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Myositis ossificans in children: a review

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Abstract The formation of lamellar bone in the soft tissues, where bone normally does not exist, is called myositis ossificans. However, it would be more accurate to describe as myositis ossificans the involvement of skeletal muscles and as ectopic or heterotopic ossification the involvement of soft tissues in general. The lesion is subdivided in genetic and non-genetic or acquired types. Myositis or fibrodysplasia ossificans progressiva is a debilitating rare genetic disorder. Clinical suspicion of the disease in the newborn on the basis of malformed great toes may lead to early clinical diagnosis, confirmatory diagnostic genetic testing and avoidance of iatrogenic harmful procedures. Acquired lesions involve the neurogenic myositis ossificans and the non-neurogenic disorder. The latter is defined either as circumscribed myositis ossificans that is post-traumatic or as idiopathic/pseudomalignant myositis ossificans that is non-traumatic and may be a form fruste of fibrodysplasia ossificans progressiva. Ossification in fibrodysplasia ossificans progressiva is irreversible, unlike other forms of heterotopic ossification. In this retrospective study, a total of 22 children with myositis ossificans treated in a 20-year period were identified and classified. Two patients were diagnosed with myositis/fibrodysplasia ossificans progressiva, one with neurogenic myositis ossificans, one with idiopathic/pseudomalignant myositis ossificans and 18 patients with circumscribed myositis ossificans. The clinical features, imaging and histological findings as well as treatment modalities and complications of myositis ossificans in our patients are presented and discussed.

Keywords Myositis ossificans · Ectopic/Heterotopic ossification · Fibrodysplasia ossificans progressiva · Children

Introduction

Myositis ossificans is the process of mature lamellar bone formation in soft tissues, in association with inflammation, caused by traumatic or neurological injury, surgery, burns or diseases. Several other terms have also been used to denote the condition such as ectopic or heterotopic ossification, ossifying fibromyopathy, paraosteoarthropathy and periarticular ossification. Although its pathogenesis is unknown, pathways including a permissive environment, inductive agents and osteoprogenitor cells are required. The differentiation of the mesenchymal progenitor cells into chondroblasts and osteoblasts is induced by the bone morphogenetic proteins (BMPs). This suggests that BMPs may be able to influence both the endochondral bone induction pathway, which is the process by which long bones develop, and direct bone formation. The responding cell population to BMP action includes fibroblasts, mesenchymal and muscle-derived connective tissue cells and many more. In ectopic bone formation, which most likely represents metaplasia of fibroblasts at the site of the lesion, the sequence of events recapitulates the process of bone

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formation that is observed during embryonic long bone development. Initial clinical presentation is generally characterized by tenderness over the palpable swelling, warmth and erythema, pain on range of motion and increased joint stiffness. After maturation of the lesion, the clinical findings include a limited range of motion and a palpable osseous mass. Treatment may be complex because accurate and early diagnosis is fundamental to a successful outcome [1–17].

Twenty-two children that were admitted for myositis ossificans in a 20-year period were included in the study. They were classified, their clinical, imaging and histological findings were reviewed, and outcome was evaluated.

Materials and methods

A total of 22 children that were admitted with a diagnosis of myositis ossificans and ectopic or heterotopic bone formation between 1984 and 2003 in the Departments of Pediatric Orthopaedics and Pediatric Surgery were identified from the hospital database. There were two patients with myositis/fibrodysplasia ossificans progressiva (Figs. 1, 2), one with neurogenic myositis ossificans (Fig. 3), one with idiopathic/pseudomalignant myositis ossificans (Fig. 4) and 18 patients with circumscribed/post-traumatic myositis ossificans. In the post-traumatic lesions, a single major traumatic insult was recorded in 17 patients, while in one patient with an iliopsoas involvement a history of multiple minor injuries to the hip region was detected. The mean age of the patients at diagnosis was 9 years (range 3–14 years). There were 11 boys and 11 girls. Diagnosis was based on the clinical and imaging findings in 18 patients that were treated conservatively and on the histological findings of the resected lesion in 4 cases (Table 1).

The patients were followed up for at least 1 year, and the dimensions of the ectopic bone as well as the functional results were assessed. The final follow-up ranged from 1 to 7 years (average 20 months). The clinical, radiological and histological data of these patients were reviewed retrospectively.

Results

Myositis ossificans was localized in the muscle groups of the hip (1 patient), chest wall (1 patient), thigh (4 patients), pelvis (6 patients) and elbow (10 patients). The neurogenic lesion was localized to the hip, while the pseudomalignant to the chest wall. The 4 thigh lesions were localized to the vastus lateralis (2 patients) and to the posteromedial thigh musculature in the genetic disorder (2 patients). No bone injury was diagnosed in the 2 post-traumatic cases with a thigh lesion that followed sport injuries (Fig. 5). The 6 pelvic lesions were localized to the anterior superior iliac spine (1 patient), to the anterior inferior iliac spine (1 patient), to the ischial tuberosity (3 patients) and to the iliopsoas muscle (1 patient). There was no evidence of osseous injury during initial major pelvic trauma on the radiographs of the traumatic lesions localized to the anterior superior and inferior iliac spine (Figs. 6, 7). However, thin flakes of avulsed bone were evident in the 3 lesions involving the ischial tuberosity that followed sport injuries (Fig. 8). The 10 elbow lesions were all localized on the lateral side of the elbow. Eight of the elbow lesions were detected following an injury of the radial head (4 dislocations and 4 fractures of the radial head), while 6 of them were treated surgically and 2 conservatively. Two other

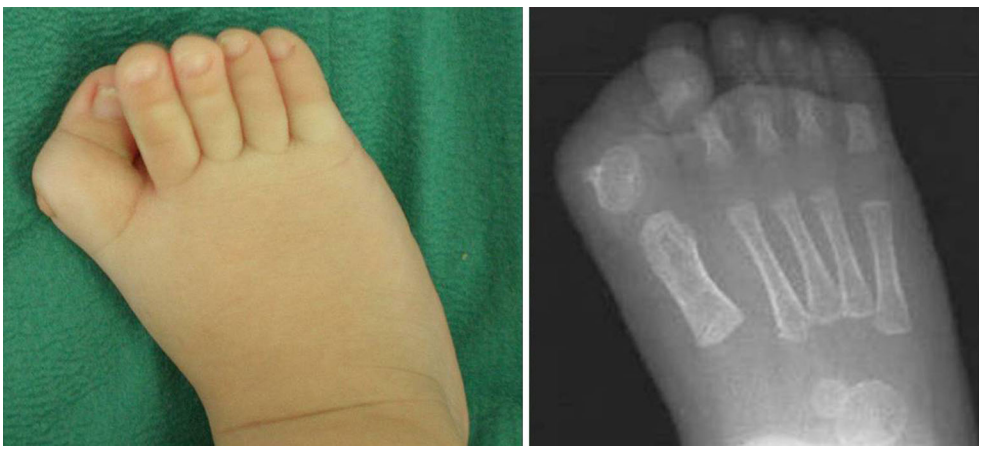

Fig. 1 Clinical and radiographic appearance of a 14-month-old boy with severe unilateral hallux valgus deformity and an incomplete preaxial polydactyly. The proximal phalanx is abnormally shaped, and the interphalangeal joint is fixed in valgus. Great toe malformation is the most critical early diagnostic feature of fibrodysplasia ossificans progressiva before the appearance of the preosseous tumor-like swellings

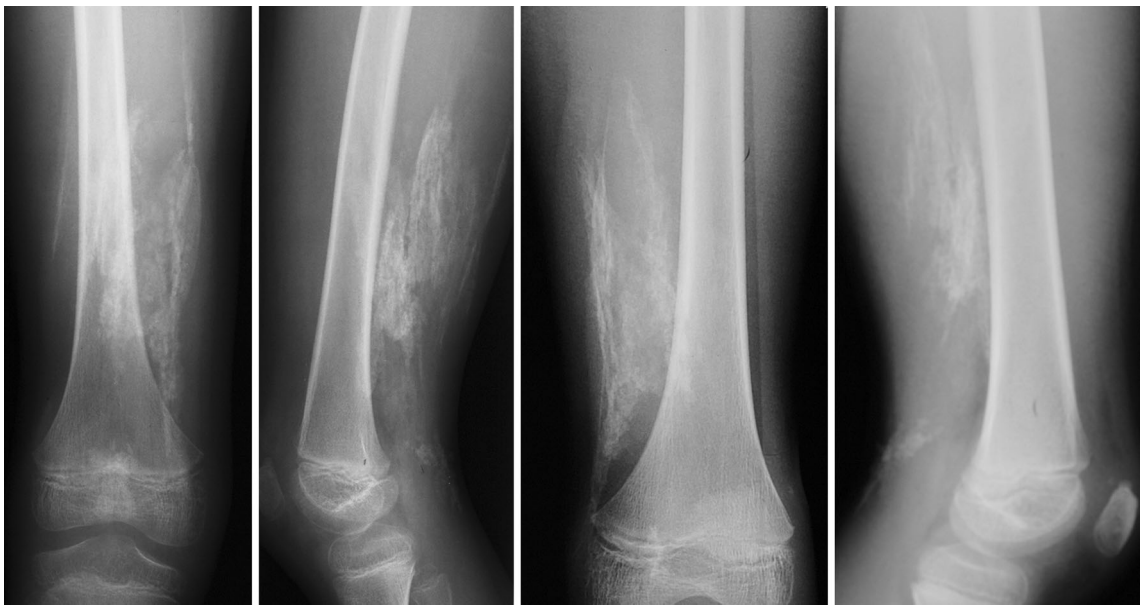

Fig. 2 Bilateral immature ectopic ossification of the posteromedial thigh in an 8-year-old boy with fibrodysplasia ossificans progressiva

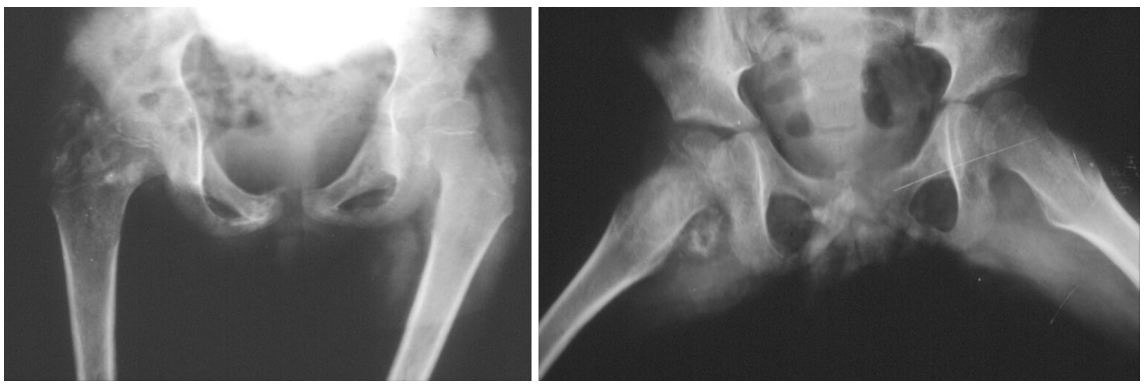

Fig. 3 Neurogenic myositis ossificans of the right hip in a 3-year-old girl 2 months post-injury

elbow lesions presented following a surgically treated supracondylar fracture of the humerus.

Four patients underwent surgical removal of the lesion. The appearance of the lesion was dated 3–4 months (average 3.5 months) prior to surgical removal. Diagnosis was based on the detection of the typical zonal phenomenon at histology. They all showed an uneventful recovery.

Two patients with a post-traumatic lesion localized to the vastus lateralis were treated surgically 4 months after the appearance of the lesion.

The circumscribed myositis ossificans of the iliopsoas muscle in the 13-year-old ballet dancer girl presented with a 3-month history of multiple minor injuries to the region of the left hip. The lesion was surgically removed. She showed an uneventful recovery and was symptom-free with no radiographic evidence of recurrence 4 years postoperatively. This case has been published previously [18].

Idiopathic/pseudomalignant myositis ossificans occurred in the right inferior thoracic wall, anterior to the seventh rib, of a 14-year-old boy. He was referred for a painless lesion that was detected 3 months ago. The lesion was surgically removed.

No invasive procedures were used in 2 genetic, 1 neurogenic and 15 post-traumatic cases. Two patients with myositis ossificans progressiva were diagnosed. The former presented with a unilateral big toe malformation at 14 months of age that was thought to be a congenital lesion, until the age of 5 years that bilateral soft tissue thigh swellings appeared. The latter presented at 8 years of age with the typical form of the disease. No invasive measures were undertaken, and diagnostic biopsies were not suggested. They showed no deterioration of the clinical and radiological findings, but were missed, after 1 year of follow-up.

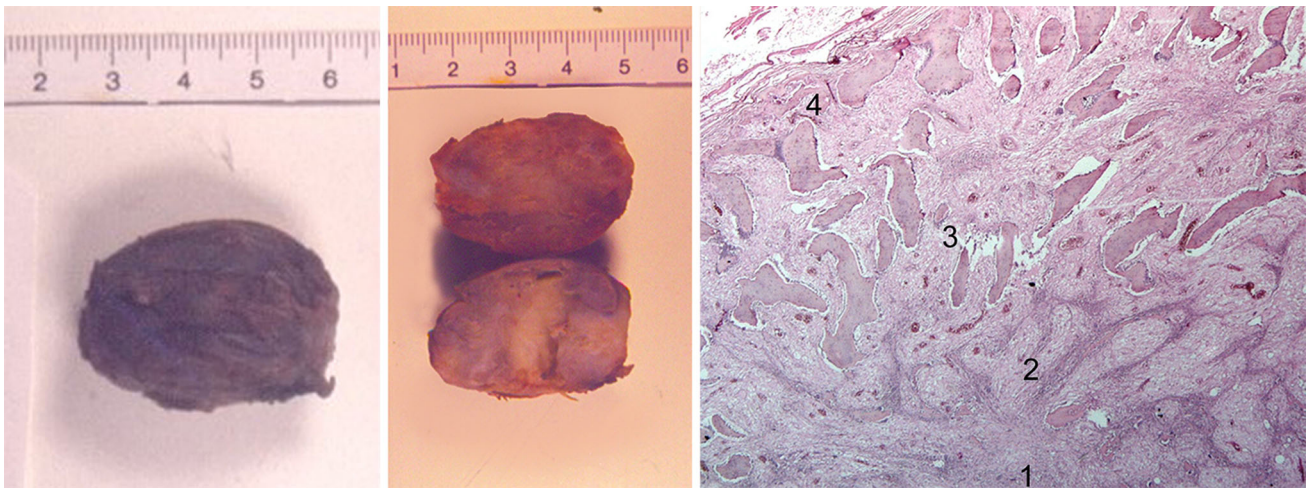

Fig. 4 Macroscopic findings of idiopathic myositis ossificans of the chest wall in a 14-year-old boy indicated a well-circumscribed ossified mass adherent to the surrounding muscle. Microscopic examination showed the typical four histologic zones: *1* a central cellular area with extreme variation in the size and shape of cells, *2* an adjacent zone with well-oriented zones of cellular osteoid separated by loose cellular stroma, *3* a more peripheral zone showing new bone formation with osteoblasts and fibrous tissue undergoing trabecular organization and *4* an outmost zone of well-oriented bone encapsulated by fibrous tissue

Table 1 Classification of the patients with myositis ossificans (MO)

Type	Location	Number of patients	Treatment
Progressiva MO	Thigh	2	Conservative
Neurogenic MO	Hip	1	Conservative
Idiopathic/pseudomalignant/non-traumatic MO	Chest wall	1	Operative
Circumscribed/post-traumatic MO	Pelvis	6	5 Conservative–1 operative
	Thigh	2	Operative
	Elbow	10	Conservative

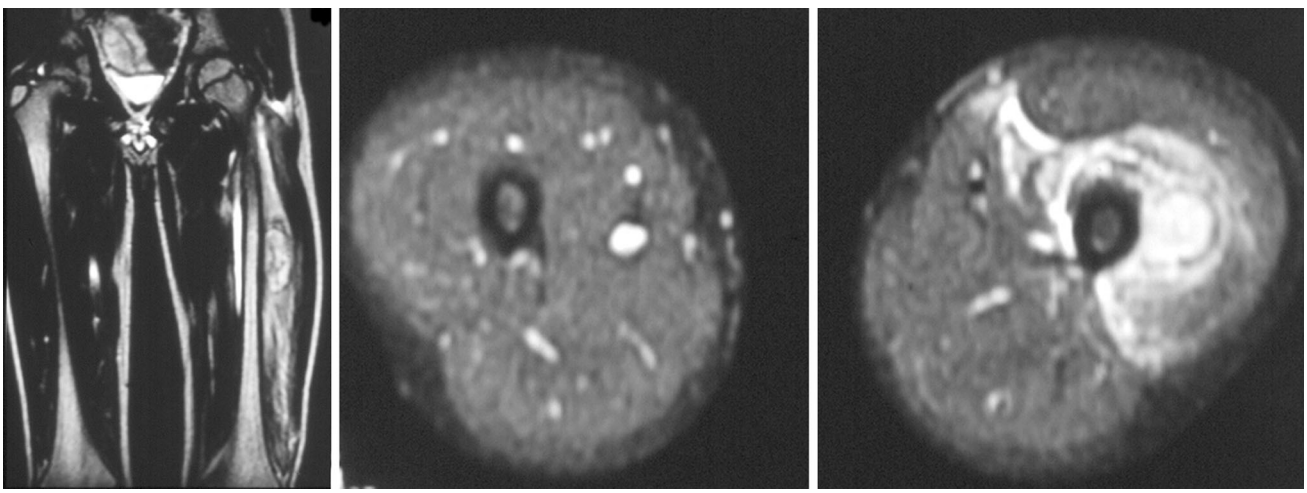

Fig. 5 Traumatic myositis ossificans of the lateral thigh in a 10-year-old girl following a thigh contusion while playing football 2 months ago that was due to a direct impact from another player

Neurogenic myositis ossificans was diagnosed in a girl aged 3 years that was struck by an automobile and was admitted to hospital unconscious with a head injury and a right hemiparesis. Pelvic and left femoral fractures were managed with skin traction. Three weeks after the injury, the range of motion of the right hip joint was reduced and

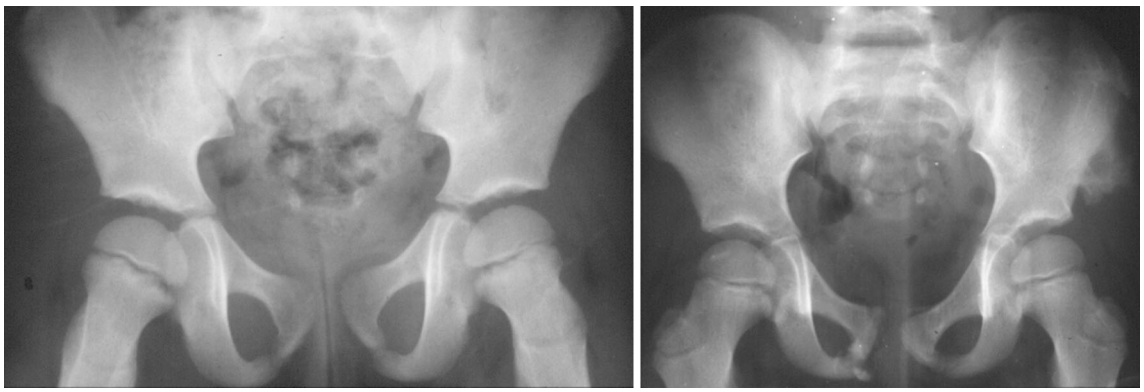

Fig. 6 A 4-year-old girl that escaped from a road accident after being run over by a truck's wheel 2 months ago. A pelvic exostosis was evident following hematoma formation at the level of the left anterior superior iliac spine

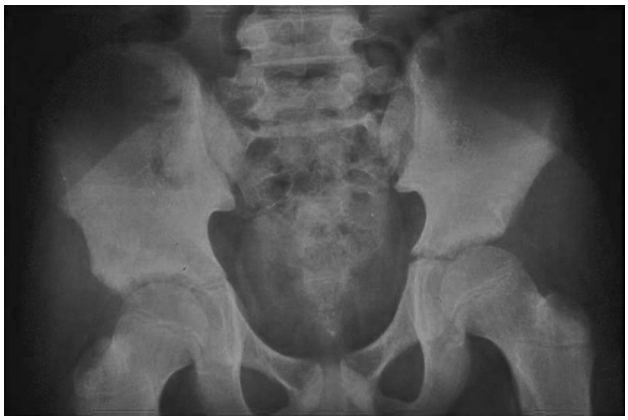

Fig. 7 New bone formation at the right anteroinferior iliac spine in a 13-year-old boy following major pelvic trauma that was due to a road accident 2 years ago

movements were painful. Radiographic examination 2 weeks later revealed heterotopic bone formation around the right hip joint. Immobilization was the only treatment offered. One year after injury, the ectopic ossification around the hip had resolved spontaneously, and she was able to walk independently with no restriction. This case has been published previously [19].

Seventeen cases of circumscribed myositis ossificans that were due to a single traumatic injury were classified according to Gilmer and Anderson into three categories on a primarily topographic basis [20]. An extraosseous lesion localized within the substance of a muscle was noted in 2 cases with thigh involvement. A periosteal lesion, which has also been referred in the past as ossifying subperiosteal hematoma or periostoma, was seen in 7 patients (5 with a pelvic and 2 with an elbow involvement). Finally, a parosteal lesion, arising in the immediate proximity of a bone, was diagnosed in 8 lesions following a radial head injury.

No symptomatology was recorded on the final follow-up in the 5 patients with a post-traumatic pelvic lesion that were treated conservatively. Radiographs indicated nonunion of the fracture in all cases with an avulsed ischial tuberosity, extensive healing with exostosis formation in the patient with the fractured anterosuperior spine and extensive new bone formation in the case with the fractured inferior spine. A reduced range of elbow motion was noted in the 10 patients with an elbow lesion. The radiographic follow-up findings in all patients with an elbow lesion showed diminished dimensions and smoother borders in the mature lesions, but complete radiographic regression was not noted in any of the patients. In only one patient, the

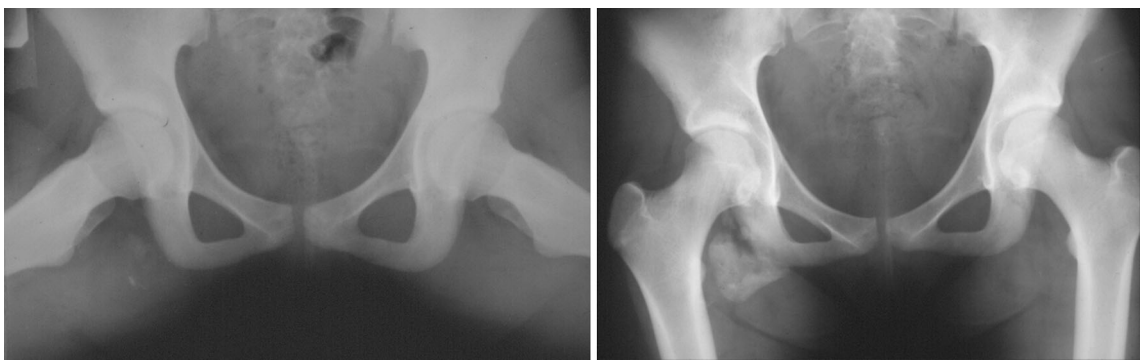

Fig. 8 Asymptomatic nonunion of an avulsion fracture of the right adductor muscles in a 12-year-old girl while distance jumping 4 months ago

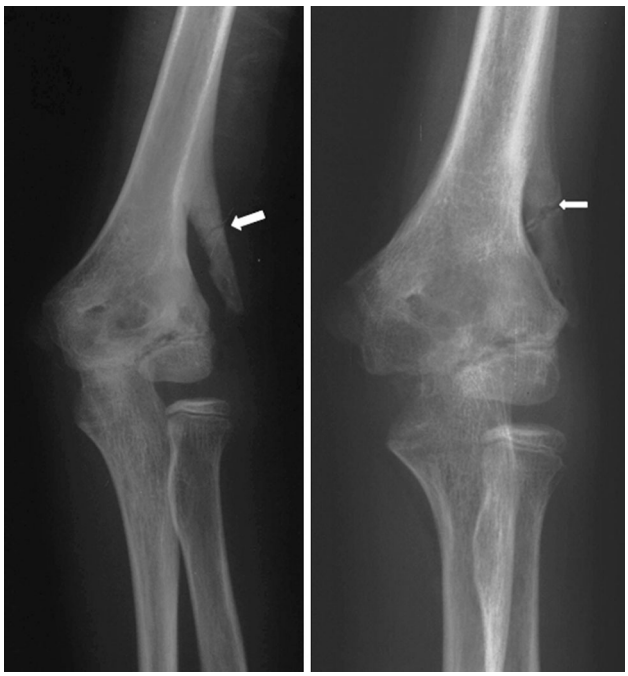

Fig. 9 Traumatic myositis ossificans of the lateral side of the left elbow in a 12-year-old boy following a supraconylar humeral fracture a year ago. Fracture of the ectopic bone following a new fall and healing a month later were noted

ectopic bone, localized in the elbow, was complicated by a fracture 1 year after the initial injury (Fig. 9). Regression of the local clinical findings and healing of the fracture of the ectopic bone followed a month of immobilization.

Discussion

Fundamentally, myositis ossificans may be subdivided into genetic and non-genetic or acquired lesions. Myositis or fibrodysplasia ossificans progressiva (also called Munchmeyer's disease) is an extremely rare and severely disabling genetic disease. It usually appears as a sporadic genetic case, which is not inherited from the parents and arises via a gene mutation, but it may also be due to an autosomal dominant hereditary disorder. The detection of activating mutations in a BMP type 1 receptor ACVR1 (activin type I receptor) in all sporadic and familial cases is a critical milestone in the understanding and treatment of the disease. Children usually appear normal at birth except for malformation of the great toes that is present in all affected individuals. The diagnosis of bilateral hallux valgus on ultrasound may be the first prenatal evidence of the disease. Progressively developing subfascial nodules, commonly located on the posterior neck and back, and heterotopic bone formation of skeletal muscles, tendons, ligaments, fascia and aponeuroses, through an endochondral process, are usually evident within the first 10 years of life. It is the most catastrophic type seen in humans. It leads to progressive immobility, so 'stone man or woman disease' is an alternative name of the disease. However, the natural history of the disease is, to a certain extent, different from one patient to another. Atypical forms referring either to the clinical presentation or to the classic defining features of the disease have been described. Prenatal testing is not indicated for general mutation screening; however, it could be considered within a family in which a child had been diagnosed previously. Definitive molecular diagnosis is possible, but correct diagnosis cannot be made if it is not first suspected. Pediatric orthopedic surgeons are often among the first physicians to see a child who has a, usually symmetrical, great toe malformation, a classic, characteristic feature of the disease. Differential diagnosis of the toe malformations includes isolated congenital malformations, brachydactyly, synostosis, symphalangism syndromes and juvenile bunions, while differential diagnosis of the disease includes progressive osseous heteroplasia, osteosarcoma, lymphedema, soft tissue sarcoma, desmoid tumors, aggressive juvenile fibromatosis and acquired heterotopic ossification. There is no efficient treatment of the disease, since biopsies and excision are not recommended because any type of trauma to the deep tissues will provoke further new growths. Intramuscular injections must be avoided, but vaccinations administered by subcutaneous injection and routine venipuncture pose little risk. Preventive oral and dental healthcare measures are essential. Many conservative treatments including retinoids, cyclo-oxygenase-2 inhibitors, leukotriene inhibitors and mast cell stabilizers have been used with no apparent positive results. High-dose glucocorticoids are used in the management of inflammatory flare-ups (painful soft tissue swellings), in addition to analgesics, etidronate and anti-inflammatory drugs. Radiation may be used in adults, but should be avoided in children. Surgery may be indicated only with a focused indication such as to prevent spinal deformity through an arthrodesis. Diagnostic errors occur up to 87% of cases and may cause severe iatrogenic harm, while the mean time to reach diagnosis is 4.1 years. The discovery of the responsible gene and of molecular mechanisms correcting the hyperfunctioning BMPs signaling pathway(s) revealed new long-term approaches to the treatment of the disease and necessitated additional studies of potential medical interventions [21–68].

Diagnosis in the patients with fibrodysplasia ossificans progressiva presented in this report was made after the appearance of the subfascial nodules and ossifications. Prevention of injuries and respiratory infections, avoidance of excessive sunlight exposure, passive physiotherapy and

regular follow-up including audiometric evaluation were the only offered approaches.

Neurogenic myositis ossificans has been observed following pathological conditions of the central nervous system, including traumatic, vascular, infectious or neoplastic lesions, associated with paraplegia, Guillain–Barré syndrome, AIDS encephalopathy, poliomyelitis, tetanus, hemiplegia and near-drowning. Its detection following closed head injuries that cause coma was reported in 1968. Since then numerous clinical factors and biochemical markers that are predictive have been identified, although very little is still known about the genetic and bio-molecular element of neurogenic myositis ossificans. The hip is the most commonly affected joint and then the knee, shoulder, elbow and non-joint sites. The features of all presented cases are similar, and extensive new bone is usually associated with fixed contractures. It may result in a variety of complications, including nerve impingement, joint ankylosis, complex regional pain syndrome, osteoporosis and soft tissue infection. The incidence is significantly lower in brain-injured children than in adults and also than spinal cord injury patients. In children, cases with a spontaneous resolution have been described. Salicylates appear to be an effective and safe prophylactic measure in minimizing the occurrence and preventing recurrence of ectopic bone formation following its excision in children. Bisphosphonates, in particular etidronate, and non-steroidal anti-inflammatory drugs have also been used in both the prevention and management of heterotopic ossification. Excision of the ectopic bone allowing correction of the caused deformity together with regaining movement is worthwhile, especially in the presence of returning motor function. The optimal timing for surgery is the neurological recovery, rather than the maturity of the bone [69–103].

The single patient with neurogenic ectopic bone formation included in this review showed spontaneous resolution of the lesion and full recovery within a year.

Non-neurogenic acquired lesions may be post-traumatic or non-traumatic. Traumatic or circumscribed myositis ossificans is also defined as myo-osteosis, extraosseous localized non-neoplastic bone, fibrositis ossificans or hematoma ossificans. It is related to evident and direct trauma in the form of a single severe injury, recurrent episodes of minor trauma and overuse injuries or sustained irritation. In the absence of any trauma or evidence of any systemic disease, the lesion is called non-traumatic or pseudomalignant. It may also be diagnosed following severe burns (the incidence in children is higher than in adults), muscular bleeding due to hemophilia and orthopaedic operations. In young infants with non-accidental trauma, the battered child syndrome should be evaluated. The lesion usually occurs in the large muscle groups of the thigh and upper limb of young men. The brachialis, the quadriceps femoris and the thigh adductor muscles are the most common sites of involvement. The soleus muscle is usually involved in ballerinas. The classical complaint is of a localized painful swelling with limitation of motion of the adjacent joint. Physical examination reveals a firm tender mass in the soft tissues, but calcific densities will become apparent in the radiographs about 4 weeks later. The lesion may be mistaken for a malignant bone or soft tissue tumor or infection, such as osteomyelitis or soft tissue abscess. The site of the lesion on a primary topographic basis may be periosteal, parosteal and extraskeletal. The imaging detection of a lucent zone between the lesion and the underlying bone, the presence of an intact cortex, the location adjacent to the shaft of a bone and the densest calcification in the periphery of the lesion are valuable radiographic findings in the differential diagnosis from bone malignancy. After a period of active growth lasting about 10 weeks, the mass becomes painless and stagnant or regresses spontaneously. This may be apparent on serial radiographs. The zonal phenomenon is an important histological diagnostic criterion of the immature lesion. However, fine-needle biopsy may not procure enough histologic specimens to demonstrate the four zones, and a single specimen taken from the center of the lesion may strongly resemble the findings of osteosarcoma. In addition, the lack of invasion of the adjacent tissues and the inclusion of viable muscle fibers in the lesion are helpful in the histological differential diagnosis from extraskeletal, parosteal or synovial sarcomas. Surgical removal should not be attempted before complete maturation of the lesion. Bone scanning has been attempted as a means of evaluating the activity of the lesion prior to surgery. Surgical removal of the calcified lesion is not necessary in children, unless it is painful or interferes with motion [104–180].

In this report, full clinical recovery with complete radiographic resorption of the ectopic bone was noted in the case with neurogenic myositis ossificans. The four patients (1 with an idiopathic and 3 with a post-traumatic lesion) that were treated operatively were also symptom-free at follow-up. An asymptomatic nonunion complicated 3 cases with a fractured ischial tuberosity and an exostosis complicated a fractured anterosuperior spine. An altered range of joint motion complicated all cases with an elbow ectopic bone formation. None of these cases showed complete clinical regression, since the clinical findings were not improved after the maturation of the lesion. Fracture of the ectopic bone was recorded in only one patient with an elbow lesion.

Compliance with ethical standards

Conflict of interest The author certifies that he has no commercial associations (such as consultancies, stock ownership, equity interest and patent/licensing arrangements) that might pose a conflict of

interest in connection with the submitted article. The author received no financial support for this study.

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.

Informed consent Informed consent was obtained from all individual participants included in the study.

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