

Fibrodysplasia ossificans progressiva in a 3-year-old female patient

Cecilia Moreira¹, Gabriel Dapueto², Gabriel Peluffo², Alejandra Vomero², Alejandra Tapié³, Soledad Rodríguez³, Victor Raggio³, Rodrigo Suárez⁴, Gustavo Giachetto⁵, and Loreley García²

¹Cuidados Intensivos Pediátricos, Centro Hospitalario Pereira Rossell; ²Clinica Pediátrica B, Facultad de Medicina, Universidad de la República;

³Departamento de Genética, Facultad de Medicina, Universidad de la República; ⁴Servicio de Reumatología Infantil, Centro Hospitalario Pereira Rossell; ⁵Clinica Pediátrica C, Facultad de Medicina, Universidad de la República. Montevideo, Uruguay

Abstract

Background: *Fibrodysplasia ossificans progressiva (FOP)* is a rare autosomal dominant disease affecting connective tissue, primarily caused by *de novo* mutations of the *ACVR1* gene. *FOP* is a disease with congenital malformations of the toes and heterotopic ossification in characteristic patterns that progresses with flare-ups and remissions. Cumulative damage results in disability and, eventually, death. This report aimed to describe a case of *FOP* to highlight the importance of early diagnosis of this rare condition. **Case report:** We describe the case of a 3-year-old female diagnosed with congenital hallux valgus, who initially presented with soft tissue tumors, predominantly in the neck and chest, with partial remission. Multiple diagnostic tests were performed, including biopsies and magnetic resonance imaging, with nonspecific results. We observed ossification of the biceps brachii muscle during evolution. The molecular genetic study found a heterozygous *ACVR1* gene mutation that confirmed *FOP*. **Conclusions:** Knowledge of this rare disease by pediatricians is critical for an early diagnosis and for avoiding unnecessary invasive procedures that may promote disease progression. In case of clinical suspicion, performing an early molecular study is suggested to detect *ACVR1* gene mutations. The treatment of *FOP* is symptomatic and focused on maintaining physical function and family support.

Keywords: Myositis ossificans. *ACVR1* gene. Hallux valgus.

Fibrodisplasia osificante progresiva en una paciente de 3 años

Resumen

Introducción: La fibrodisplasia osificante progresiva (FOP) es una enfermedad autosómica dominante rara que afecta el tejido conectivo, cuya causa principal son mutaciones *de novo* del gen *ACVR1*. Se trata de una enfermedad con malformaciones congénitas de los primeros ortejos y osificación heterotópica en patrones característicos que progresan en empujes y remisiones. El daño acumulativo provoca discapacidad y, eventualmente, la muerte. El objetivo de este trabajo fue describir un caso de FOP para favorecer el diagnóstico precoz de esta enfermedad infrecuente. **Caso clínico:** Se describe el caso de una paciente de 3 años, portadora de hallux valgus congénito, que inicialmente presentó tumoraciones dolorosas de tejidos blandos, de predominio en cuello y tórax, con remisión parcial de las mismas. Se realizaron múltiples pruebas diagnósticas, incluyendo biopsias e imágenes de resonancia magnética con resultados inespecíficos. En la evolución se

***Correspondence:**

Gabriel Dapueto
E-mail: gdapueto@gmail.com

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observó osificación de músculo bíceps braquial. El estudio genético molecular encontró una mutación del gen ACVR1 en heterocigosis que confirmó el diagnóstico de FOP. **Conclusiones:** El conocimiento de esta enfermedad por los pediatras es clave para realizar un diagnóstico precoz y evitar procedimientos invasivos innecesarios que pueden promover la progresión de la enfermedad. Ante la sospecha clínica, se sugiere realizar tempranamente el estudio molecular para detectar mutaciones del gen ACVR1. El tratamiento de la FOP es sintomático, centrado en el mantenimiento de la función física y el apoyo familiar.

Palabras clave: Miositis osificante. Gen ACVR1. Hallux valgus.

Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease, with an estimated incidence of 0.6-1.3 per million individuals¹, characterized by progressive heterotopic endochondral ossification and congenital malformations of the great toes². It is included in the Online Mendelian Inheritance in Man (OMIM) registry under number 135100³.

FOP evolves in flare-ups that produce new areas of ossification, leading to progressive motor disability and death, mainly due to restrictive respiratory complications⁴. It is an autosomal dominant disease caused by heterozygous mutations in the ACVR1 gene encoding the activin receptor IA (ACVR1/ALK2), a protein in the bone morphogenetic signaling pathway⁵.

Although several drugs are used to treat this pathology, there is yet to be a treatment with proven clinical efficacy¹.

We report the case of a female patient diagnosed with FOP at the age of 3 years. The objective is to inform the case of a rare disease that generated diagnostic difficulties. Knowledge of this entity can avoid unnecessary paraclinical evaluations that can be iatrogenic and favor disease progression.

Clinical case

We describe the case of a 3-year-old female patient with good growth and development, healthy parents, and two healthy siblings. The patient showed congenital bilateral *hallux valgus* and had a complete immunization scheme. The patient was evaluated for presenting 2-week evolution of multiple painful cervical tumors in both jugular-carotid regions, predominantly on the right side. She showed fever in the first two days of onset of the disease, remaining in apyrexia afterward. No symptoms of intercurrent infection and general compromise were further observed.

Initially, the tumors were of firm-elastic consistency, 3 cm in diameter, and adhered to the muscular planes. They were accompanied by erythema of the overlying

skin, which disappeared during evolution, acquiring a stony consistency. Lymphoganglionic examination revealed multiple mobile adenomegalies in jugular-carotid, submaxillary, axillary, inguinal, and abdominal regions; a painful pole of the spleen was palpated. On admission, the sternocleidomastoid and trapezius muscles had a stony consistency, generating painful torticollis (Figure 1).

During the 2-week hospital stay, tumors with similar characteristics were detected in other regions related to muscular structures: posterior cervical region, trapezius muscles, right subscapular region, and left paravertebral level (Figure 2). The rest of the physical examination showed no alterations.

An anatomopathological study and imaging follow-up of the lesions by ultrasound and magnetic resonance imaging (MRI) were performed. Malignancy and ossification were excluded. The rest of the complementary studies showed no alterations.

During outpatient follow-up after discharge, the patient presented partial regression of the tumors that motivated the initial consultation and similar lesions in the pectoral region, right dorsum, and abdominal wall.

Clinical and functional improvement occurred after initiating treatment with prednisolone at 2 mg/kg. However, the symptomatology returned when this dose was reduced. After five months of evolution, the patient presented pain and limitation of movement. The trapezius and sternocleidomastoid muscles, biceps, and triceps of the right upper limb showed a stony consistency, as well as at the biopsy sample extraction sites. Plain radiography of the right upper limb showed calcification of the right biceps brachii muscle (Figure 3).

The presence of muscular calcifications, in addition to the reevaluation in the diagnostic reasoning of congenital *hallux valgus*—interpreted until now as an isolated morphological alteration—allowed the establishment of the clinical diagnosis of FOP.

The molecular genetic study found ACVR1:c.617G>A (p.Arg206His) in heterozygosity, confirming the clinical diagnosis.



Figure 1. Hypertrophy of sternocleidomastoid and trapezius muscles.

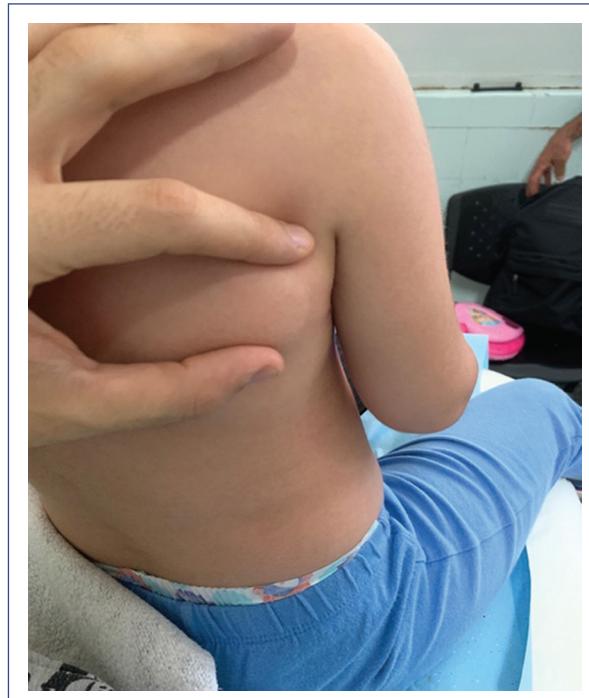


Figure 2. Tumor in the right subscapular region.

Discussion

This present case is the second case of FOP reported in Uruguay⁶. It is one of the so-called “ultra-rare” diseases, with an estimated incidence of 0.6-1.3 per million individuals. Diagnosis is clinical and confirmed by molecular studies^{1,4}. No sex predominance has been established.

This autosomal dominant disease is caused by gain-of-function mutations in the *ACVR1* gene, located on chromosome 2q23-24. More than 95% of patients have the missense mutation c.617G > A (p.Arg206His), as this patient⁵.

The *ACVR1* gene encodes for the activin receptor type IA, a membrane protein member of the family of intercellular signaling protein receptors called bone morphogenetic proteins (BMP) type I^{5,7}. The p.Arg206His mutation, which consists of changing the amino acid arginine to histidine at position 206, resides in a domain critical for regulating this protein called the GS (glycine-serine) domain. This change causes a gain of function, leading to constitutive or ligand-independent deregulated activation, which explains its dominant expression. This mutation modifies the folding of the protein at the binding site of another protein (FKBP12) with inhibitory activity on *ACVR1*. The inability to be inactivated by its negative regulator generates

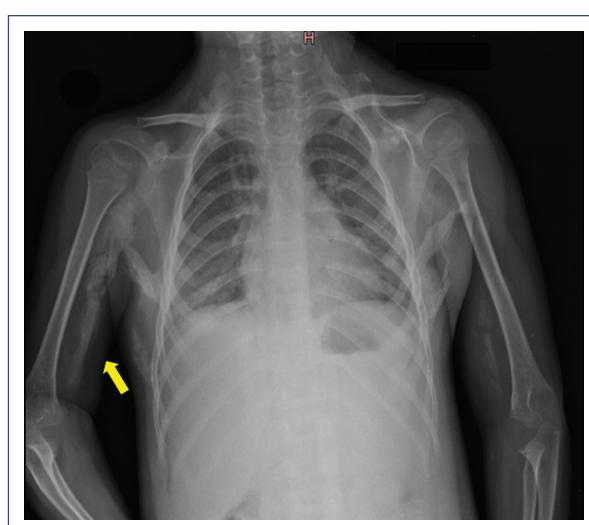


Figure 3. Radiographic evidence of ossification of the biceps brachii muscle.

constitutive activity of the receptor encoded by *ACVR1*. The consequent dysregulation of the BMP signaling pathway would lead to aberrant cartilage production from mesenchymal cells⁸.

Morphological alterations of the distal bones of the limbs are one aspect of the disease. Other recurrent mutations in this gene (p.Gly328Arg, p.Gly328Trp, and

p.Gly328Glu) are associated with characteristic limb alterations that may be mistaken for amniotic flange disruptions or type B brachydactyly. The penetrance of gain-of-function mutations in the *ACVR1* gene is estimated to be complete, as no cases with these mutations or their clinical expression have been reported⁵. As in most dominant diseases, wide phenotypic variability can be observed, and other genes and environmental factors likely modulate the presentation of the disease⁵.

As we propose, most cases are sporadic, arising from a *de novo* mutation, since none of the parents have elements suggestive of this condition¹.

Two clinical elements classically define FOP: malformations of the great toe and progressive heterotopic endochondral ossification in characteristic anatomical patterns. Patients with FOP present as healthy neonates, except for the malformation of the great toe, which is present in all affected individuals, as observed in this case^{2,4,9}.

Initially, this patient presented tumors of firm-elastic consistency in the neck, with adherence to muscular planes. This observation led to other diagnoses, including hemato-oncologic causes, usually one of the most frequent initial approaches¹⁰. Initial imaging studies showed no calcifications, which generated diagnostic confusion. Current evidence demonstrates that the development of heterotopic ossification occurs after soft tissue inflammation^{4,11}. Routine biochemical studies are usually normal, as observed in this patient. To date, no specific biomarkers have been identified¹.

Hallux valgus in the pediatric age group is usually acquired during infancy and childhood; it is infrequently congenital, as in this case¹². Although congenital malformations of the great toes are a constant feature of FOP, their presence is not pathognomonic^{1,2}. In addition, it is possible to observe other alterations that this patient did not present, such as malformation of the thumbs, clinodactyly, tibial osteochondromas, and wide and short femoral necks^{1,5}.

Affected patients develop episodic flare-ups of pain and soft tissue inflammation. Some episodes remit spontaneously, but in most of them, the soft connective tissues are transformed into bone tissue by endochondral ossification, leading progressively to permanent immobility. In addition, minor trauma, such as intramuscular immunizations, dental anesthesia, muscle fatigue, hematomas, falls, and infections, can trigger new flare-ups^{1,4}.

As observed in this patient, heterotopic endochondral ossification progresses following anatomical and temporal patterns that mimic the patterns of bone formation in the normal human embryo. It initially occurs in the

dorsal, axial, cranial, and proximal regions of the body and is subsequently seen in the ventral, appendicular, caudal, and distal regions. Some skeletal muscles are unaffected, including the diaphragm, tongue, and extraocular muscles. Cardiac and smooth muscle tissues are also unaffected^{5,13}.

Most patients require assistance with activities of daily living in the early stages. Mandibular involvement is usually followed by significant malnutrition. A frequent cause of death in affected patients is progressive cardiorespiratory failure due to thoracic insufficiency syndrome, which results in the inability of the thorax to achieve normal ventilation. The median age at death is 40 years^{13,14}.

There is currently no definitive medical treatment for FOP. Therefore, management consists of supportive care. Since this is a chronic disease with a significant impact on quality of life, it is recommended that the care of patients with FOP be multidisciplinary^{1,15}.

High doses of glucocorticoids have shown efficacy in the early treatment of flare-ups affecting the major joints, mandible, and submandibular region^{1,4}. They also help prevent flare-ups after trauma and surgery, decreasing the probability of heterotopic ossification in the affected sites^{1,16}. The administration is suggested in the first 24 hours of the outbreak, at a daily dose of 2 mg/kg/day, for no more than 4 days. This patient received corticosteroids and presented a good initial response.

Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, mast cell stabilizers, and anti-leukotrienes are helpful in pain management¹⁷. Other drugs, such as bisphosphonates and imatinib, are not routinely used but may contribute to managing difficult-to-control flare-ups¹⁸.

New therapies are being investigated, including palovarotene derived from retinoic acid. This drug reduced the percentage of FOP patients who developed heterotopic ossification and is currently in a phase 3 study¹⁹.

Surgical interventions to remove heterotopic bone tissue result in reactive bone regrowth, as observed at the biopsy specimen extraction sites in this patient, and are therefore contraindicated^{1,10}.

Preventive measures aimed at reducing flare-ups and subsequent ossification are essential. Patients with FOP should have prophylactic dental control, excluding mandibular anesthetic blocks. There is consensus on avoiding vaccination and intramuscular administration during flare-ups. Administration of vaccines with diphtheria, pertussis, and tetanus components, which are associated with a higher incidence of flare-ups, is not

routinely recommended²⁰. For the same reason, muscle fatigue should be limited, and falls and respiratory infections should be prevented^{1,10}.

In conclusion, FOP is a sporadic disease often underdiagnosed, especially in its early stages. If clinical suspicion exists, early molecular testing is suggested to detect the most frequent mutations of the ACVR1 gene. Current management of FOP consists mainly of symptomatic treatment, maintenance of physical function, and family support.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interests.

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