CASO CLINICO

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A challenging case of melorheostosis involving the right upper limb

Un caso difficile di meloreostosi che coinvolge l'arto superiore destro

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Summary

We report a case of a 35 years old man with melorheostosis involving right upper limb. This patient presented with a long history of arm-forearm and 2nd- 3rd-4th finger hypertrophy. The patient experienced dull discomfort and complained of elbow-wrist and finger stiffness.
The X-ray provided the diagnosis of melorheostosis in infancy, showing the flowing candle pattern covering humerus-ulna and fingers, and the structural observations here reported allow us to suggest the hypothesis that the compression of the painful free periosteal nerve terminations could be the cause of pain symptoms. In the first operation carried out at the age of 32 years, the contracted elbow capsule and calcifications were excised with a temporary good outcome. Following a severe recurrence both in relationship to pain and elbow stiffness a total elbow arthroplasty was carried out with a good outcome in a mid-term follow-up.

Key words: melorheostosis, prosthesis, elbow

Riassunto

Riportiamo il caso di un uomo di 35 anni con meloreostosi che coinvolge l'arto superiore destro. Il paziente si è presentato con una lunga storia di ipertrofia del braccio-avambraccio e del 2°-3°-4° dito. Il paziente avvertiva un fastidio sordo e lamentava rigidità del gomito-polso e delle dita.
La radiografia ha fornito la diagnosi di meloreostosi infantile, mostrando il disegno a candela fluente che ricopre omero-ulna e dita, e le osservazioni strutturali qui riportate ci permettono di suggerire l'ipotesi che la compressione delle terminazioni nervose periostali possa essere la causa dei sintomi del dolore. Nel primo intervento effettuato all'età di 32 anni, la capsula del gomito contratta e le calcificazioni sono state asportate con un risultato temporaneamente buono. In seguito a una grave recidiva sia in relazione al dolore che alla rigidità del gomito, è stata eseguita un'artroplastica totale di gomito con un buon risultato in un follow-up a medio termine.

Parole chiave: *meloreostosi, protesi, gomito*

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Conflitto di interessi
Gli Autori dichiarano di non avere alcun conflitto di interesse con l'argomento trattato nell'articolo.

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Introduction

Melorheostosis is a bone disorder characterized by linear hyperostosis that appears to flow along the cortex. It can be either monostotic or polyostotic and tends to be monomelic. It has a predilection for long bones of the limbs, although it can be seen almost anywhere. It occurs in early childhood. In only approximately half of the cases diagnosis is made before the age of 20 years. Generally patients complain of pain, swelling, soft tissues contractures gradually leading to joints stiffness. Isolated melorheostosis is usually a sporadic disease with no Mendelian pattern.

Few histological data are published on the structure of the hyper-secreted bone, that shows altered porosity, mineralization and collagen arrangement [1-2]; ultrastructural observations, instead, have not been reported so far in the literature, so that sub-microscopic details, like osteocyte viability for instance, are still unknown in this type of hyperostosis. Etiology also remains speculative, but recent studies involve somatic gene mutation of genes of the MAP kinase cascades regulating cell proliferation, differentiation, and death [3]. The treatment remains challenging.

We report the case of a male patient with melorheostosis, involving the upper limb, treated with an elbow prosthesis and hyperostosis remotion of the capitate, where structural and ultrastructural studies were carried out.

Case report

In 2015 a 35 year old man presented with anchylosis of the right elbow and wrist and pain in the flexion of the 2nd, 3rd and 4th finger of the right hand (Fig.1 a,b). At birth and during infancy the limbs were apparently normal until the age of six years, when the patient began to notice a gradual loss of motion. The diagnosis of melorheostosis was made on

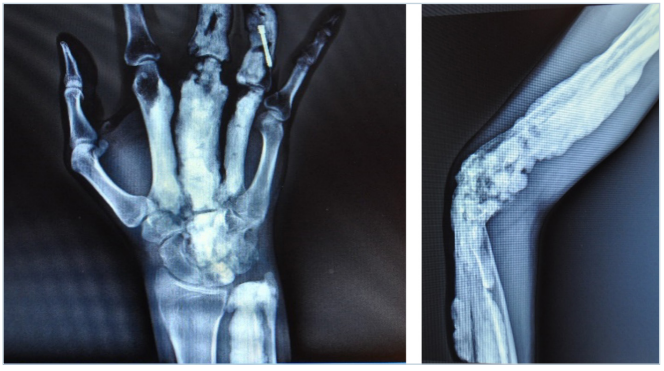

Figure 1. X-Rays showing of the right hand following the debulking of the third and fourth metacarpal and osteotomy and fixation by a Herbert screw of the first phalanx of the ring finger were carried out in order to correct clinodactyly of the finger (Fig. 1a). X-Rays showing upper limb with massive hyperostosis of the elbow (Fig. 1b).

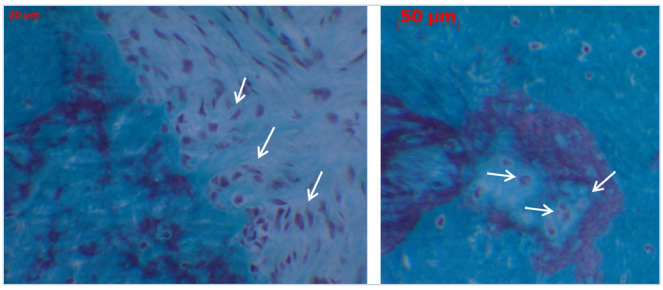

Figure 2. Micrographs showing histological features of the removed bone. Note (Fig. 2a) the osteoblasts arranged in cords (pointed by arrows); note also (Fig. 2b) osteocytes located in confluent lacunae (arrows).

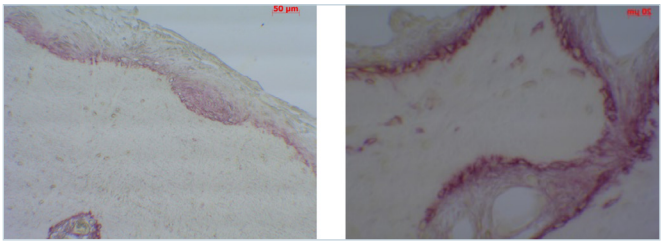

Figure 3. Micrographs showing the intense ALP activity at the subperiosteal (Fig. 3a) and perivascular (Fig. 3b) level of the removed bone. Red color indicates positivity for ALP.

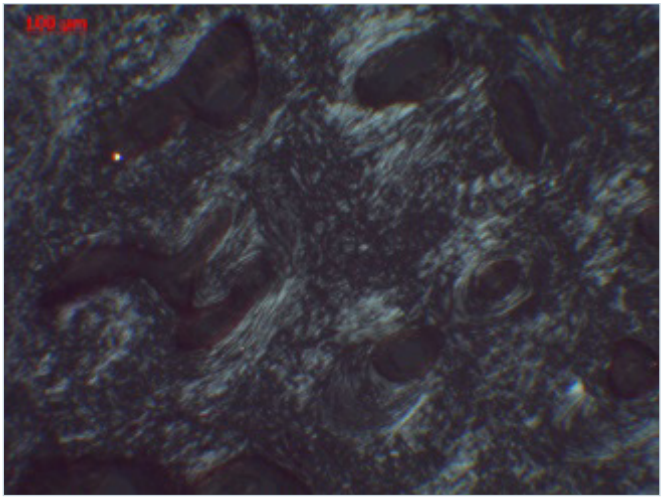

Figure 4. Micrograph under transmitted polarized light showing that exuberant formation of subperiosteal bone is mostly made up of woven-fibered collagen texture.

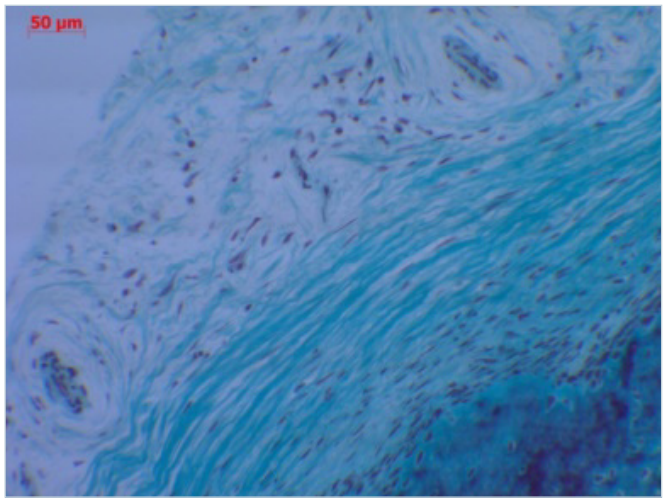

Figure 5. Histology of removed subperiosteal bone suggestive of nervous structures distributed in the inner layer of the periosteum.

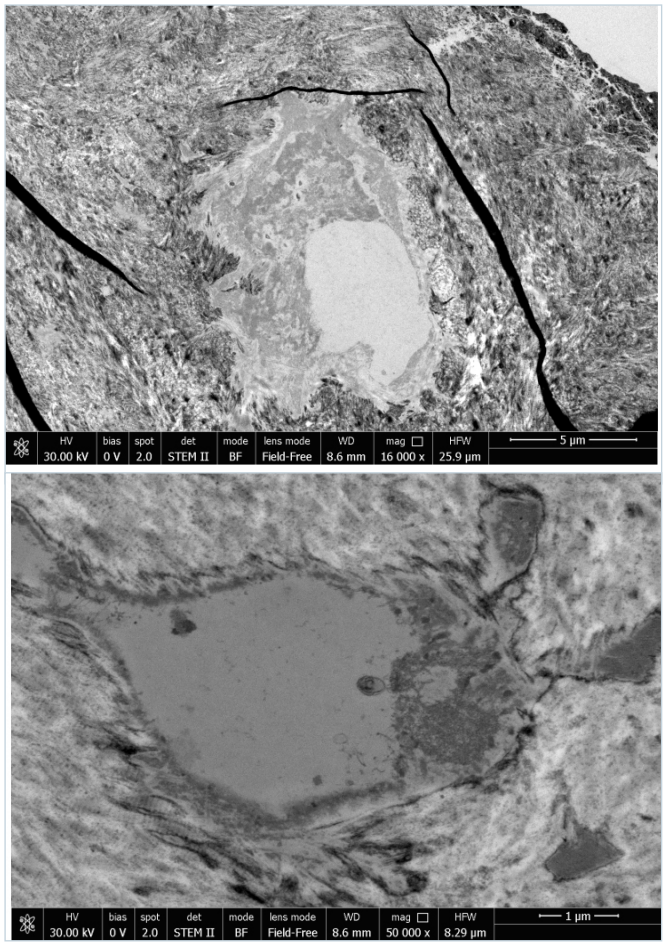

Figure 6. TEM Micrographs showing not viable osteocytes enclosed in their lacunae inside the pathologic bone (Fig. a and b).

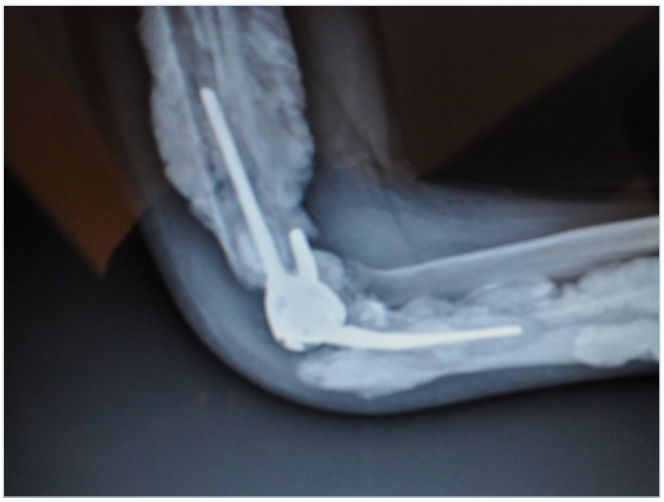

Figure 7. Device implant in the elbow.

X-ray. Family history was negative for bone disorders. In 2012 pathological specimen after the evaluation of the multidisciplinary Group of Hand Malformation at the Modena University Hospital [4,5], calcifications around the distal half of the humerus were removed, debridement of the joint and multiple perforations of the both cortex were also carried out on the basis that perforations might be effective in the treatment of pain as they will decrease the pressure within the medullary space. Debulking of the third and fourth metacarpal and osteotomy and fixation by a Herbert screw of the first phalanx of the ring finger were carried out in order to correct clinodactyly of the finger (Fig.1 a)

Concerning the histological features of the removed bone, it emerged an enhanced osteoblast activity mostly by *static osteogenesis*, characterized by osteoblasts initially arranged in cords (Fig. 2a) following whose activity the osteocytes appear often located in confluent lacunae (Fig. 2b), as already described in literature [5,6]. Intense ALP (alkaline phosphatase) activity at the subperiosteal and perivascular level was also recorded (Fig. 3 a,b), with consequent exuberant formation of subperiosteal bone, mostly made up of woven-fibered collagen texture (Fig. 4), that probably compresses the periosteal painful free terminations, which are distributed in the inner layer of the periosteum (Fig. 5).

Concerning the ultrastructural observations, besides the aspect of osteoblasts whose ultramicroscopic features confirm the intense activity (data not shown), it emerged the absence of osteocyte viability inside the pathologic bone (Fig. 6 a-b).

In the following years, the elbow became stiff and painful. Following, the patient underwent genetic counseling, where, after informed consent, a genetic test was proposed for the LEMD3 gene, which had been previously reported in the pathogenesis of melorheostosis [7]. The analysis was

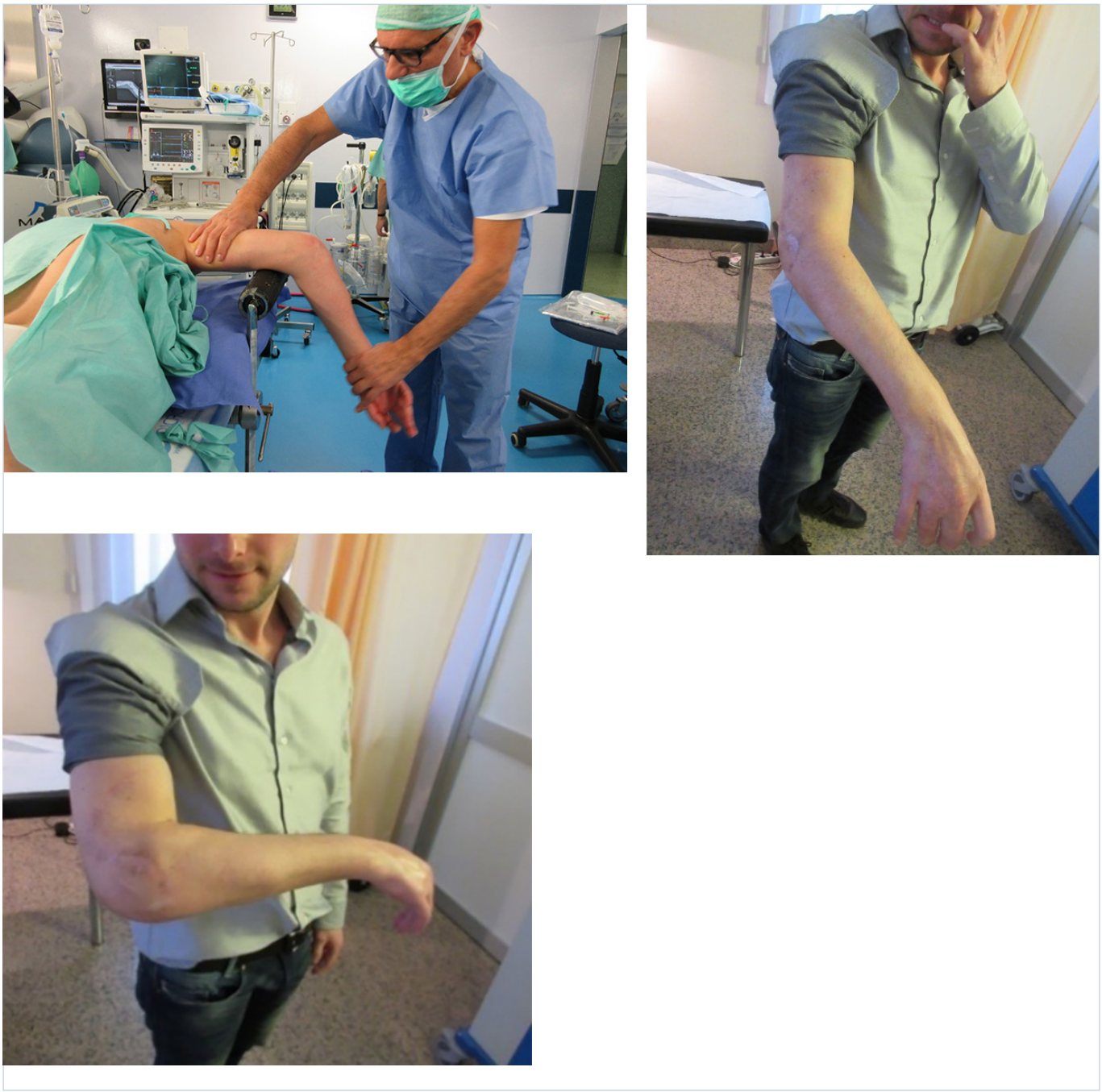

Figure 8. Elbow motion before the implant (Fig. 8a), and ROM recovery after the implant (Fig. 8b and Fig. 8c).

performed through the screening of all coding exons and flanking exon–intron junctions of LEMD3 gene by direct sequencing on DNA extracted by peripheral blood, and real time PCR was used to quantitatively exclude whole-gene or whole exon deletions/duplications [8]. No pathogenetic variant or rearrangement of the gene was found [7].
Our surgical plan was concentrated on dealing with the painful and stiff elbow (AROM + 80° of flexion and- 60° of extension (Fig. 8a).
After release a total semi-constrained prosthesis of the elbow was implanted (Fig. 7). The AROM improved significantly to+ 120° of flexion and- 20° of extension. The patient was treated by an early rehabilitation program both by a physiotherapist and a daily program of passive mobilization by Kinetec.

An extension splint was worn at night. Two years after surgery the patient showed a recurrence of the elbow stiffness with pain and calcifications on X-rays. A new periprosthetic debridement was carried out which reestablished the previous AROM with flexion of+ 120°and extension of -10° at two years follow-up (Fig. 8 b,c).

Discussion

A paper of Anthropology reports a case of massive hyperostotic alterations observed in the skeleton of an adult women from a necropolis of Basilicata, a region of Southern Italy, attributed to the Enotrian culture and dated to the 6th century BC 9. Until 2012 there are about 360 cases described in literature [10]. Melorheostosis was described for the first time by Lery-Joanny in 1922 [11]. Different hypotheses were made to explain the etiology and pathogenesis of the disease. Putti in 1927 [12] postulated a sclerodermic vascular disturbance as the underline cause. In 1968, Campbell [13] suggested a congenital mutation causing an early disturbance in the embryonic development of the neural crest. An attempt to correlate sclerosing lesions with a sclerotoma was published by Murray, Mc Credie [14] Ikuko et al. in 1979 [15]. Hellemans and others [7] speculated that loss of function mutations of the LEMD-3 gene, also known as MAN1, could be implicated in sclerotic bone disorders.

A paper by Couto et al., [16] focused on LEMD-3 mutations in patients with and without melorheostosis analyzing an Azorean family with osteopoikilosis and melorheostosis and two sporadic cases of this latter. A mutation was found only in the familial cases, whereas the two sporadic melorheostosis were negative for LEMD-3 mutations. LEMD-3 is an inner nuclear membrane protein which hinders the transmission of signals that lead to bone formation and when signals are lacking the bone formation becames excessive and uncontrolled. Gnoli et al. [8], on the other hand, recently suggested that LEMD3 germline mutations are not the main cause of isolated melorheostosis. Kim et al. [17] believes that the TGF-beta-induced gene product might contribute to the onset melorheostosis as well as MAP2K1 somatic mutations [1-3].

Melorheostosis has a prevalence of about 0,9 per million; males and females are equally affected. One bone or a number of adjacent bone causing hyperostosis and, typically, long bones of the limbs and sometimes small bones of the hands [18] and feet might be involved. The condition is predominantly unilateral. Rarely the vertebral column can be affected. The condition is not limited to bone and may affect the surrounding soft tissue.

Melorheostosis may be diagnosed at any age, but generally in childhood or adolescence were a rapid progression is observed, whilst progression in adulthood is variable.

The usual clinical symptoms are: pain, stiffness, limitation of AROM, swelling, deformity and soft tissue contracture. Concerning pain, a recent paper showed that the periosteum is the most densely innervated bone compartment, both in youth and during aging, and that, even if the bone itself undergoes a marked decline with age, the nociceptors that detect injuries and signal skeletal pain remain relatively intact [19]; in line with these observations, our findings, showing intense subperiosteal osteogesis (demonstrated by both abundant osteoblast population and ALP (alkaline phosphatase) activity, suggest the working hypothesis that the abnormal bone formation, typical of melorheostosis, can compress the subperiosteal nociceptive fibers whose stress, as is well known, induces "periosteal" pain referred to the bones.

The diagnosis is confirmed by X-ray which show hyperostosis of the osseous cortex of the surrounding the medullary space, characterized by the appearance of dripping candle wax, covering the surface of the long bones at the subperiosteal level, in association to accompanying soft tissue calcification or ossification. Moreover, the endosteal space may be obliterated and the compression of periostal innervation by subperiosteal abnormal ossification might become the source of pain.

CT and MRI are not usually performed, although a positive MRI might obviate biopsy [20]. Bone scintigraphy is helpful, sometime, to differentiate melorheostosis from other rare bone disorders. Histologic analysis confirms the clinical and instrumental diagnosis and reveals dense sclerotic bone of cortical pattern. Bone lesions do not metastasize, but progression to osteosarcoma has been exceptionally reported [21].

The treatment options range from nonsurgical management in order to decrease pain through physical therapy, orthosis etc... to surgical interventions such as resection or excision of the calcification and joint debridement. Other treatments include osteotomies and bone lengthening, tendon lengthening, sympathectomies, contralateral epiphysiodesis, arthrodesis or amputation [22]. Joint replacement might be the ultimate option as in our case. Generally, surgical interventions, even if usually have a poor outcome, nevertheless might improve or maintain the overall function. Most reported case involving the upper are focused on the hand. In literature up to date there are only two cases reported, where the elbow stiffness was simply treated by joint release [23]. Ours case apparently represents the first report of a prosthetic joint replacement at the elbow.

Conclusion

Melorheostosis pathogenesis is to date largely unknown. All papers, despite genetic and molecular researches, agree on

the necessity of the further studies.
From the literature review the patients with melorheostosis including our reported case usually undergo recurrence of the disease, but the progression tends to decline with age, therefore surgery should be deferred in the late phase when the recurrence rate usually decreases.

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