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CASE REPORT

Multicentric carpotarsal osteolysis syndrome: long-term follow-up of three patients

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Abstract
Multicentric carpotarsal osteolysis (MCTO) is a rare skeletal disorder characterized by progressive carpal and tarsal destruction. The upper and lower limbs may be involved, leading to deformities and joint limitation. These anatomic features may be associated with progressive renal failure. The radiographs obtained during childhood showed a carpal and tarsal osteolysis and an asymmetrical involvement. Here, we report on the long-term clinical and radiological findings of three patients with skeletal manifestations of MCTO.

Keywords Multicentric carpotarsal osteolysis

Introduction

Multicentric carpotarsal osteolysis (MCTO), first described in 1964 by Shurtleff, is a rare genetic disease with autosomal dominant inheritance [1, 2]. Heterozygous mutations in the *MAFB* gene, encoding the transcription factor MafB (V-maf musculoaponeurotic fibrosarcoma oncogene homolog B), are responsible for MCTO [3]. The RANKL-dependent differentiation of monocytes into osteoclasts is negatively regulated by MafB. The mutation induces reduced activity of MafB expression and increases the osteoclastogenesis responsible for bone destruction. The disease is characterized by (i) the progressive but ultimately resorption of the carpal and tarsal bones after a period of normal development [4, 5], and (ii) an inflammatory arthropathy of other joints. The proximal joints are usually unaffected, and spinal deformities are rare. The disease progresses with exacerbations during the first two decades of life, leading to joint deformities. Renal dysfunction appears later in life in most cases, and progresses rapidly to end-stage renal disease. This report presents the long-term clinical and radiologic follow-up (over 23 years) of three patients with MCTO. The first two cases illustrate progressive osteolysis, and the third case shows asymmetrical involvement. In all cases, the diagnosis was confirmed by DNA sequencing (i.e., the presence of a heterozygous *MAFB* mutation).

Case report

Patient #1 is a male, currently aged 24. His father had MCTO with end-stage renal disease (treated with a kidney transplant), and so a diagnosis of MCTO was rapidly established. The first symptoms (bilateral wrist pain) were observed at the age of 4. The hands were short, and ulnar deviation appeared progressively. The elbows were stiff and painful. The shoulders and hips were pain free. At the age of 10, both knees became painful and stiff, resulting in walking disabilities with an irreducible left knee flexion and valgus deformity. The patient presented bilateral pes cavus and irreducible claw toes. He presented a cervicothoracic scoliosis (Cobb angle: 78°) and a cervical deformity (C6-C7 block). At the age of 24, he presented with high blood pressure and proteinuria but had a normal serum creatinine level.

Left hand radiologic assessments at age of 8 (Fig. 1a), at age of 16 (Fig. 1b), and at age of 22 (Fig. 1c) demonstrated the

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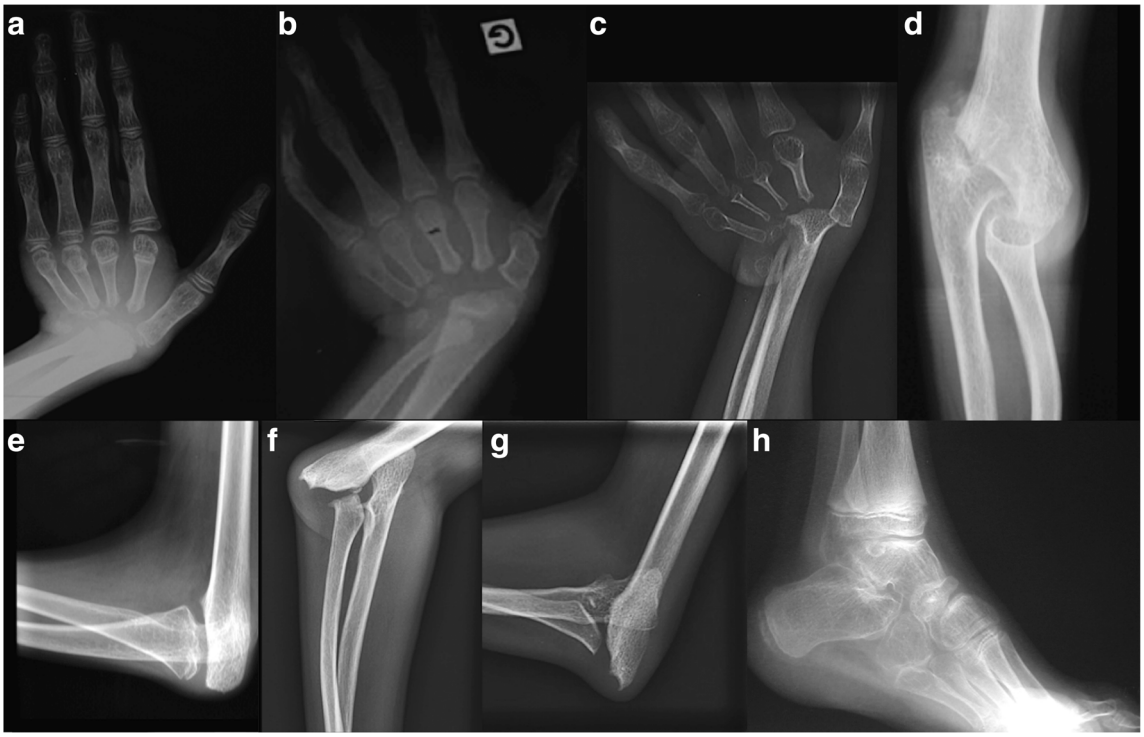

Fig. 1 Patient #1's radiographs. **a** The patient's left hand at the age of 8 showing the carpal osteolysis. **b** The left hand at the age of 16, showing carpal osteolysis, a short first metacarpal, and ulnar deviation. **c** Left hand at age of 22 demonstrating the "sucked candy appearance of the metacarpals and ulna extremity. **d**, **e** Plain and lateral view radiographs of the left elbow at the age of 12 showing complete osteolysis of the trochlea and swollen soft tissues. **f**, **g** Plain and lateral view the left forearm at the age of 22 showing an anteromedial dislocation of the olecranon, complete osteolysis of the humeral distal epiphysis, and the ulnar deviation of the wrist. **h** Lateral view radiographs of the foot at age of 14 revealing partial tarsal osteolysis

progressive and partial carpal osteolysis and ulna deviation during childhood and in adulthood. In this case at 22 years of age, metacarpals were very short with a tapered extremity as a "sucked candy" appearance. The first metacarpal presented a large base. The distal extremity of the ulna showed a very fine appearance as the bases of the metacarpals. Left elbow radiograph respectively performed at age of 12 (Fig. 1d, e) and 22 (Fig. 1f, g) revealed a destruction of the capitellum and trochlea, and a dysplastic olecranon and coracoid process, leading to a radial head dislocation and ulna dislocation in adulthood.

Foot radiograph at the age of 14 (Fig. 1h) revealed subchondral destruction of the talus, and partial osteolysis associated with the navicular and pes cavus deformity.

Patient #2 is a male and now aged 33. The first symptoms (a painful, swollen left wrist, followed by swollen elbows, knees, and ankles) appeared at the age of 2. A diagnosis of juvenile idiopathic arthritis was initially suspected. Several months of treatment with salicylate did not relieve the symptoms. Following the observation of carpal bone osteolysis on radiograph at the age of 7, MCTO was then suspected.

The patient progressively developed ulnar deviation of the wrists and short forearms. Stiff elbows and knees (with a limited range of motion and flexion deformity) resulted in a gait impairment from the age of 9 onwards. Bilateral pes cavus was observed. At last follow-up, the elbow, knee, and hip joints displayed a severely limited range of motion but were stabilized by adult age. No spine deformity was observed. End-stage renal disease was diagnosed at the age of 17 and treated with a kidney transplant.

Hand radiographs (Fig. 2a, b, c) performed respectively at 4, 7, and 30 years of age showed the progressive carpal osteolysis with a complete destruction of all carpal bones. The base of metacarpals presented the "sucked candy" aspect. At age of 30, the first metacarpal was very short but its base was large. A metacarpophalangeal joint subluxation and dorsal wrist subluxation was noted.

Right elbow radiographs performed respectively at age of 7 (Fig. 2d), 11 (Fig. 2e), and 30 (Fig. 2f) showed destruction of the humeral epiphysis, posterior dislocation of the ulna, total destruction of the subchondral zone, and swollen soft tissue. Radiograph of the feet (Fig. 2h) at the age of 14 revealed partial tarsal osteolysis with dorsal subluxation of the first metatarsal.

Patient #3 is a girl now aged 16. Her history began at the age of 3 in a context of acute arthritis of the left knee. Septic arthritis was the first diagnosis considered. Disease progression was marked by pain in all four limbs, and difficulty with walking and writing. The forearms became abnormally short, with an ulnar deviation of the hands and wrist instability. The

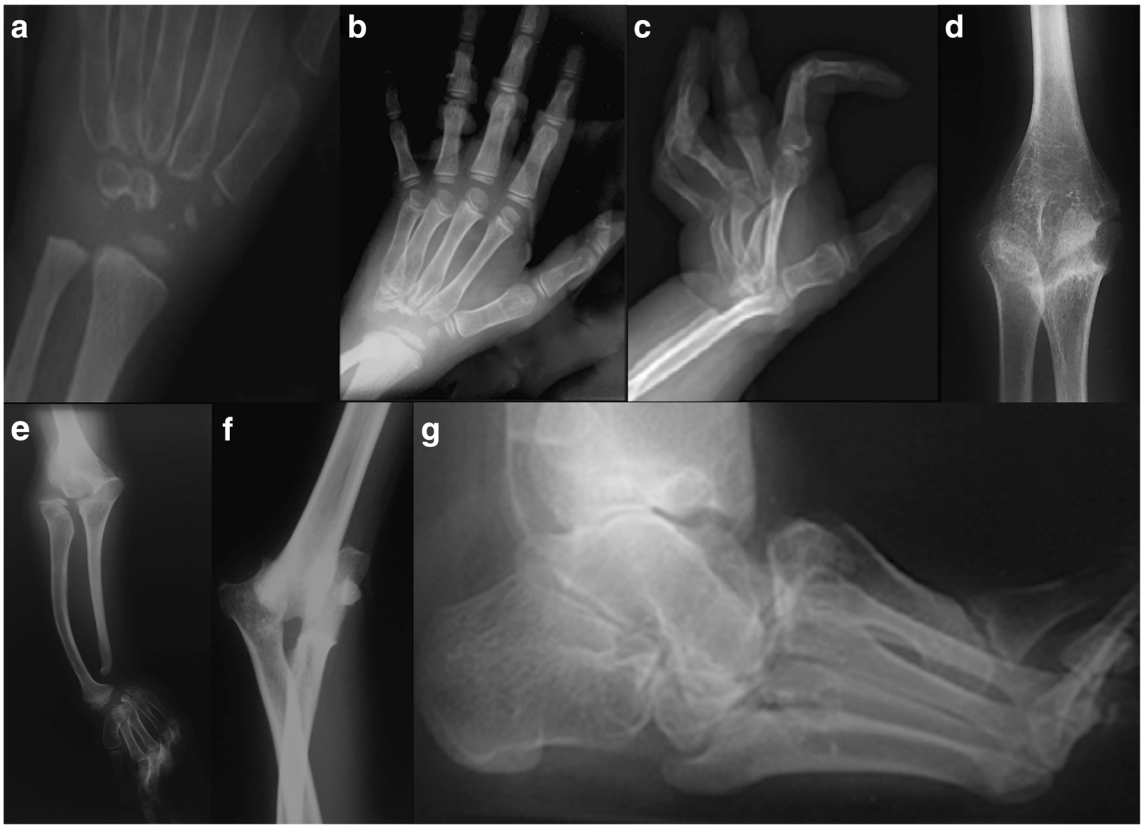

Fig. 2 Patient #2's radiographs. **a**, **b**, **c** Left hand radiographs at 4, 7, and 30 years of age, respectively, showing progressive carpal osteolysis. At 30 years of age (Fig. 3g), we observed a dorsal wrist subluxation and the metacarpophalangeal joint subluxation. **d** Plain view radiograph of right elbow at the age of 7 showing extensive osteolysis of the capitellum and trochlea. **e** Plain view radiograph of the right forearm at the age of 11 showing radial head subluxation and an ulnar club hand. **f** The right elbow at the age of 30 showing complete posterior dislocation of the radial head and the olecranon. **g** Lateral view radiograph of the foot at age of 30 with total tarsal osteolysis

right elbow was stiff. Both knees and ankles became swollen, with restricted range of motion. She presented a bilateral knee valgus deformity, a painful left pes cavus, and a moderate scoliosis of the thoracolumbar spine. The only non-skeletal manifestations were hypertelorism and asymptomatic mitral valve regurgitation. No renal signs were observed at the last follow-up. Given joint limitation and the carpal osteolysis on radiographs from the age of 8 onwards, a diagnosis of MCTO was suspected.

Hand radiographs at age of 8 (Fig. 3a, b) showed an osteolysis of all carpal bones and a "sucked-candy" appearance of the base of all the metacarpals in contrast with the normal appearance of the metacarpals heads and metacarpophalangeal joint. An ulnar deviation of the wrist was also noted. The distal radius, ulna, and phalanges were normal. The radiologic features were asymmetric since the osteolysis was more severe for the right hand.

At the age of 16, the asymmetrical features were still present on radiograph. Left elbow radiograph (Fig. 3c) showed a normal joint surface contrasting with a severe destruction of the capitellum and partial osteolysis of the trochlea and radial head subluxation contrasting of the right elbow (Fig. 3d). Ankle radiographs (Fig. 3e, f) showed a cartilage and bone destruction on the distal tibia with a medial lysis area. A talus valgus deformity was observed only on the right side (Fig. 3f). Knees radiographs (Fig. 3g, h) revealed a lateral space narrowing (more severe on the right) and a severe valgus deformity. On left foot radiograph, the mid-tarsal joints (Fig. 3i) were partially destroyed and a pes cavus deformity was observed.

Discussion

MCTO is a rare skeletal disorder, and few cases have been reported in the literature. The disease is difficult to diagnose during early childhood, since most patients present with features of rheumatic disease (such as monoarthritis) and have normal X-ray results. The first clinical signs (swelling and progressive joint limitation) appear at the age of 2 or 3, and initially resemble those of juvenile rheumatoid arthritis or septic arthritis (as was the case for two of our patients) [6, 7]. Deformities, swelling, and pain are important features of MCTO. Gluck and Tunckbilek reported that pain was present at disease onset during the bone resorption phase [8, 9]. The phenotypic expression is reportedly variable (even for genetic

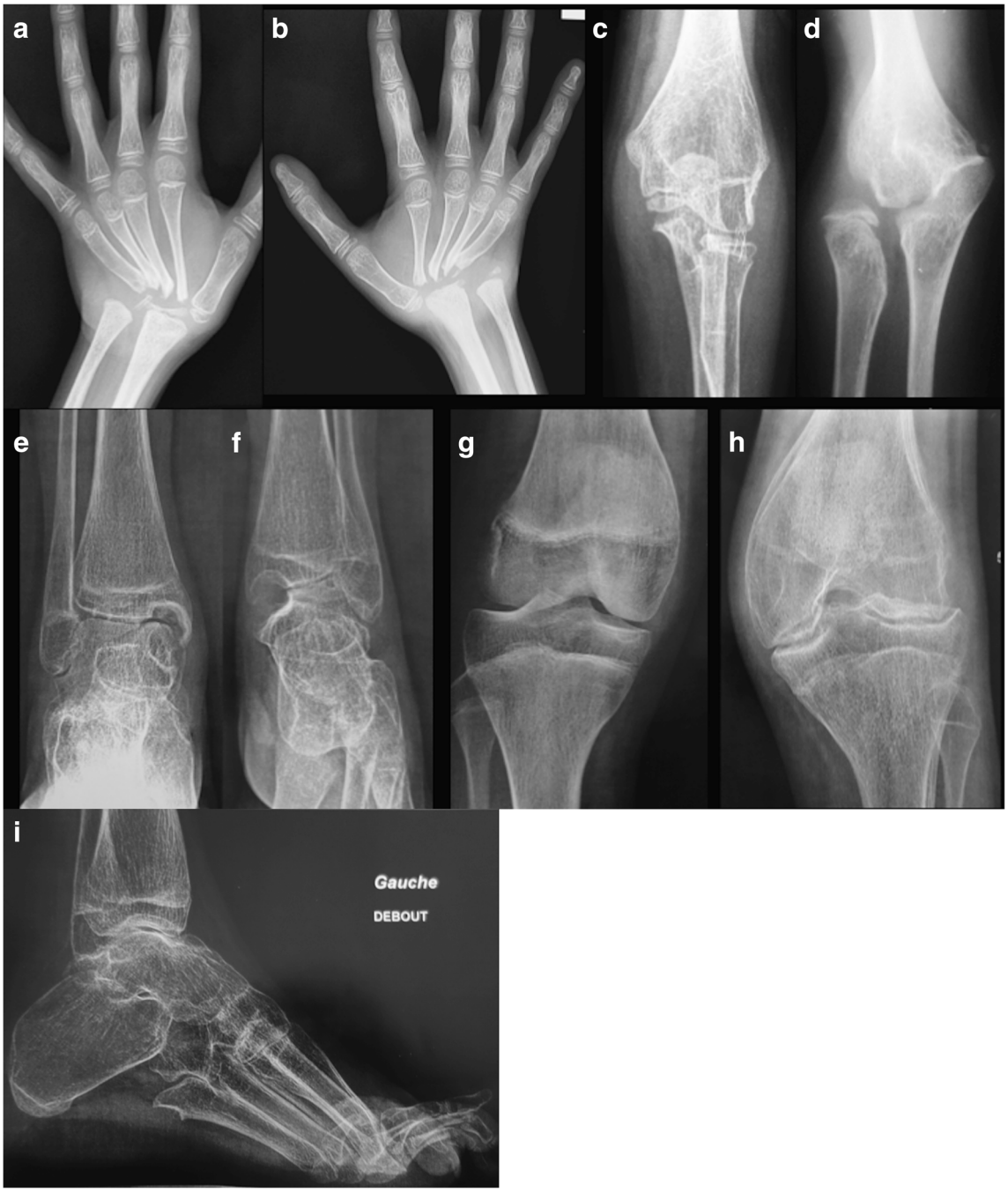

Fig. 3 Patient #3's radiographs. **a** The left hand at the age of 8 showing the partial carpal osteolysis. **b** The right hand at the age of 8, showing asymmetrical osteolysis of the carpal bone with complete resorption. **c**, **d** The left elbow radiograph at the age of 16 with normal joint surface which contrasts with the right elbow radiograph (**d**) at the same age with a dysplastic olecranon and radial head subluxation. **e**, **f** The left and right ankle radiographs at the age of 16 showing lysis of the medial bone and cartilage, and a right-side valgus deformity. **g**, **h** The left and right knee radiographs at the age of 16 showing a lateral joint space narrowing and a severe valgus deformity on the right side. **i** Lateral view radiograph of foot at the age of 15 revealing a partial tarsal osteolysis

homogeneity) [10]. All the patients in our study presented with carpal and tarsal bone destruction, stiffness of the elbows, ankles and knees, and limb deformities (including pes cavus). These lesions led to progressive, severe, and functional impairment. The shoulders and hips were not affected, and cognitive performance was not impaired in any of the three cases [11].

The radiological features of MCTO are observed later in childhood, with the progressive destruction of the carpal and tarsal bones [10] and as reported in patient #3, limb

involvement was not necessarily symmetric. As previously reported by Tyler and Rosenbaum, all the carpal bones are degraded, and the tarsal bones are partially destroyed [5]. In the present cases, the proximal metacarpals displayed "sucked candy" damage. The ulna was more involved than the radius, with distal osteolysis leading to ulnar deviation of the wrist. Elbow deformities in MCTO have been described more recently, and this feature was present in our three cases [7, 12]. The observed distal osteolysis of the humerus, epiphyseal dysplasia, and capitellum resorption might lead to dislocation of the radial head and the ulna. The olecranon was dysplastic, with hypoplasia of the coronoid process.

Faber described the foot deformities in MCTO as "clubfoot", although pes cavus is more common [6]. In the three cases presented here, MRI of the hand or foot was not performed; however, this imaging modality is of diagnostic value because it can highlight bone resorption and exclude inflammatory pathology (i.e., normal soft tissue and residual cartilage) [6, 7]. Genetic testing can also help to establish a diagnosis as early as possible by identifying disease-causing mutation in *MAFB*. Lastly, the histological findings are non-specific [8, 12].

None of the drug treatment tested to date has long-term efficacy. Immunosuppressants, salicylates, and non-steroidal anti-inflammatory drugs may attenuate the inflammatory response at the beginning of the disease but do not have a lasting effect on pain. Surgical treatment should be tailored to each patient, as a function of the clinical signs and symptoms and the patient's age. A better understanding of this disease and its clinical course is essential for appropriate surgical management. Multidisciplinary management (involving an orthopedic surgeon, a radiologist, a nephrologist, a geneticist, and a physician or pediatrician) is an important aspect of patient care.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest All authors declare that they have no conflicts of interest and no financial support.

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