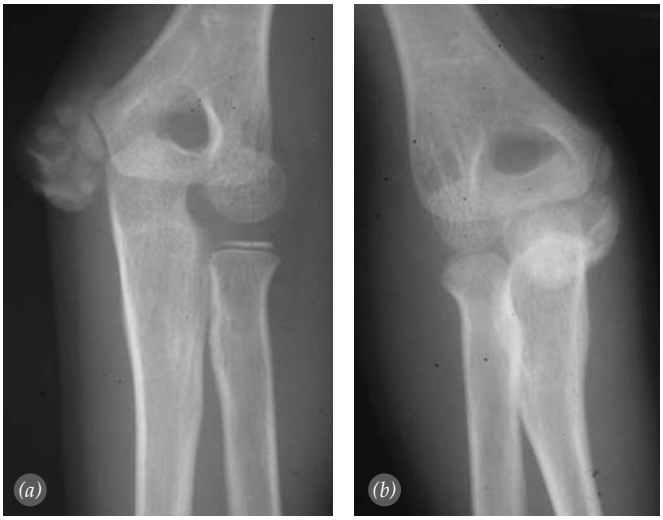

Fig. 6. A view of multilobular calcification islets of the tumoral calcinosis mass on oblique **(a)** and antero-posterior **(b)** roentgenograms of the right elbow.

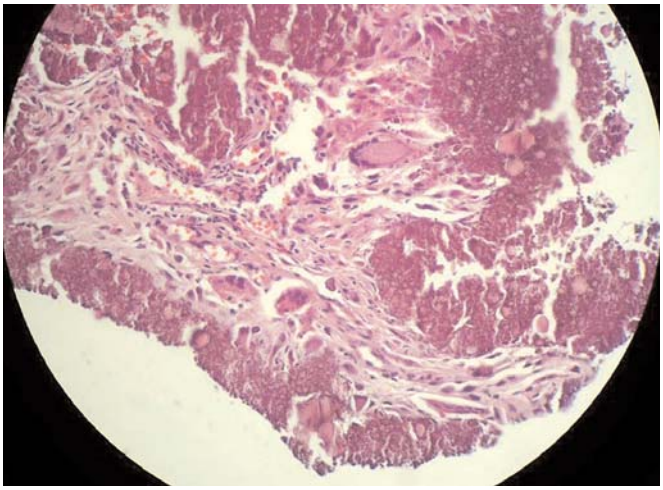

Fig. 7. A histopathological view of the resection material (H-E X400). [Color figure can be viewed in the online issue, which is available at www. aott. org.tr]

Discussion

CRMO is a rare disease mimicking osteomyelitis clinically and radiologically, thus unnecessary surgical treatments are sometimes performed. Its most definitive feature is its recurring nature and its appearance at more than one location. Clinically, it has an insidious progression. The clinical picture does not include high fever and fatigue as in acute and subacute osteomyelitis. The bone involved shows signs of local inflammation.[1,6] Radiologically, it is almost impossible to differentiate it from osteomyelitis. On radiographs, there are lytic and sclerotic lesions and subperiosteal new bone formations.[7] In contrast to osteomyelitis, laboratory examination show that white blood cell count, ESR, CRP levels are either slightly increased or within normal limits. In general, no causative aerobic or anaerobic bacteria, mycobacteria, fungus, or virus can be determined in blood and tissue cultures.[6] Hematogenous osteomyelitis, leukemia, neuroblastoma, eosinophylic granuloma, osteoblastoma, osteoid osteoma, and other neoplasies should be considered in differential diagnosis.[6-8] Signs of acute and chronic inflammation are observed histopathologically and this allows differentiation from neoplasies in the biopsies taken. However, one cannot determine a definitive diagnosis solely with pathology as the diagnosis hematogenous ostemyelitis can not be excluded.[9]

CRMO has been reported to be associated with various chronic inflammatory diseases, including palmoplantar pustulosis, psoriasis, inflammatory bowel disease, and arthritis.[2,10] Furthermore, it has

been evaluated as a component of SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) or Sweet (acute febrile neutrophylic dermatosis) syndromes.[2,11] The presence of chronic inflammation suggests the role of autoimmunity in etiopathogenesis.[12]

CRMO progresses with relapses and recurrences. The mean duration of activity is reported as 2-5 years.[2,11,13] The disease has been thought to be a self-limiting process without sequelae, but further studies performed on a large number of patients revealed that the duration of disease can be extended and it can lead to sequelae in the long term.[2] Sequelae like kyphosis, early epiphyseal growth arrest, and angulations of the long bones have been reported in patients with vertebral involvement.[2,11] The possibility of sequela development or chronic pain is reported in the range of 7-20%.[2,11,13]

Various methods have been proposed for treating CRMO. In contrast to osteomyelitis, antibiotics and operative treatment are ineffective in CRMO. Non-steroidal anti-inflammatory drugs are the first choice in the treatment. Treatments like interferon gamma, TNF-alpha blockers, and drugs of the biphosphonate group have been used in more persistent cases and successful results have been reported. However, these should be used only in selected patients because of their serious adverse effects.[14-16]

Tumoral calcinosis is a disease with calcified mass development at the periarticular soft tissues. Clinically, it generally manifests itself with a slowly growing and painless mass.[3] Our patient had a rapidly growing and very painful mass, with extreme sensitivity on palpation. The etiology of tumoral calcinosis is unclear, but it has 3 distinct types.[3,17] In the normophosphatemic type, blood calcium and phosphor levels are normal and this form is referred to as the sporadic type.[17] In the hyperphosphatemic type serum phosphorous levels are high while calcium levels are normal. It has been reported that the disease has familial predisposition and a defect in the regulation of the 25-hydroxy-1-alpha-hydrolase enzyme role in vitamin D metabolism was suggested as a cause.[18] Another form of the disease is secondary tumoral calcinosis. In this type, the secondary hyperparathyroidism observed in patients under hemodialysis for chronic renal failure leads to calcifications.[19]

Radiography reveals multilobular calcifications of different sizes around the joint. The histopathology reveals multinuclear macrophages, osteoclastic giant cells, fibroblasts, and amorphous or granular calcified material surrounded by chronic inflammatory elements.[3,20,21] Macroscopically, a white, milk-like, chalky discharge can be observed on the mass, along with infected ulcerations.[3] The radiological and clinical view was similar in the present case.

Although medications that decrease the absorption of phosphorus have been reported as an alternative treatment,[22] the generally accepted treatment method is surgical excision of the mass. Apart from sporadic cases, recurrences are observed in patients with associated biochemical abnormality. However, as in our case, if the mass lesion is not encapsulated and cannot be completely excised, recurrences may be seen following the first surgical excision.[3,23,24]

In the literature, two cases have been reported with both CRMO and tumoral calcinosis[4,5] (Table 1). The first patient was a Jordanian girl under follow-up because of CRMO.[4] In this patient, family history regarding CRMO and the painless mass of hyperphosphatemic type tumoral calcinosis differ from the present patient.[4] Another case was reported in 2007 in Germany, regarding a Turkish girl.[5] This patient also had hyperphosphatemic type tumoral calcinosis, similar to the Jordanian case.

The reason for CRMO and hyperphosphatemic type tumoral calcinosis could be autoinflammation with familial inheritance, manifesting itself with genetic problems. Autoinflammation can lead hyperphosphatemia together with the defect in vitamin D metabolism, while causing recurrent chronic inflammation in the long bones. Our patient had no family history and developed a sporadic type of tumoral calcinosis without any laboratory findings. Thus the etiology of the calcification remained obscure.

CRMO should be kept in mind in the differential diagnosis of osteomyelitis to avoid unnecessary surgery and antibiotherapy. It can be seen together with chronic diseases associated with chronic inflammation. Tumoral calcinosis is one of these co-existing diseases and although the association of normophosphatemic type tumoral calcinosis has never been reported in the literature, it can be seen together with CRMO.

Conflicts of Interest: No conflicts declared.

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