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REVIEW ARTICLE

Fibrodysplasia Ossificans Progressiva : Diagnosis and surgical management

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Fibrodysplasia (or Myositis) Ossificans Progressiva (FOP) is a rare genetic disease with variable expression, characterized by the association of congenital anomalies of the toes and fingers and progressive appearance of ectopic bone within the skeletal muscles, often following a trauma or an infection. FOP initially affects the nape and thoracic paravertebral muscles. With age, there is a progression of ossifications to other muscular groups following a proximo-distal and cranio-caudal extension. Patients develop a restrictive respiratory insufficiency with atelectasis.

The diagnosis of FOP is clinical and does not require biopsy. Circumscribed post-traumatic ossifying myositis is the most important differential diagnosis. It is characterized by the appearance of painful ossifications, in young adults, following a trauma and is limited to one localisation.

The conservative treatment of FOP remains unsatisfactory. Surgical removal of osteomas to restore joint mobility leads to the development of additional heterotopic ossifications. Each surgical attempt brings about a quasi-inevitable recurrence. Anaesthesia of patients with FOP is difficult because of spinal rigidity and ankylosis of the jaw. Surgery is indicated only with a focused indication to correct an invalidating deformity.

Keywords : myositis (fibrodysplasia) ossificans progressiva ; heterotopic ossifications ; surgical treatment.

INTRODUCTION

Fibrodysplasia (or Myositis) Ossificans Progressiva (FOP or MOP) is a rare genetic disease first described in 1692 by Patin (*11*). It combines skeletal malformations, especially of toes, and heterotopic progressive ossifications, with ectopic bone tissue formation inside and around the muscles, tendons and aponeuroses (*18*). Conservative treatment is unsatisfactory (*10,11,12*). Surgical treatment is considered similarly ineffective and generally contraindicated because of anaesthetic difficulties and of the inevitable recurrence of ossifications (*17*). We present a new illustrative case treated surgically, and we review the main clinical features of this disease, its medical treatment and discuss the role of surgical treatment.

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ILLUSTRATIVE CASE

A-25-year-old woman was referred to the orthopaedic department for painful polyarticular stiffness. There was no family history of a similar condition. The disease began at the age of six, following a fall ; she had pain about her right knee without a fracture, followed by progressive stiffness of her right knee. Subsequently she progressively developed pain with stiffness of the spine, shoulders, then of the hips and knees. At the age of 18, she had after a trauma a non-displaced fracture of the left olecranon which was treated with a plaster cast for one month ; after removal of the cast, the elbow was completely stiff. Radiographs showed an osteoma at the anterior aspect of the elbow.

Physical examination revealed a good general condition, a normal intelligence, a torticollis with loss of cervical lordosis and limitation of movements. She had a left lumbar scoliosis, an oblique pelvis and multiple painless and fixed subcutaneous masses of osseous consistency (Fig. 1). The right shoulder was completely stiff ; the left shoulder had very limited mobility and the left elbow remained stiff. The right hip had a 45° fixed adduction deformity with major difficulties for perineal hygiene. The mobility of the left hip was limited. The right knee was ankylosed in extension and the left knee had a limited flexion to 90°. The mobility of the wrists and fingers was normal ; she had a bilateral short fifth finger. Examination of the feet revealed shortness of the big toes with deformations of the other toes, in particular hypertrophy of the 2nd toe (Fig. 2). Standard radiographs showed a left thoracic and right lumbar scoliosis with complete fusion of the spine and sacro-iliac joints by irregular osseous bridges. A radiograph of the right shoulder showed osteomas between the scapula and the proximal end of the humerus. The radiograph of the pelvis showed several bony bridges between the right ischiopubic ramus and the femur, fixing the hip in 45° adduction (Fig. 3). A radiograph of the knees disclosed the presence of osteochondromas of the distal end of the femur and the proximal end of the tibia. The inflammatory and phosphocalcic biological workups were normal. Phenotype HLA highlighted the alleles A1, A23, B35, B40.

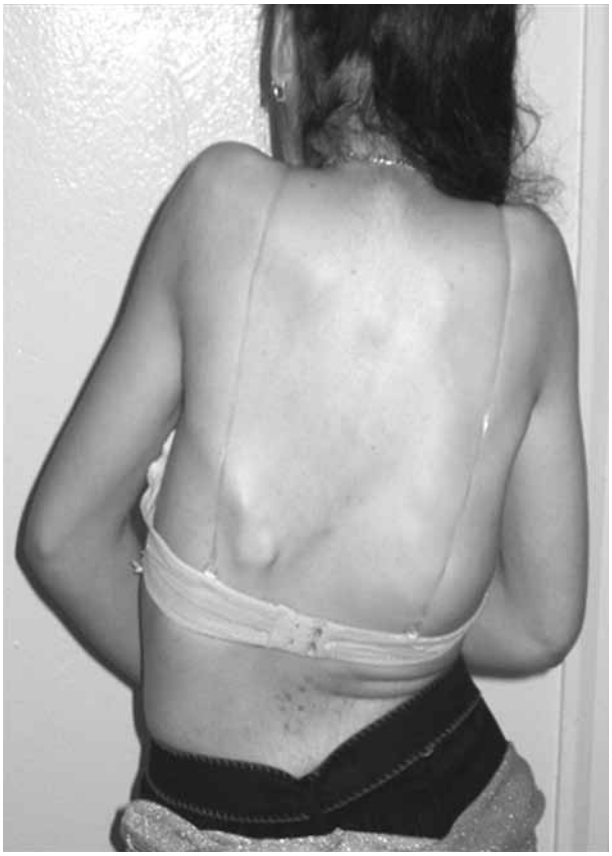

Fig. 1. — Clinical aspect of the trunk with left lumbar scoliosis and subcutaneous osseous masses.

Radioisotope bone scan showed several sites of increased radioisotope uptake. Resection of the osseous bridges about the right hip was carried out under general anaesthesia through a medial approach, which allowed to restore 40° abduction and 30° flexion under anaesthesia. After the intervention, she was put in traction, and received physiotherapy and corticosteroids and bisphosphonates. An extensive recurrence of these ossifications was observed on radiographs two months after surgery, but the ankylosis was in a better position with a slight adduction as recommended in hip arthrodesis (Fig. 4). The surgery did not trigger ossifications in other locations. Two years after surgery, the patient is still autonomous ; she can stand and walk with a cane ; her ossifications appear to have stabilized.

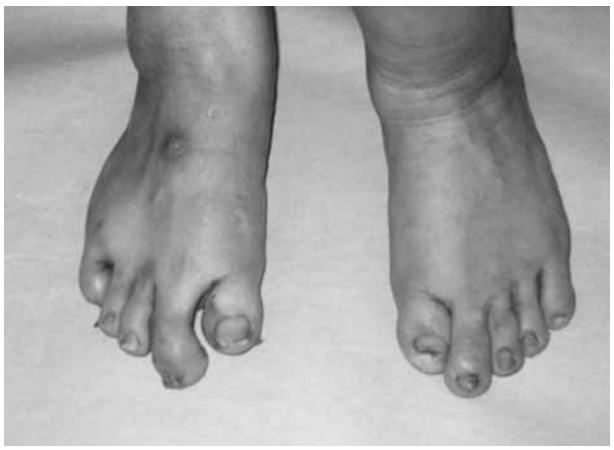

Fig. 2. — The feet of the patient have short, deformed big toes and hypertrophy of the 2nd toes.

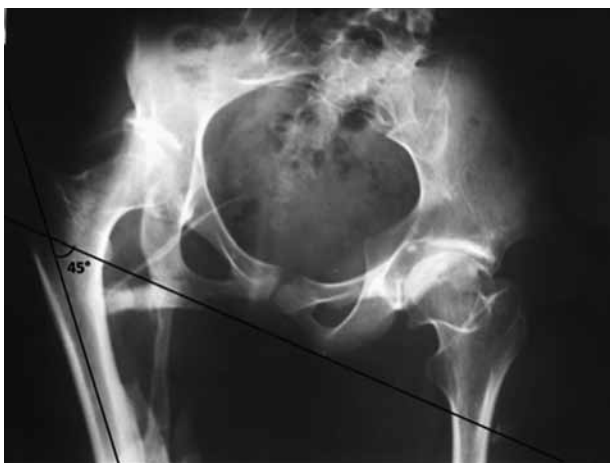

Fig. 3. — AP radiograph of the pelvis showing ossifications between the right ischiopubic branch and the femur fixing the hip in 45° adduction.

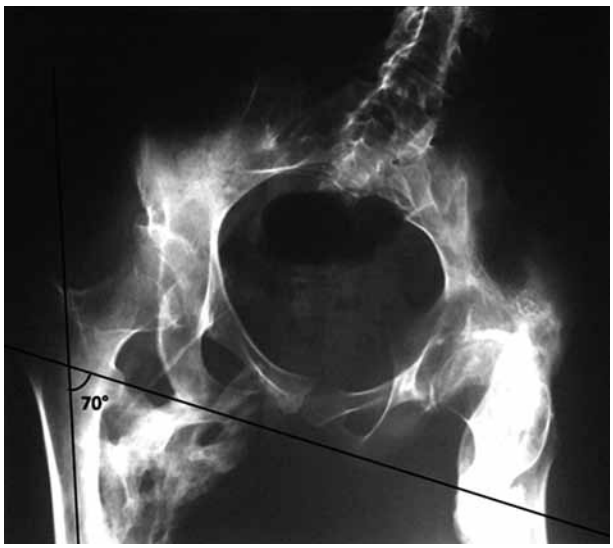

Fig. 4. — AP radiograph, 2 months after surgery, showing a spectacular recurrence of the ossifications, but in a better position.

DISCUSSION

FOP is an autosomic dominant disease, with a complete expression for congenital malformations and a variable expressivity for ossifications (*8*). Little is known about the pathogenesis of FOP. A possible defect in induction of endochondral osteogenesis was put forward. Recent studies suggest an anomaly of bone morphogenetic proteins, in particular BMP4. High production of BMP4 would be implied in the preosseous inflammatory process, with a dysregulation of the production of the cells and mediators in the connective and muscular tissue. This increase in BMP4 would be related to an anomaly of the regulation of its synthesis because of a mutation of the Noggin gene affecting an antagonist of BMP4 (*12*).

The clinical picture combines congenital anomalies of the toes and fingers and progressive ossifications. The characteristic congenital skeletal anomaly affects the big toes. They have a short aspect with sometimes side deviation and stiffness (*6,21*). Similar anomalies can be seen on the thumb with a short first metacarpal (*12,21*), and sometimes a brachymesophalangy of the fifth finger with clinodactyly (*11*). Ossifications start towards the age of 2 to 6 years, often following a trauma or an infection. FOP initially affects the nape and thoracic paravertebral muscles. With age, new episodes may occur ; after each episode, there is a progression of ossifications including other muscular groups while following a proximo-distal and cranio-caudal extension. The episodes will affect the shoulders, the lumbar spine, and the hips. Later, the distal articulations may be affected towards the third decade of life (*20*). However, certain muscular groups are spared, including the tongue, the larynx, the ocular muscles, the diaphragm, the abdominal

wall, the cardiac muscle, and the smooth muscles (*13,20*). Because of the progressive ankylosis of the costovertebral articulations and the vertebral deformation, patients develop a restrictive respiratory insufficiency with atelectasy. Pneumonia and right cardiac insufficiency are usually the causes of death.

Plain radiographs show ectopic ossifications of soft tissues. At an advanced stage, they can show bony bridges between various parts of the skeleton, with an ectopic skeleton. They can also show absence of a phalanx in the big toes, shortening of the first metatarsal or interphalangeal ankylosis (*4*). More elaborate imaging is not necessary for the diagnosis, especially at an advanced stage. A CT scan can be useful to better analyze ossifications ; MRI and technetium bone scan can show lesions at an early stage, when they are not yet ossified (*2*). Laboratory investigations generally do not reveal any anomalies (*12,21*).

The diagnosis of FOP is clinical and does not require biopsy. Besides being useless, the biopsy can result in a new ectopic ossification and can be misleading, given the heterogeneous character of the lesions (*2*). Several differential diagnoses can be considered, especially at the beginning of the disease and in the absence of an examination of the toes and fingers. For Debeney-Bruyerre *et al* (*7*), the only differential diagnosis of this condition is circumscribed post-traumatic ossifying myositis. In this condition there are no associated congenital anomalies of the toes and fingers, the ossifications are generally limited to one localization, are painful, and occur in young adults following a trauma (*7*) ; this condition can be treated surgically and generally there is no recurrence after surgery (*2*). Other differential diagnoses could be suggested in the presence of FOP. Soft tissue sarcomas could be considered, based on the results of the biopsy of incipient lesions (*15,17*). Hereditary Albright osteodystrophy is characterized by an ossification in the muscle and connective tissue, but ossifications are more marked in the subcutaneous fat and are associated with a pseudohypoparathyroidism syndrome (*1*). Ankylosing spondylitis could be suggested when confronted with ankylosis of the spine and sacro-iliac joints (*9*).

A trauma is often the triggering factor of the disease or of an episode of progression, as observed in this case (*7*). The natural history of this condition is characterized by inflammatory episodes of 2 to 3 weeks, with latency periods of several months in between. Thromboembolic, neurological, cutaneous, infectious or respiratory complications can occur. The prognosis depends especially on the occurrence of a respiratory insufficiency at a late stage (20).

To date, no treatment has proved its effectiveness. Corticosteroids and non-steroid anti-inflammatory drugs were largely used to control the acute symptoms during the inflammatory phases of FOP, but their effectiveness is uncertain and the potential severity of their side effects should be taken into account (*11*). Aminobisphosphonates, the inhibitors of leucotrienes, and the stabilizers of the mastocytes in theory prevent the inflammatory oedema of the muscles, fibroproliferation and angiogenesis (*12*). They were used to prevent the development of new ossifications. To date, there is no evidence of their effectiveness or their ability to modify the natural history of the disease (*10*). Gene therapy using Noggin, an antagonist of BMP4, remains the most promising treatment. It was suggested because of the over-expression of BMP4 among patients with FOP. Knowing that FOP is a genetic disease, its treatment will presumably be based on gene therapy (*12*).

There is little place for surgery mainly because anaesthesia of these patients is difficult due to spinal and mandibular rigidity (*16,22*). The surgical correction of the spinal deformities by excision of osteomas is often ineffective in view of the high number of osteomas and their extent. Surgical removal of the osteomas to mobilize the joints represents an additional trauma and leads to the development of additional heterotopic ossifications. Each surgical attempt, therefore, results in a quasi-inevitable recurrence. In 1918, Rosenstirn, in his report of a case, emphasized the inconstant and poor results of the surgery aiming at improving articular mobility. He concluded that there was no effective treatment for this disease (*19*). According to many authors, surgical treatment should be avoided inasmuch as possible because it is danger-

ous and may cause inflammatory outburst of the disease (*11,18*). It is even recommended to avoid any surgical biopsy which is not necessary for the diagnosis, because it can trigger a progression episode of the disease (*7*). Anaesthesia in FOP patients is difficult and many precautions should be taken because of the stiffness of the neck, temporo-mandibular ankylosis, intercostal osteomas, pulmonary restrictive syndrome, etc (*1*). Forceful opening of the mouth for intubation can cause an additional trauma to the temporo-mandibular articulation (*18*). When mobility of the temporo-mandibular articulations is limited, anaesthesia should be carried out by a nasofibroscope and intubation should be made under light sedation to control secretions (*18*). In a series of Rogers and Geho (*18*), comprising 42 patients, 37 patients had been subjected to one or more operations because of this disease. Seven patients had had a biopsy only, six patients had had a biopsy as well as an operation to increase the mobility of a joint, and a further twenty-four patients had had operations to improve mobility or joint position. Thirteen had such operations on only one occasion ; four, on two occasions ; and seven, on three or more occasions. There was a comment on the outcome in fifty-five episodes of operation or biopsy. Thirty-four patients reported that they were worse after the procedure ; in fifteen, the procedure produced no change ; and in six patients the procedure produced improvement. Three of those six improved following surgery for hallux valgus, and one patient had a total hip replacement that made nursing easier. The other patients (one of whom also had surgery for hallux valgus) felt that they improved following an operation on the hip, thigh, and scapula in one each. The patients can however undergo a surgical operation for abdominal pathology without formation of ossifications on the operative site (*7,18*). A patient reported by Rachkidi *et al* (*16*) was operated on at the age of 4 for severe bilateral hallux valgus. Recurrence of the deformation was noted with the appearance of ossifications at the medial edge of the metatarso-phalangeal articulations. Two years later, he had a limitation of the knee flexion to 20° ; excision of ossifications of the thigh was carried out and was followed by radiotherapy. Pre and latero - trochanteric ossifications reappeared 6 weeks later and his ambulation deteriorated because of the recurrence of the stiffness of the knee and a 40° flexion deformity of the hip. According to Debeney-Bruyerre *et al* (7), surgery can trigger an acceleration in the progression of the disease. This was not observed in our case. However, Corfield *et al* (*5*) obtained a good result after resection of ossifications of the wrist followed by arthrodesis in a physiological position. The surgical correction of the fixed adduction deformity of the hip in our patient was beneficial in spite of the recurrence of ossifications. Ankylosis was achieved in a more convenient position. If a surgery is decided, many precautions should be taken :

– attention should be paid to the positioning of the patient during surgery to prevent trauma of soft tissues.
– if inflammatory signs develop postoperatively, steroids are recommended.
– respiratory functional exploration before anaesthesia is mandatory in order to explore the restrictive pulmonary syndrome due to the intercostal ossifications (*5,7*) ; early postoperative thoraco-pulmonary physiotherapy is essential to prevent respiratory infections.

Surgery is not contraindicated, but has only a limited place in this condition. It is indicated in a focused way to correct an invalidating deformity, while warning the patient that the goal is not improvement of mobility, but correction of the deformity to achieve ankylosis in a more favourable position. In the case reported, surgery did not trigger remote ossifications. Atraumatic physiotherapy and respiratory rehabilitation are useful to aid these patients to keep their autonomy for a long time (*14*).

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